Review Report

August 26, 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	Yervoy Injection 50 mg (for intravenous use)
Non-proprietary Name	Ipilimumab (Genetical Recombination) (JAN*)
Applicant	Bristol-Myers Squibb K.K.
Date of Application	November 12, 2019
Dosage Form/Strength	Injection: One 10 mL vial contains 50 mg of ipilimumab (genetical recombination).
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that combination therapy with nivolumab (genetical recombination) and ipilimumab (genetical recombination) has 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 that the combination therapy has acceptable safety in view of its benefits (see Attachment).

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

Indications

○ Unresectable malignant melanoma
○ Unresectable or metastatic renal cell carcinoma
○ Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy

(Underline denotes additions.)

Dosage and Administration

~~1.~~ Unresectable malignant melanoma:

The usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 doses. Ipilimumab (genetical recombination) should not be used in combination with antineoplastic agents other than nivolumab (genetical recombination).

~~2.~~ Unresectable or metastatic renal cell carcinoma, or unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy:

In combination therapy with nivolumab (genetical recombination), the usual adult dosage is 1 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 doses.

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

July 15, 2020

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

Products Submitted for Approval

(a) 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	November 12, 2019, November 27, 2019[1)]
Dosage Form/Strength	Injection: Each vial of 2, 10, or 24 mL, respectively contains 20, 100, or 240 mg of nivolumab (genetical recombination).
Proposed Indications	○ 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 ○ 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 ○ Unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy (No change after the approval dated February 21, 2020)

Proposed Dosage and Administration

Malignant melanoma:

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

[1)] (a) An application for partial change was filed on November 12, 2019 to add a new dosage regimen for combination therapy with nivolumab (genetical recombination) and ipilimumab (genetical recombination) for microsatellite instability-high (MSI-High) colorectal cancer. (b) An application for partial change was filed on November 27, 2019 to update the dosage and administration of nivolumab (genetical recombination) to include an infusion regimen of 480 mg every 4 weeks for all of the approved indications.

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

Unresectable or metastatic renal cell carcinoma:

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

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

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

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

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

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~~, 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 or 480 mg administered as an intravenous infusion every 4 weeks.

(Underlines and strikethroughs denote additions and deletions, respectively, which were made after the approval dated February 21, 2020.)

(b)	**Brand Name**	Yervoy Injection 50 mg (for intravenous use)
	Non-proprietary Name	Ipilimumab (Genetical Recombination)
	Applicant	Bristol-Myers Squibb K.K.
	Date of Application	November 12, 2019
	Dosage Form/Strength	Injection: One 10 mL vial contains 50 mg of ipilimumab (genetical recombination).
	Proposed Indications	○ Unresectable malignant melanoma ○ Unresectable or metastatic renal cell carcinoma ○ Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy (Underline denotes additions.)

Proposed Dosage and Administration

~~1.~~ Unresectable malignant melanoma:

The usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 doses. Ipilimumab (genetical recombination) should not be used in combination with antineoplastic agents other than nivolumab (genetical recombination).

~~2.~~ Unresectable or metastatic renal cell carcinoma, or unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy:

In combination therapy with nivolumab (genetical recombination), the usual adult dosage is 1 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 doses.

(Underline denotes additions. Strikethrough denotes deletions.)

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed products

Nivolumab (genetical recombination) (hereinafter, referred to as "NIVO") is a human monoclonal antibody against human programmed cell death-1 (PD-1) belonging to the immunoglobulin (Ig)G4 subclass, discovered by Ono Pharmaceutical Co., Ltd. and Medarex, Inc., US (currently Bristol-Myers Squibb). NIVO binds 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.

Ipilimumab (genetical recombination) (hereinafter, referred to as "IPI") is a human monoclonal antibody of the IgG1 subclass against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), discovered by Medarex, Inc., US (currently Bristol-Myers Squibb). IPI suppresses tumor growth by inhibiting the binding of CTLA-4, a negative costimulatory receptor (a negative regulator of T cell activation), to CD80 (B7.1) and CD86 (B7.2) molecules expressed on antigen-presenting cells to promote the immune response of T cells against tumors, and through other mechanisms.

In Japan, NIVO 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. After the present application for partial change was filed, NIVO was approved for the indications of "unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy" and "unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy" in February 2020. In addition, the above indication (a) was modified to "malignant melanoma" in August 2018.

IPI was approved for the indications of (a) "unresectable malignant melanoma" in July 2015 and (b) "unresectable or metastatic RCC" in August 2018.

The applicants have submitted applications for partial changes around the same time to: (i) add a new indication of MSI-High colorectal cancer and a new dosage and administration for combination therapy with NIVO and IPI (NIVO/IPI therapy) on November 12, 2019, and (ii) update the dosage and administration of NIVO to include an infusion regimen of 480 mg every 4 weeks, for all of the approved indications on November 27, 2019. This review report summarizes the reviews of both applications. In the review report, "patients with MSI-High colorectal cancer" are expressed as (a) "patients with MSI-High colorectal cancer," when the term refers to patients in whom a deficiency of the DNA mismatch repair system was detected either by polymerase chain reaction (PCR) or immunohistochemistry (IHC) assay (broad term), or (b) "patients with MSI-High

(PCR) colorectal cancer," when the term refers to patients in whom a deficiency of the DNA mismatch repair system was detected by PCR (narrow term).

1.2 Development history etc.

1.2.1 NIVO/IPI therapy for MSI-High colorectal cancer [(i) in Section 1.1]

In March 2014, Bristol-Myers Squibb initiated a foreign phase II study to evaluate NIVO/IPI therapy and other treatment regimens, in chemotherapy-treated patients with unresectable, advanced or recurrent mismatch repair deficient (dMMR) or MSI-High (PCR) colorectal cancer (Study 142). With the results of Study 142 serving as pivotal data, the applicants have filed an application for partial change for NIVO to update the dosage and administration to include a dosage regimen of NIVO/IPI therapy for MSI-High colorectal cancer, and an application for partial change for IPI to add an indication and a dosage regimen of NIVO/IPI therapy for MSI-High colorectal cancer.

In the US, approval applications for NIVO and IPI were filed in January 2018 based on the pivotal data from Study 142, and NIVO and IPI received approval in July 2018 for the following indications. As of May 2020, NIVO/IPI therapy has been approved for MSI-High colorectal cancer in 3 countries or regions.

- NIVO:
  OPDIVO, as a single agent or in combination with ipilimumab, 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. These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.
- IPI:
  YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age 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 clinical benefit in confirmatory trials.

1.2.2 NIVO 480 mg infused every 4 weeks [(ii) in Section 1.1]

The approved dosage and administration for NIVO is an infusion regimen of 240 mg every 2 weeks, for all of the approved indications. Primarily based on the results from population pharmacokinetics (PPK) analyses, the applicant has filed an application for partial change to update the dosage and administration of NIVO to include an infusion regimen of 480 mg every 4 weeks, for all of the approved indications.

In the US, approval applications were filed based on data, including the results of PPK analyses, to update the dosage and administration of NIVO to include an infusion regimen of 480 mg every 4 weeks for (a) malignant melanoma, NSCLC, RCC, cHL, head and neck cancer, and urothelial carcinoma in May 2017, for (b) adjuvant

therapy of malignant melanoma, and hepatocellular carcinoma in January 2018, and for (c) MSI-High colorectal cancer in June 2018, and NIVO received approval for (a) and (b) in March 2018, and for (c) in April 2019.

Also in the EU, approval applications were filed based on data, including the results of PPK analyses, to update the dosage and administration of NIVO to include an infusion regimen of 480 mg every 4 weeks for (a) malignant melanoma and RCC in May 2017, and for (b) adjuvant therapy of malignant melanoma in May 2019, and NIVO received approval for (a) in April 2018 and for (b) in October 2019.

As of May 2020, the infusion regimen of 480 mg every 4 weeks for NIVO has been approved in 24 countries or regions.

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

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

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

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

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

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

5. Toxicity and Outline of the Review Conducted by PMDA

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

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

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

6.1 Clinical pharmacology

The applicants have submitted the results of the PPK and exposure-response analyses based on the data from the clinical studies presented in Table 1, as clinical pharmacology data for the present application.

Table 1. Clinical studies used in PPK and exposure-reaction analyses

Region	Study identifier	Phase	Cancer type	Dosage regimen for NIVO
Japan	Study ONO-4538-01	I	Solid cancers	1, 3, 10, or 20 mg every 2 weeks
	Study ONO-4538-02	II	Malignant melanoma	2 mg/kg every 3 weeks
	Study ONO-4538-05/CA209131	II	SQ-NSCLC	3 mg/kg every 2 weeks
	Study ONO-4538-06/CA209132	II	NSQ-NSCLC	3 mg/kg every 2 weeks
	Study ONO-4538-08/CA209315	II	Malignant melanoma	3 mg/kg every 2 weeks
	Study ONO-4538-15/CA209372	II	cHL	3 mg/kg every 2 weeks
Global	Study ONO-4538-22/CA209275	II	Urothelial carcinoma	3 mg/kg every 2 weeks
	Study ONO-4538-03/CA209025	III	RCC	3 mg/kg every 2 weeks
	Study ONO-4538-10/CA209026	III	NSCLC	3 mg/kg every 2 weeks
	Study ONO-4538-11/CA209141	III	Head and neck cancer	3 mg/kg every 2 weeks
	Study ONO-4538-12/CA209316	III	Gastric cancer	3 mg/kg every 2 weeks
Foreign	Study CA209001/MDX1106-01	I	Solid cancers	0.3, 1, 3, or 10 mg/kg every 4 weeks (for 2 doses)
	Study CA209003/MDX1106-03	I	Solid cancers	0.1, 0.3, 1, 3, or 10 mg/kg every 2 weeks
	Study CA209009	I	RCC	0.3, 2, or 10 mg every 3 weeks
	Study CA209039	I	cHL	1 or 3 mg/kg every 2 weeks
	Study CA209032	I/II	Solid cancers	3 mg/kg every 2 weeks
	Study CA209010	II	RCC	0.3, 2, or 10 mg every 3 weeks
	Study CA209063	II	SQ-NSCLC	3 mg/kg every 2 weeks
	Study CA209205	II	cHL	3 mg/kg every 2 weeks
	Study CA209017	III	SQ-NSCLC	3 mg/kg every 2 weeks
	Study CA209037	III	Malignant melanoma	3 mg/kg every 2 weeks
	Study CA209057	III	NSQ-NSCLC	3 mg/kg every 2 weeks
	Study CA209066	III	Malignant melanoma	3 mg/kg every 2 weeks
	Study 067	III	Malignant melanoma	3 mg/kg every 2 weeks

6.1.1 PPK analyses

A PPK analysis was conducted using the pharmacokinetic data for NIVO (3,939 patients, 21,098 sampling points) obtained from the 24 clinical studies presented in Table 1 (NONMEM, Version 7.3). The pharmacokinetics of NIVO was well-described by a 2-compartment model. Among the Japanese patients included in the PPK analysis (420 patients), the pharmacokinetic parameters (estimates) of NIVO administered with dosage regimens, including the 480 mg every 4 weeks regimen and the approved regimen, are summarized in Table 2. The exposure to NIVO in the Japanese patients was characterized, as follows.

- The $C_{avg,ss}$ value of NIVO 480 mg every 4 weeks was comparable to that of NIVO 240 mg every 2 weeks.
- The $C_{min,ss}$ value of NIVO 480 mg every 4 weeks was lower than that of NIVO 240 mg every 2 weeks, but higher than that of NIVO 3 mg/kg every 2 weeks.
- The $C_{max,ss}$ value of NIVO 480 mg every 4 weeks was higher than that of NIVO 240 mg every 2 weeks, but lower than that of NIVO 10 mg/kg every 2 weeks, a dosage regimen that has been demonstrated to be tolerable in Japanese patients (see “Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated June 18, 2014”).

Table 2. Pharmacokinetic parameters (estimates) of NIVO in Japanese patients

Dosage regimen	C_{max1} (μg/mL)	$C_{avg,d28}$ (μg/mL)	$C_{min,d28}$ (μg/mL)	$C_{max,ss}$ (μg/mL)	$C_{avg,ss}$ (μg/mL)	$C_{min,ss}$ (μg/mL)
3 mg/kg every 2 weeks	50.9 (21.3)	30.8 (21.5)	26.6 (26.6)	113 (26.4)	76.3 (33.2)	59.6 (38.9)
240 mg every 2 weeks	72.6 (21.9)	43.7 (20.6)	37.8 (26.9)	161 (27.5)	108 (34.7)	84.7 (40.9)
480 mg every 4 weeks	145 (21.9)	52.9 (21.7)	28.3 (31.7)	218 (24.3)	108 (34.7)	67.6 (46.7)
10 mg/kg every 2 weeks	186 (16.1)	119 (14.8)	103 (15.8)	412 (16.8)	287 (18.0)	226 (19.4)

Geometric mean (coefficient of variation %)

A PPK analysis using the pharmacokinetic data from patients treated with NIVO, including those treated for esophageal cancer or MSI-High colorectal cancer, suggested that the difference in exposure to NIVO between the 3 mg/kg or 240 mg every 2 weeks regimen and the 480 mg every 4 weeks regimen in patients with esophageal cancer or MSI-High colorectal cancer was largely comparable to that among patients treated for other approved indications.

The pharmacokinetic data from a global phase II study (Study ONO-4538-63/CA209907) investigating NIVO administered at a dose of 480 mg every 4 weeks in patients with NSCLC, which were submitted after the present application for partial change, revealed that the observed C_{max1} and $C_{min,d28}$ values (geometric means [coefficients of variation%]) of 136 μg/mL (24.5%) and 26.6 μg/mL (51.8%) were comparable to the above C_{max1} and $C_{min,d28}$ values estimated in Japanese patients treated with NIVO 480 mg every 4 weeks.

6.1.2 Relationship between exposure and efficacy or safety

6.1.2.1 Efficacy

On the basis of the data collected from patients receiving NIVO for malignant melanoma (Studies CA209003/MDX1106-03, CA209037, CA209066, and ONO-4538-08/CA209315), squamous non-small cell lung cancer (SQ-NSCLC) (Studies CA209003/MDX1106-03, CA209017, CA209063, and ONO-4538-05/CA209131), non-squamous non-small cell lung cancer (NSQ-NSCLC) (Studies CA209003/MDX1106-03, CA209057, and ONO-4538-06/CA209132), or RCC (Studies CA209003/MDX1106-03, CA209010, and ONO-4538-03/CA209025), at a dose of 1 to 10 mg/kg every 2 weeks or at a dose of 0.3 to 10 mg/kg every 3 weeks, an exposure-response model describing the relationship between exposure to NIVO and its efficacy (overall survival [OS] or overall response rate) was established for each cancer type, and the following assessments were performed.

- Using the data from Japanese and foreign clinical studies in patients with malignant melanoma (Studies CA209037, CA209066, and ONO-4538-08/CA209315), exposure to NIVO ($C_{avg,d28}$) was estimated, and OS and overall response rate were compared among the dosage regimens of 3 mg/kg every 2 weeks, 240 mg every 2 weeks, and 480 mg every 4 weeks. The results predicted no clear differences in OS or overall response rate among the dosage regimens (Figures 1 and 2). Similar results were predicted when exposure to NIVO was measured by $C_{min,d28}$.

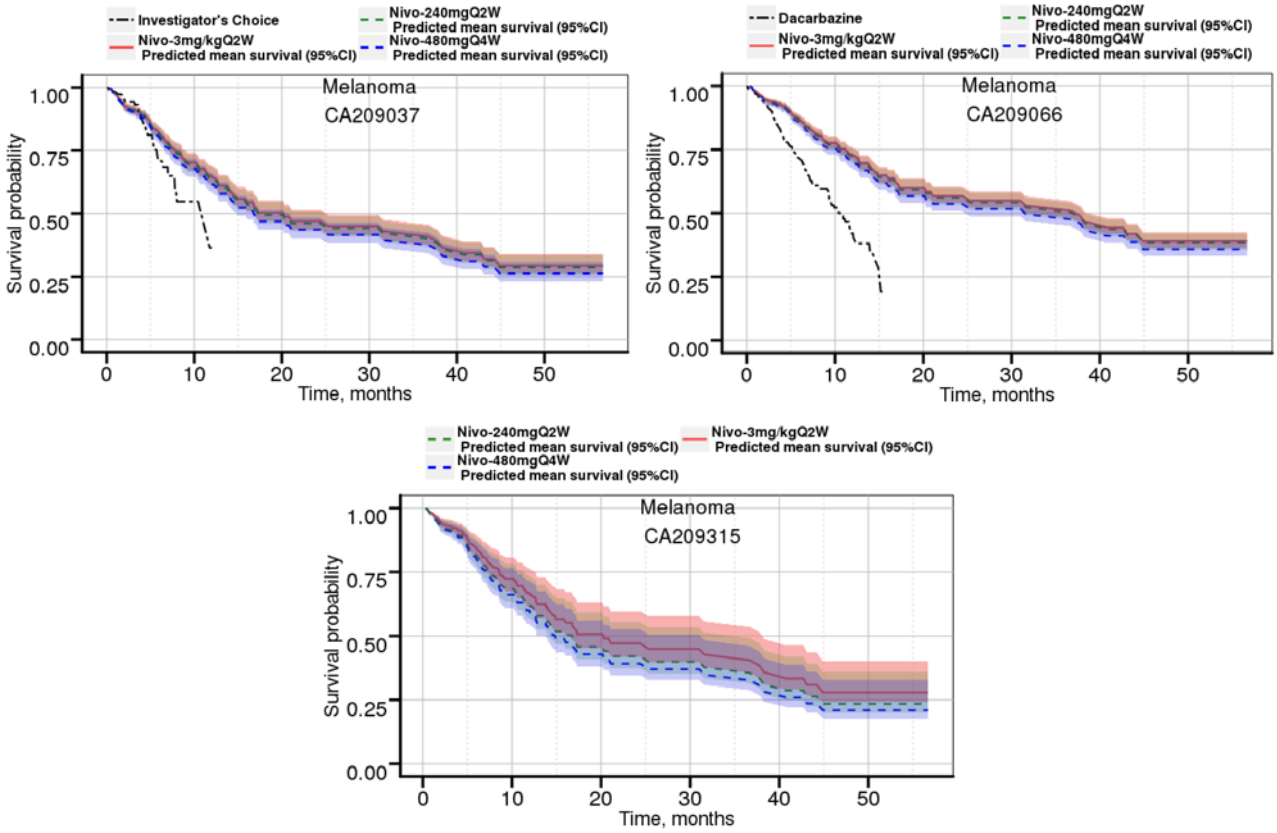

Figure 1. Kaplan-Meier curves for OS predicted using estimated $C_{avg,d28}$ values, by dosage regimen (patients with malignant melanoma)

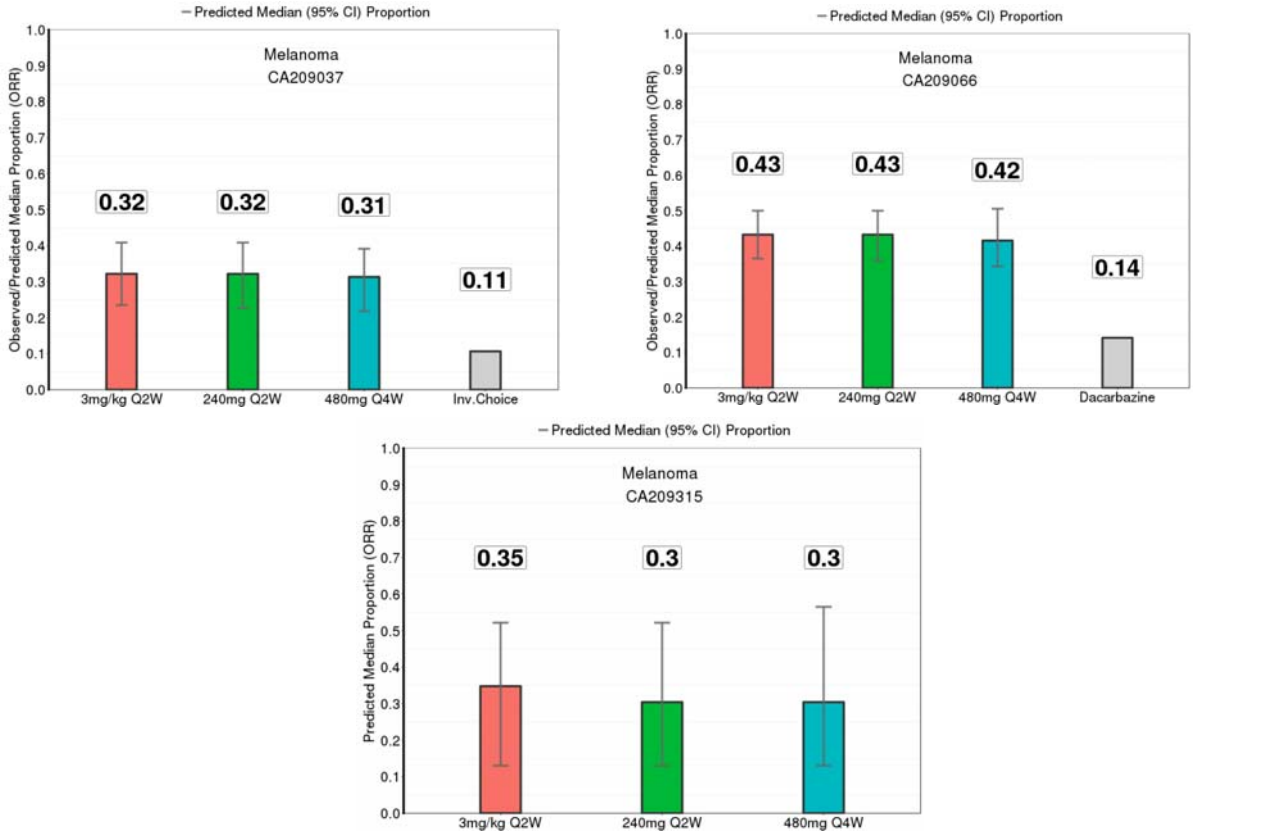

Figure 2. Overall response rates predicted from estimated $C_{avg,d28}$ values, by dosage regimen (patients with malignant melanoma)

- Also in patients with SQ-NSCLC (Studies CA209017 and ONO-4538-05/CA209131), patients with NSQ-NSCLC (Studies CA209057 and ONO-4538-06/CA209132), and patients with RCC (Studies ONO-4538-03/CA209025), no clear differences in OS or overall response rate were predicted among the dosage regimens as was predicted in patients with malignant melanoma.

6.1.2.2 Safety

On the basis of the data from patients who received NIVO at a dose of 1 to 10 mg/kg every 2 weeks or at a dose of 0.3 to 10 mg/kg every 3 weeks for malignant melanoma (Studies CA209003/MDX1106-03, CA209037, and CA209066), SQ-NSCLC (Studies CA209003/MDX1106-03, CA209017, and CA209063), NSQ-NSCLC (Studies CA209003/MDX1106-03 and CA209057), RCC (Studies CA209003/MDX1106-03, CA209010, and ONO-4538-03/CA209025), head and neck cancer (Study ONO-4538-11/CA209141), urothelial carcinoma (Studies CA209032 and ONO-4538-22/CA209275), cHL (Studies CA209039 and CA209205), or other disease conditions, an exposure-response model describing the relationship between exposure to NIVO and its safety (as measured by (a) adverse events leading to drug discontinuation or death, (b) Grade ≥3 adverse events, and (c) Grade ≥2 immune-mediated adverse events) was established by adverse events of (a) to (c), and the following assessments were conducted.

- Using the data from Japanese patients with malignant melanoma (Studies ONO-4538-01, ONO-4538-02, and ONO-4538-08/CA209315), NSCLC (Studies ONO-4538-01, ONO-4538-05/CA209131, ONO-4538-06/CA209132, and ONO-4538-10/CA209026), RCC (Study ONO-4538-03/CA209025), head and neck cancer (Study ONO-4538-11/CA209141), or urothelial carcinoma (Study ONO-4538-22/CA209275), the exposure ($C_{avg,d28}$) to NIVO in Japanese patients was estimated, and the incidence of adverse events leading to drug discontinuation or death in the above (a) was compared among dosage regimens of 3 mg/kg every 2 weeks, 240 mg every 2 weeks, and 480 mg every 4 weeks in Japanese patients with malignant melanoma, SQ-NSCLC, NSQ-NSCLC, RCC, head and neck cancer, or cHL. The comparison results predicted no clear differences in the incidence of the adverse events in the above (a) among the dosage regimens in any of the patient populations (Figure 3). A similar result was predicted when exposure was measured by C_{max1}.

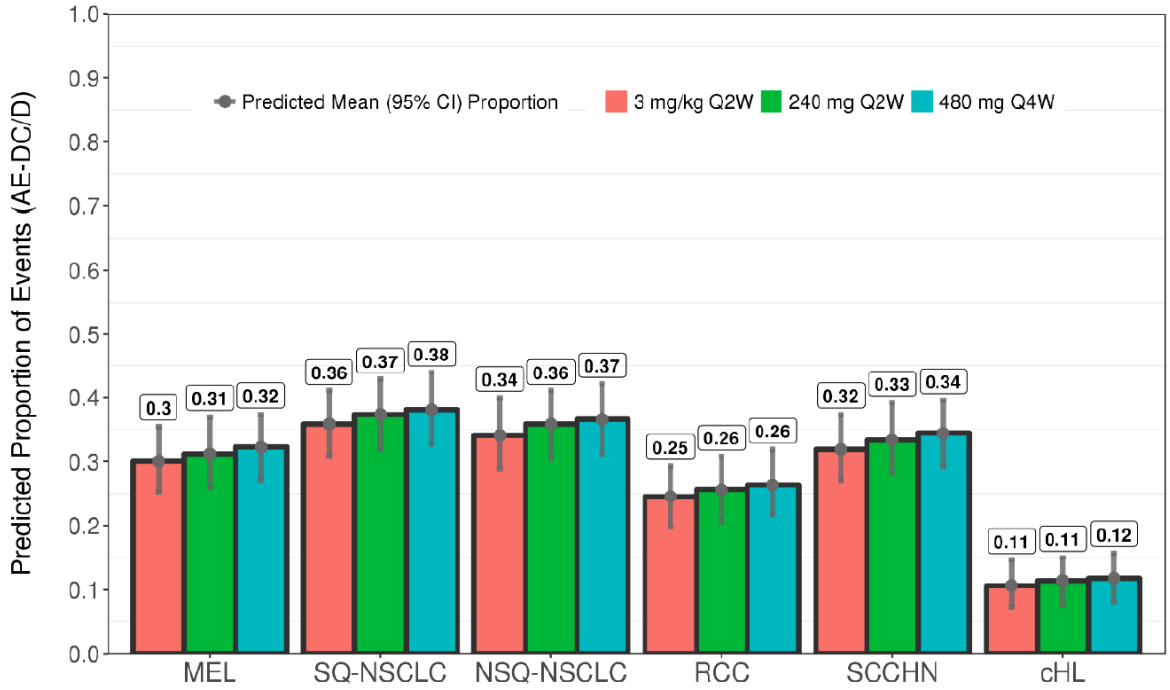

Figure 3. Incidences of adverse events leading to drug discontinuation or death, predicted from estimated $C_{avg,d28}$ values, by dosage regimen

- Also for the incidence of the adverse events in the above (b) and (c), no clear differences were predicted among the dosage regimens in all of the patient populations.

The applicant's explanation:

The results of the PPK analyses and exposure-response analyses described above predicted no clear differences in the efficacy or safety of NIVO for all of the approved indications, including esophageal cancer and MSI-High colorectal cancer, between dosage regimens of 240 mg every 2 weeks and 480 mg every 4 weeks.

6.R Outline of the review conducted by PMDA

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

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

The applicants submitted efficacy and safety evaluation data, in the form of results data from the 4 clinical studies presented in Table 3: a Japanese phase II study, a global phase III study, a foreign phase II study, and a foreign phase III study. The applicants also submitted the results of a foreign phase II study, as reference data. This review report does not describe the results of (a) a Japanese phase II study (Study 17) and a foreign phase III study (Study 067), (b) a global phase III study (Study 214), or (c) a foreign phase II study (Study 142 [the monotherapy stage]), which were evaluated during the reviews for approvals for (a) NIVO/IPI therapy for malignant melanoma [see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated April 13, 2018" and "Review Report for Yervoy Injection 50 mg [for intravenous use] dated April 13, 2018"), for (b) NIVO/IPI therapy for RCC (see "Review Report for Opdivo Intravenous

Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg dated July 26, 2018" and "Review Report for Yervoy Injection 50 mg [for intravenous use] dated July 26, 2018"), and for (c) NIVO monotherapy for MSI-High colorectal cancer and esophageal cancer (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg dated January 9, 2020").

Table 3. Clinical studies on the efficacy and safety

Data type	Region	Study identifier	Phase	Population	N	Brief description of dosage regimen	Main endpoint
Evaluation data	Japan	Study 17	II	Chemotherapy-naïve patients with unresectable malignant melanoma	30	Intravenous NIVO 1 mg/kg and intravenous IPI 3 mg/kg every 3 weeks for 4 doses each, followed by intravenous NIVO 3 mg/kg every 2 weeks	Efficacy Safety
	Global	Study 214	III	Chemotherapy-naïve patients with unresectable or metastatic clear cell RCC	1,096 (a) 550 (b) 546	(a) Intravenous NIVO 3 mg/kg and intravenous IPI 1 mg/kg every 3 weeks for 4 doses each, followed by intravenous NIVO 3 mg/kg every 2 weeks (b) Oral sunitinib 50 mg once daily for 4 weeks, followed by 2-week rest period, in each 6-week cycle	Efficacy Safety
	Foreign	Study 142	II	(a) Combination therapy stage: Chemotherapy-treated patients with unresectable, advanced or recurrent dMMR or MSI-High (PCR) colorectal cancer (b) Non-MSI-High safety cohort: Chemotherapy-treated patients with unresectable, advanced or recurrent non-dMMR or non-MSI-High (PCR) colorectal cancer	142 (a) 119 (b) 23	(a) Intravenous NIVO 3 mg/kg and intravenous IPI 1 mg/kg every 3 weeks for 4 doses each, followed by intravenous NIVO 3 mg/kg every 2 weeks (b) Intravenous NIVO at 1 or 3 mg/kg and intravenous IPI at 1 or 3 mg/kg every 3 weeks for 4 doses each, followed by intravenous NIVO 3 mg/kg every 2 weeks	Efficacy Safety
		Study 067	III	Chemotherapy-naïve patients with unresectable malignant melanoma	945 (a) 314 (b) 316 (c) 315	(a) Intravenous NIVO 1 mg/kg and intravenous IPI 3 mg/kg every 3 weeks for 4 doses each, followed by intravenous NIVO 3 mg/kg every 2 weeks (b) Intravenous NIVO 3 mg/kg every 2 weeks (c) Intravenous IPI 3 mg/kg every 3 weeks for 4 doses	Efficacy Safety
Reference	Foreign	Study 142	II	Monotherapy stage: Chemotherapy-treated patients with unresectable, advanced or recurrent dMMR or MSI-High (PCR) colorectal cancer	74	Intravenous NIVO 3 mg/kg every 2 weeks	Efficacy Safety

A summary of the clinical studies is presented below. Major adverse events other than deaths reported in the studies are detailed in Section "7.2 Adverse events reported in the clinical studies."

7.1 Evaluation Data

7.1.1 Foreign clinical study

7.1.1.1 Foreign phase II study (CTD 5.3.5.2-1.1, Study 142, ongoing since March 2014 [data cutoff on July 6, 2017])

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of NIVO monotherapy, NIVO/IPI therapy, and other treatments in patients with unresectable, advanced or recurrent colorectal cancer. This study involved 7 cohorts or stages[2)], including a cohort that comprises chemotherapy-treated[3)] patients with MSI-High[4)] colorectal cancer enrolled at 31 sites outside Japan (target sample size: 48 patients for the NIVO monotherapy group [the monotherapy stage] and 48 for the NIVO/IPI therapy group [the combination therapy stage]). (This review report describes only results from the combination therapy stage in that cohort in Study 142.)

Patients in the NIVO/IPI therapy group received intravenous doses of NIVO 3 mg/kg and IPI 1 mg/kg every 3 weeks for 4 doses each, followed by an intravenous dose of NIVO 3 mg/kg every 2 weeks, until either disease progression or a withdrawal criterion was met.

The primary endpoint was overall response rate as assessed by 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%[5)] and an expected response rate of 52%, with a 1-sided significance level of 0.05 and 90% power.[6)] The original study plan had specified that the efficacy analysis set was to include patients with locally assessed dMMR or MSI-High (PCR) colorectal cancer, enrolled in the study, and subsequently confirmed centrally as having MSI-High (PCR) colorectal cancer. However, approximately 30% of the patients who were enrolled in Stage 1 of the NIVO/IPI therapy group or the NIVO monotherapy group based on the local assessment of dMMR or MSI-

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2) Study 142 involved the following cohorts and stages.
(a) A NIVO monotherapy cohort comprised chemotherapy-treated patients with MSI-High colorectal cancer (the monotherapy stage)
(b) A NIVO/IPI therapy cohort comprised chemotherapy-treated patients with MSI-High colorectal cancer (the combination therapy stage)
(c) A NIVO/IPI therapy cohort comprised chemotherapy-treated patients with non-MSI-High colorectal cancer (the non-MSI-High safety cohort)
(d) A NIVO/IPI therapy cohort comprised chemotherapy-naïve patients with MSI-High colorectal cancer
(e) A NIVO/IPI + cobimetinib therapy cohort comprised [redacted] patients with non-MSI-High colorectal cancer
(f) A NIVO + BMS-986016 therapy cohort comprised [redacted] patients with MSI-High colorectal cancer
(g) A NIVO + daratumumab (genetical recombination) therapy cohort comprised [redacted] patients with non-MSI-High colorectal cancer

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

4) Enrolled patients had 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)."

5) 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 and *N Engl J Med.* 2015;372:1909-19).

6) If ≥7 of 19 patients treated with the study drugs in Stage 1 had a response, Stage 2 would be initiated. In addition, if a total of ≥20 of 48 patients had a response in Stages 1 and 2 combined, the study drugs were determined to have expected efficacy.

High (PCR), were not centrally confirmed to have MSI-High (PCR) colorectal cancer. This resulted a change in the definition of the efficacy analysis set to include all patients who were enrolled based on the local assessment. Thus, patient enrollment proceeded to ensure that ≥48 patients with centrally confirmed MSI-High (PCR) colorectal cancer would participate in the study. Consequently, a total of 119 patients were enrolled based on the local assessment, received the study drugs, and were included in the efficacy analysis set.

With the above change in the definition of the efficacy analysis set, it was decided not to adopt the 2-stage design 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 overall response rate was changed from the Atkinson-Brown method to the Clopper-Pearson method. Furthermore, the efficacy of NIVO and IPI as an immune checkpoint inhibitors was to be comprehensively evaluated based on the endpoints, including duration of response, and the originally planned hypothesis tests for efficacy evaluation were cancelled (Statistical Analysis Plan Ver. [redacted], dated [redacted], 20[redacted]).

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

Table 4 shows the efficacy results based on the primary endpoint, overall response rate as assessed by investigator using RECIST Ver. 1.1 (data cutoff on July 6, 2017).

Table 4. Best overall response and overall response rate
(RECIST Ver. 1.1, efficacy analysis set, investigator assessment, data cutoff on July 6, 2017)

Best overall response	n (%)
	N = 119
CR	4 (3.4)
PR	61 (51.3)
SD	37 (31.1)
PD	14 (11.8)
NE	3 (2.5)
Response (CR + PR) (Overall response rate [95% CI*] [%])	65 (54.6 [45.2, 63.8])

*: Clopper-Pearson method

The safety analysis revealed deaths in 2 of 119 patients (1.7%) during the treatment period or within 30 days after the last dose. The cause of death was disease progression in both of these 2 patients, for which a causal relationship to the study drugs was denied. In the non-MSI-High safety cohort, 5 of 23 patients (21.7%) died during the treatment period or within 30 days after the last dose. The causes of death, other than disease progression in 3 patients, were pulmonary embolism and sudden death in 1 patient each, for which a causal relationship to the study drugs was denied for both of the events.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

Among the evaluation data submitted, 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 NIVO/IPI therapy. The efficacy and safety of NIVO/IPI therapy for MSI-High colorectal

cancer were thus to be evaluated primarily based on the submitted results from Study 142. The applicants submitted no clinical study results regarding the efficacy or safety of NIVO/IPI therapy in Japanese patients with MSI-High colorectal cancer for the present application for partial change. However, PMDA concluded that the efficacy and safety of NIVO/IPI therapy in Japanese patients could be evaluated based on the results of Study 142, in view of the following facts.

- No clear differences have been found in the pharmacokinetics of NIVO or IPI between Japanese and non-Japanese patients (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014" and "Review Report for Yervoy Injection 50 mg [for intravenous use] dated May 19, 2015").
- There are no clear differences in the diagnostic or therapeutic system for unresectable, advanced or recurrent colorectal cancer, between in and outside of Japan.
- There have been no clear differences in the efficacy or safety of NIVO/IPI therapy 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," "Review Report for Yervoy Injection 50 mg [for intravenous use] dated July 26, 2018," etc).

7.R.2 Efficacy

PMDA concluded that a certain level of efficacy of NIVO/IPI therapy had been demonstrated in chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer, based on the discussion presented below.

7.R.2.1 Efficacy endpoints and efficacy evaluation results

The applicants' explanation about the primary endpoint selected in Study 142 and the efficacy of NIVO/IPI therapy in patients with MSI-High colorectal cancer, taking account of the molecular pathogenesis 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 causes 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 DNA mismatch repair system deficiency described above, and a large burden of neoantigens, which can serve as targets for cancer antigen-specific T cells are formed, and a microenvironment characterized by an abundance of activated cytotoxic T cells is created. Meanwhile, immunosuppressive signaling molecules (e.g., PD-1, CTLA-4), which are highly expressed by MSI-High colorectal cancer, make the cancer cells resistant to tumor rejection (*N Engl J Med*. 2015;372:2509-20, *Cancer Discov*. 2015;5:43-51, etc). This suggests that NIVO/IPI therapy, as a combination of immune checkpoint inhibitors, is expected to show 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 is thus clinically meaningful in such patients. Therefore, Study 142 employed "overall response rate" as the primary endpoint. The results of the study showed (a) an overall response rate [95% CI], as assessed by investigator using RECIST Ver. 1.1 (the primary endpoint), of 54.6 [45.2, 63.8]% [see Section 7.1.1.1] and (b) an overall response rate, as assessed by the independent radiology review committee (IRRC) using RECIST Ver. 1.1 (a secondary endpoint), of 48.7 [39.5, 58.1]%. In view of the fact that these overall response rates were higher than the study results obtained with conventional therapies, including NIVO monotherapy (data presented below), NIVO/IPI therapy was expected to show efficacy in the treatment of chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer.

- The overall response rates with fluoropyrimidine-based chemotherapies were from 11% to 22.7% in patients with unresectable, advanced or recurrent colorectal cancer that had progressed after chemotherapy with a fluoropyrimidine, and oxaliplatin (L-OHP) or irinotecan hydrochloride hydrate (CPT-11) (*J Clin Oncol.* 2007;25:1539-44, etc).
- In a global phase III study aiming 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 a fluoropyrimidine, L-OHP, CPT-11, and bevacizumab (if the *KRAS* gene was wild-type in the tumor tissue, the treatment also had to include cetuximab or panitumumab), the investigator-assessed response rate was 1.0% in the regorafenib group (*Lancet.* 2013;381:303-12).
- In a global phase III study aiming 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 a fluoropyrimidine, L-OHP, CPT-11, and bevacizumab (if the *KRAS* gene was wild-type in the tumor tissue, patients also had to be refractory or intolerant to cetuximab or panitumumab), the investigator-assessed response rate was 1.6% in the trifluridine/tipiracil hydrochloride group (*N Engl J Med.* 2015;372:1909-19).
- The monotherapy stage of Study 142, which aimed to evaluate the efficacy and safety of NIVO monotherapy in the similar target patient population as that in the combination therapy stage of the same study, provided investigator- and IRRC-assessed overall response rates [95% CIs] of 31.1 [20.8, 42.9]% and 27.0 [17.4, 38.6]%, respectively (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg dated January 9, 2020").

Figure 4 shows the best percentage change from baseline in the sum of target lesion diameters, as assessed by investigator using RECIST Ver. 1.1, in Study 142. In 65 patients with a demonstrated overall response (complete response [CR] or partial response [PR]), the median duration of response[7)] was not reached.[8)]

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7) The duration of response was defined as the period from the time the overall response (CR or PR) was first documented, until the time progressive disease (PD) or death was documented. Patients who had no documented PD or survived at the data cutoff were censored at the time of the last imaging assessment.

8) The duration of response ranged from 1.0 month (censored) to 21.8 months (censored).

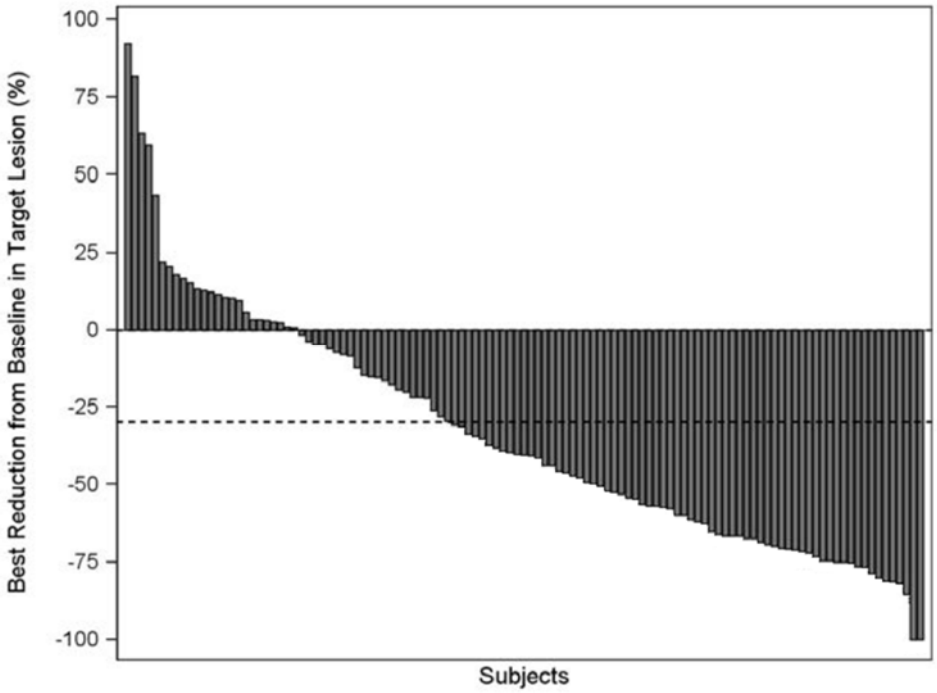

Figure 4. Best percentage change from baseline in the sum of target lesion diameters (RECIST Ver. 1.1, Study 142, efficacy analysis set, investigator assessment, data cutoff on July 6, 2017)

In Study 142, the efficacy analysis set was changed to a population of 119 patients with locally assessed dMMR or MSI-High (PCR) colorectal cancer, after efficacy evaluation was conducted for Stage 1 of the Simon 2-stage design, as had been planned at the start of the study. PMDA asked the applicants to explain the effects of the change in the protocol on efficacy evaluation.

The applicants' explanation:

Study sites tested microsatellite status via standard assays that are widely used in clinical practice, at laboratories that were certified under the Clinical Laboratory Improvement Amendments or accredited by the College of American Pathologists, or at locally certified measurement organizations. Selecting a population of the 119 patients with locally-assessed dMMR or MSI-High (PCR) colorectal cancer as the efficacy analysis set was thus appropriate. Further, this change in the protocol was unlikely to affect the efficacy results for NIVO/IPI therapy, for reasons including the following.

- In 48 patients who should have comprised the efficacy analysis set as per the protocol before the change, the investigator-assessed overall response rate [95% CI] was 62.5 [47.4, 76.0]% (Atkinson and Brown method), which was similar to that in the efficacy analysis set of 119 patients as per the protocol after the change.

PMDA's view:

The relationship between OS (the true endpoint) and overall response rate has not been clarified in patients with unresectable, advanced or recurrent colorectal cancer, and it is thus difficult to evaluate the survival benefit of NIVO/IPI therapy in such patients based on the results for overall response rate (the primary endpoint) in Study 142. Further, the definition of the efficacy analysis set was changed after the efficacy evaluation for

Stage 1 of the Simon 2-stage design was conducted in Study 142. The results of Study 142 should be thus interpreted carefully.

Nevertheless, the applicants' explanation about the efficacy of NIVO/IPI therapy was understandable. PMDA concluded that the efficacy of NIVO/IPI therapy is expected in the treatment of chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer.

7.R.3 Safety [For adverse events, see Section "7.2 Adverse events reported in the clinical studies."]

PMDA's view:

As a result of the following discussion, PMDA concluded that special attention should be paid to the onset of myocarditis associated with IPI, in addition to the adverse events identified as requiring attention at the regulatory reviews for the approved indications of (a) NIVO and (b) IPI.

(a) 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 thrombosis and embolism; adrenal disorder; encephalitis; type 1 diabetes mellitus; serious blood disorder, cardiac disorder, tuberculosis; and pancreatitis (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg dated January 9, 2020," etc.)

(b) Diarrhoea, colitis, and gastrointestinal perforation; skin disorder; liver disorder; hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency; peripheral neuropathy; renal disorder; ILD; myositis; and infusion reaction (see "Review Report for Yervoy Injection 50 mg [for intravenous use] dated July 26, 2018.")

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

7.R.3.1 Safety profiles

The applicants' explanation about the safety profiles of NIVO and IPI in chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer, based on the safety data from Study 142:

Table 5 presents a summary of the safety data from Study 142.

Table 5. Safety summary (Study 142, safety analysis set)*

	n (%)
	N = 119
All adverse events	118 (99.2)
Grade ≥3 adverse events	67 (56.3)
Adverse events leading to death	5 (4.2)
Serious adverse events	57 (47.9)
Adverse events leading to drug discontinuation	17 (14.3)
Adverse events leading to drug interruption	53 (44.5)

*: Adverse events that developed or worsened during the treatment period, or within 30 days after the last dose were counted.

In Study 142, adverse events of any grade reported with ≥10% incidence were diarrhoea in 53 patients (44.5%), pyrexia in 42 patients (35.3%), fatigue in 39 patients (32.8%), pruritus in 33 patients (27.7%), nausea in 31 patients (26.1%), anaemia in 28 patients (23.5%), abdominal pain in 26 patients (21.8%), vomiting, decreased appetite, back pain, and aspartate aminotransferase (AST) increased in 24 patients (20.2%) each, asthenia and cough in 22 patients (18.5%) each, alanine aminotransferase (ALT) increased in 21 patients (17.6%), headache in 20 patients (16.8%), constipation in 18 patients (15.1%), hypothyroidism and arthralgia in 17 patients (14.3%) each, rash in 16 patients (13.4%), blood creatinine increased and insomnia in 15 patients (12.6%) each, hyperthyroidism and dyspnoea in 14 patients (11.8%) each, lipase increased and dry skin in 13 patients (10.9%) each, and weight decreased in 12 patients (10.1%). Grade ≥3 adverse events reported with a ≥2% incidence were AST increased in 12 patients (10.1%), anaemia and ALT increased in 9 patients (7.6%) each, lipase increased in 8 patients (6.7%), abdominal pain, diarrhoea, fatigue, transaminases increased, and hyponatraemia in 4 patients (3.4%) each, and colitis, small intestinal obstruction, asthenia, back pain, malignant neoplasm progression, acute kidney injury, and rash in 3 patients (2.5%) each. Serious adverse events reported with a ≥2% incidence were pyrexia in 4 patients (3.4%), colitis, small intestinal obstruction, malignant neoplasm progression, and acute kidney injury in 3 patients (2.5%) each. Adverse events that led to drug interruption with a ≥2% incidence were AST increased in 8 patients (6.7%), ALT increased in 6 patients (5.0%), hyponatraemia in 4 patients (3.4%), and adrenal insufficiency, hyperthyroidism, hypophysitis, influenza like illness, pyrexia, and pneumonitis in 3 patients (2.5%) each. There were no adverse events that led to death or led to drug discontinuation, with a ≥2% incidence.

The applicants' explanation about the differences in the safety profile of NIVO/IPI therapy between Study 142, and a global phase III study in patients with RCC (Study 214) or a foreign phase III study in patients with malignant melanoma (Study 067), which, as with Study 142, examined the efficacy and safety of NIVO/IPI therapy:

Table 6 presents a safety summary in the NIVO/IPI therapy groups of Studies 142, 214, and 067.

Table 6. Safety summary[*1] in Studies 142, 214, and 067[*2]

	n (%)		
	Study 142 N = 119	Study 214 N= 547	Study 067 N = 313
All adverse events	118 (99.2)	544 (99.5)	312 (99.7)
Grade ≥3 adverse events	67 (56.3)	374 (68.4)	241 (77.0)
Adverse events leading to death	5 (4.2)	29 (5.3)	28 (8.9)
Serious adverse events	57 (47.9)	305 (55.8)	223 (71.2)
Adverse events leading to drug discontinuation	17 (14.3)	168 (30.7)	147 (47.0)
Adverse events leading to drug interruption	53 (44.5)	293 (53.6)	182 (58.1)

*1: Adverse events that developed or worsened during the treatment period or within 30 days after the last dose were counted.
*2: NIVO/IPI therapy was administered as per the following dosage regimens: an intravenous infusion of NIVO 3 mg/kg and intravenous infusion of IPI 1 mg/kg every 3 weeks for 4 doses each, followed by an intravenous infusion of NIVO 3 mg/kg every 2 weeks in Studies 142 and 214; an intravenous infusion of NIVO 1 mg/kg and an intravenous infusion of IPI 3 mg/kg every 3 weeks for 4 doses each, followed by an intravenous infusion of NIVO 3 mg/kg every 2 weeks in Study 067.

The adverse event of any grade reported with a ≥10% higher incidence in Study 142 than in either Study 214 or 067 was anaemia (28 patients [23.5%] in Study 142 vs. 72 patients [13.2%] in Study 214 or 35 patients [11.2%] in Study 067). Grade ≥3 adverse events reported with a ≥3% higher incidence in Study 142 than in either Study 214 or 067 were AST increased (12 patients [10.1%] vs. 19 patients [3.5%] or 21 patients [6.7%]) and anaemia (9 patients [7.6%] vs. 20 patients [3.7%] or 4 patients [1.3%]). There were no serious adverse events, or adverse events that led to death, drug discontinuation or drug interruption, with a ≥3% higher incidence in Study 142 than in either Study 214 or 067.

Currently available post-marketing information regarding the use of NIVO or IPI in Japan has raised no new safety concerns, other than myocarditis associated with IPI.

PMDA's view:
Some adverse events were reported more frequently in patients receiving NIVO/IPI therapy for MSI-High colorectal cancer in Study 142, than in patients treated for the approved indications. However, taking into consideration that all of these events were known adverse events of NIVO or IPI, NIVO/IPI therapy is tolerable in patients with MSI-High colorectal cancer as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy through appropriate measures such as monitoring of adverse events, differential diagnosis and management of excessive immune-mediated adverse drug reactions, and interruption of NIVO or IPI.

In the subsection below, PMDA focuses on myocarditis, which has been reported in the post-marketing setting, etc. as an adverse event for which a causal relationship to IPI cannot be ruled out.

7.R.3.2 Myocarditis

The applicants' explanation about myocarditis, which has been reported in the post-marketing setting, etc. as an adverse event for which a causal relationship to IPI cannot be ruled out:
As myocarditis-related adverse events, events coded as the following MedDRA preferred terms (PTs) were counted: "coxsackie myocarditis," "eosinophilic myocarditis," "myocarditis," "myocarditis meningococcal,"

"myocarditis septic," "myocarditis syphilitic," "myocarditis toxoplasmal," "viral myocarditis," "malarial myocarditis," "cytomegalovirus myocarditis," "myocarditis mycotic," "autoimmune myocarditis," "myocarditis post infection," "myocarditis bacterial," "myocarditis helminthic," "lupus myocarditis," "myocarditis infectious," "enterovirus myocarditis," "radiation myocarditis," "hypersensitivity myocarditis," and "immune-mediated myocarditis."

In Japanese and foreign clinical studies, and post-marketing settings in and outside of Japan for IPI, 1, 28, 3, and 40 patients, respectively, died from myocarditis. Among these patients, a causal relationship to IPI could not be ruled out in 1, 27, 3, and 40 patients. Serious myocarditis was reported in 3, 96, 27, and 151 patients, respectively. Among these patients, a causal relationship to IPI could not be ruled out in 3, 94, 27, and 151 patients.

PMDA's view:
For myocarditis reported in clinical studies or post-marketing settings for IPI in and outside of Japan, there were patients in whom the causal relationship to IPI or concomitant medications could not be easily determined, and there were many patients in whom contributing factors other than IPI could not be ruled out. On the other hand, there were several cases of serious to fatal myocarditis with a suspected relation to IPI. Thus, the use of IPI requires particular attention to the onset of myocarditis. The incidence of myocarditis in clinical studies and other relevant information should be properly communicated to healthcare professionals through the package insert or other materials, and an information leaflet should be used to communicate measures to be taken at the onset of such events to healthcare professionals.

7.R.4 Clinical positioning and indication

The proposed indication of NIVO for MSI-High colorectal cancer was the same as the approved indication. The proposed indication of IPI was the same as the approved indication of NIVO (i.e., "unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy"). The proposed "Precautions Concerning Indications" sections for NIVO and IPI contained the following statements.

NIVO:

- The efficacy and safety of NIVO as a first-line treatment have not been established.
- NIVO should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic should be used in the test.
- The efficacy and safety of NIVO as an adjuvant therapy have not been established.
- Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of NIVO, after fully understanding the "Clinical Studies" section.

IPI:

- The efficacy and safety of IPI as a first-line treatment have not been established.
- IPI should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic should be used in the test.
- The efficacy and safety of IPI as an adjuvant therapy have not been established.
- Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of IPI, after fully understanding the "Clinical Studies" section. In particular, when administering IPI as a monotherapy to chemotherapy-naïve patients with unresectable malignant melanoma, other therapeutic options should also be carefully considered.

After the present application for partial change was filed, the applicants changed the proposed statements for the "Precautions Concerning Indications" sections as follows, based on the approved statements for the "Precautions Concerning Indications" section for NIVO monotherapy for MSI-High colorectal cancer.

NIVO:

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

IPI:

- The efficacy and safety of IPI have not been established in patients who have not received prior treatments with a fluoropyrimidine, L-OHP, and CPT-11.
- IPI should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic should be used in the test.

- The efficacy and safety of IPI as an adjuvant therapy have not been established.
- Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of IPI, after fully understanding the "Clinical Studies" section. In particular, when administering IPI as a monotherapy to chemotherapy-naïve patients with unresectable malignant melanoma, or when administering IPI to patients with unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy, other therapeutic options should also be carefully considered.

PMDA's view:

As a result of the reviews in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the subsections below, PMDA concluded that the indications of NIVO and IPI should be "unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy," as proposed by the applicants, and the following statements should be included in the "Precautions Concerning Indications" sections for NIVO and IPI.

NIVO:

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

IPI:

- The efficacy and safety of IPI have not been established in patients who have not received prior treatments with a fluoropyrimidine, L-OHP, and CPT-11.
- IPI should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An *in vitro* diagnostic or medical device that is approved to assist assessment of patient eligibility for NIVO therapy for MSI-High colorectal cancer should be used in the test.
- The efficacy and safety of IPI as an adjuvant therapy have not been established.
- Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of IPI, after fully understanding the "Clinical Studies" section and carefully considering the choice of alternative therapies.

7.R.4.1 Intended population and indication of NIVO/IPI therapy

In representative clinical practice guidelines and leading clinical oncology textbooks in and outside of Japan, NIVO/IPI therapy in the treatment of patients with MSI-High colorectal cancer is as shown below:

Clinical practice guidelines

- NCCN guidelines (colon cancer) (v.4, 2020):
  - The use of NIVO/IPI 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.6, 2020):
  - The use of NIVO/IPI is recommended for the second- or third-line treatment of unresectable, advanced or recurrent dMMR or MSI-High rectal cancer.

The applicants' explanation about the intended population of NIVO/IPI therapy in the present application for partial change, based on the results of Study 142:

In Study 142 in patients with ≥1 prior chemotherapies, NIVO/IPI therapy was administered to (a) 40 patients who had received 1 prior chemotherapy and (b) 82 patients who had received treatments with a fluoropyrimidine, L-OHP, and CPT-11. The investigator-assessed overall response rates [95% CIs] in patient populations (a) and (b) were 57.5 [40.9, 73.0]% and 52.4 [41.1, 63.6]%, respectively, both of which were higher than the overall response rates with existing second-line or subsequent treatments for unresectable, advanced or recurrent colorectal cancer [see Section 7.R.2.1]. These results suggest that NIVO/IPI therapy can be recommended as an option for the second-line or subsequent treatment of MSI-High colorectal cancer that has progressed after chemotherapy. The clinical usefulness of NIVO/IPI therapy as a first- or second-line treatment for MSI-High colorectal cancer will continue to be evaluated in an ongoing open-label, randomized, global phase IIIb study, aiming to evaluate the efficacy and safety of NIVO administered alone or in combination with IPI in chemotherapy-naïve or -treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer (Study CA2098HW; target sample size, 494 patients). Available results from the study will be promptly communicated to healthcare professionals, and the necessities of application for partial change or changes in the precautionary statements in the package inserts, etc. will be considered.

Despite the above explanation, the applicant proposed the indications of NIVO and IPI as "unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy," and to include the following cautionary statements in the "Precautions Concerning Indications" sections, in view of the absence of data from clinical studies comparing NIVO/IPI therapy with standard second-line treatments.

NIVO:

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

IPI:

- The efficacy and safety of IPI have not been established in patients who have not received prior treatments with a fluoropyrimidine, L-OHP, and CPT-11.
- IPI should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic should be used in the test.
- The efficacy and safety of IPI as an adjuvant therapy have not been established.
- Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of IPI, after fully understanding the "Clinical Studies" section. In particular, when administering IPI as a monotherapy to chemotherapy-naïve patients with unresectable malignant melanoma, or when administering IPI to patients with unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy, other therapeutic options should also be carefully considered.

Because no clinical study data are available on the efficacy and safety of NIVO/IPI therapy, as compared with the currently approved therapies for unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy (i.e., NIVO monotherapy and pembrolizumab), there are no clear standards for when to choose NIVO/IPI therapy, NIVO monotherapy, or pembrolizumab, at present. The choice of regimen should be made on a patient-by-patient basis according to their condition, with a good understanding of the efficacy and safety of each therapy.

PMDA's view:

PMDA accepted the applicants' explanation, and concluded that selection of NIVO/IPI therapy could not be recommended over standard treatments with a fluoropyrimidine, L-OHP, and CPT-11 for chemotherapy-naïve patients with unresectable, advanced or recurrent MSI-High colorectal cancer, due to absence of data from confirmatory studies evaluating the efficacy and safety of NIVO/IPI therapy for MSI-High colorectal cancer, and for other reasons. The "Precautions Concerning Indications" sections for NIVO and IPI should thus include a statement that the efficacy and safety of NIVO/IPI therapy have not been established in patients who have not received prior treatments with a fluoropyrimidine, L-OHP, and CPT-11, as the applicants have proposed to clarify that NIVO/IPI therapy is intended for patients who have received all standard treatments with a fluoropyrimidine, L-OHP, and CPT-11.

Furthermore, the efficacy of NIVO/IPI therapy was primarily evaluated based on overall response rate results, not on survival benefit data, for the present application for partial change. Thus, the "Precautions Concerning Indications" sections should advise to carefully consider the choice of alternative therapies before deciding to initiate NIVO/IPI therapy, as proposed by the applicants. In addition, the approved companion diagnostic for NIVO, "MSI test kit (FALCO)," should be used to select eligible patients for NIVO/IPI therapy, and this should be stated in the "Precautions Concerning Indications" section for IPI.

On the basis of the above, PMDA concluded that the indications of NIVO and IPI should be "unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy," as proposed

by the applicants, and that the following cautionary statements should be included in the "Precautions Concerning Indications" sections for NIVO and IPI.

NIVO:

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

IPI:

- The efficacy and safety of IPI have not been established in patients who have not received prior treatments with a fluoropyrimidine, L-OHP, and CPT-11.
- IPI should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An *in vitro* diagnostic or medical device that is approved to assist assessment of patient eligibility for NIVO therapy for MSI-High colorectal cancer should be used in the test.
- The efficacy and safety of IPI as an adjuvant therapy have not been established.
- Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of IPI, after fully understanding the "Clinical Studies" section and carefully considering the choice of alternative therapies.

7.R.4.2 Efficacy and safety of NIVO/IPI therapy by PD-L1 expression status, and its intended population

NIVO is an antibody against human PD-1. PMDA asked the applicants to explain the efficacy and safety of NIVO/IPI therapy by the expression status of PD-L1, a ligand of PD-1, and to identify the intended population of NIVO/IPI therapy.

The applicants' explanation:

In Study 142, PD-L1 expression status[9)] 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 NIVO/IPI therapy were evaluated by PD-L1 expression status in patients who had evaluable PD-L1 data.

9) Percentage of tumor cells with PD-L1 in tumor tissue

(a) Efficacy

Table 7 shows the investigator-assessed overall response rates by PD-L1 expression status (cutoff values, 1% and 5%) in patients with evaluable PD-L1 data.

At both cutoff values, the overall response rates with NIVO/IPI therapy were higher than study results with the existing treatments, including NIVO monotherapy [see Section 7.R.2.1], in both the PD-L1-positive and -negative populations. The efficacy of NIVO/IPI therapy is expected based on these available data, regardless of PD-L1 expression status.

Table 7. Efficacy by PD-L1 expression status (Study 142)

Percentage of cells with PD-L1	Responders/N	Overall response rate [95%CI*] (%)
<1%	34/65	52.3 [39.5, 64.9]
≥1%	14/26	53.8 [33.4, 73.4]
<5%	37/77	48.1 [36.5, 59.7]
≥5%	11/14	78.6 [49.2, 95.3]

* Clopper-Pearson method

(b) Safety

The incidences of adverse events of any grade in patients with <1% PD-L1 and those with ≥1% PD-L1 were 98.5% and 100%, respectively. The respective incidences of Grade ≥3 adverse events were 63.1% and 50.0%, while the incidences of serious adverse events were 50.8% and 38.5%. The incidences of adverse events of any grade in patients with <5% PD-L1 and those with ≥5% PD-L1 were 98.7% and 100%, respectively. The respective incidences of Grade ≥3 adverse events were 62.3% and 42.9%, while the incidences of serious adverse events were 48.1% and 42.9%.

The safety of NIVO/IPI therapy did not clearly differ between PD-L1-positive and -negative populations at both cutoff values, suggesting that NIVO/IPI therapy is tolerable, regardless of PD-L1 expression status.

The results described in the above (a) and (b) indicate that response to NIVO/IPI therapy in patients with MSI-High colorectal cancer is independent of PD-L1 expression status.

On the bases of the above, when administering NIVO/IPI therapy to chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer, it is not necessary to specify the intended population based on PD-L1 expression status.

PMDA's view:

PMDA accepted the applicants' explanation, in general. However, the applicants should continue to collect information on possible predictors of response to NIVO/IPI therapy, other than PD-L1 expression, and appropriately communicate new findings to healthcare professionals.

7.R.5 Dosage and administration

The present application for partial changes have proposed the “Dosage and Administration” and “Precautions Concerning Dosage and Administration” sections for NIVO and IPI, as presented in the table below, based on the submitted results of clinical pharmacology studies and data on MSI-High colorectal cancer. (Underlines have been added to the approved statements.)

	Dosage and administration	Precautions concerning dosage and administration
NIVO	Malignant melanoma: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. In combination therapy with IPI for unresectable malignant melanoma, the usual adult dosage of NIVO is 80 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable or metastatic RCC: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. When administered in combination with IPI to chemotherapy-naïve patients with unresectable or metastatic RCC, the usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. When administered in combination with IPI, the usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, 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, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.	All indications: • NIVO should be administered intravenously over ≥30 minutes. Unresectable or metastatic RCC: • The efficacy and safety of NIVO 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 MSI-High colorectal cancer that has progressed after cancer chemotherapy: • The dosage regimen of NIVO should be chosen based on a good understanding of the efficacy and safety of NIVO, after being familiar with the "Clinical Studies" section. Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, 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, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy: • The efficacy and safety of NIVO in combination with other antineoplastic drugs have not been established. Malignant melanoma: • When administered in combination with IPI to patients with unresectable malignant melanoma, the necessity of the combination therapy should be carefully determined based on a careful review 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 NIVO. The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy.
IPI	Unresectable malignant melanoma: • The usual adult dosage is 3 mg/kg (body weight) of IPI administered intravenously every 3 weeks for a total of 4 doses. IPI should not be used in combination with antineoplastic agents other than NIVO. Unresectable or metastatic RCC, or unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • In combination therapy with NIVO, the usual adult dosage is 1 mg/kg (body weight) of IPI administered intravenously every 3 weeks for a total of 4 doses.	All indications: • The criteria for interruption or discontinuation of treatment in the event of adverse reactions (omitted, since they are identical to those at the previous approval) Unresectable malignant melanoma: • When administered in combination with NIVO, the necessity of the combination therapy should be carefully determined based on a careful review of the "Clinical Studies" section, particularly regarding the characteristics, such as prior treatments, of patients enrolled in the clinical studies, and a thorough understanding of the efficacy and safety of IPI. The add-on effect of IPI to NIVO on survival prolongation tends to differ according to the percentage of tumor cells expressing PDL1 (PD-L1 expression rate). In patients who have been confirmed to have a high PD-L1 expression rate, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy. • IPI should be administered intravenously over 90 minutes. Unresectable or metastatic RCC, or unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • IPI should be administered intravenously over 30 minutes.

As a result of the discussions described in Sections “7.R.2 Efficacy,” “7.R.3 Safety,” and “7.R.4 Clinical positioning and indication,” as well as the subsection below [Section 7.R.5.1], the “Dosage and Administration” and “Precautions Concerning Dosage and Administration” sections for NIVO and IPI should be set or modified as presented in the table below. (Underlines have been added to the approved statements.)

	Dosage and administration	Precautions concerning dosage and administration
NIVO	Malignant melanoma: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. In combination therapy with IPI for unresectable malignant melanoma, the usual adult dosage of NIVO is 80 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable or metastatic RCC: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. • When administered in combination with IPI to chemotherapy-naïve patients with unresectable or metastatic RCC, the usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. When administered in combination with IPI, the usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, 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, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.	All indications: • NIVO should be administered intravenously over ≥30 minutes. Unresectable or metastatic RCC: • The efficacy and safety of NIVO 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 NSCLC, relapsed or refractory cHL, 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, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy: • The efficacy and safety of NIVO in combination with other antineoplastic drugs have not been established. Malignant melanoma: • When administered in combination with IPI to patients with unresectable malignant melanoma, the necessity of the combination therapy should be carefully determined based on a careful review 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 NIVO. The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy.
IPI	Unresectable malignant melanoma: • The usual adult dosage is 3 mg/kg (body weight) of IPI administered intravenously every 3 weeks for a total of 4 doses. IPI should not be used in combination with antineoplastic agents other than NIVO. Unresectable or metastatic RCC, or unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • In combination therapy with NIVO, the usual adult dosage is 1 mg/kg (body weight) of IPI administered intravenously every 3 weeks for a total of 4 doses.	All indications: • The criteria for interruption or discontinuation of treatment in the event of adverse reactions (omitted, since they are identical to those at the previous approval) Unresectable malignant melanoma: • When administered in combination with NIVO, the necessity of the combination therapy should be carefully determined based on a careful review of the "Clinical Studies" section, particularly regarding the characteristics, such as prior treatments, of patients enrolled in the clinical studies and a thorough understanding of the efficacy and safety of IPI. The add-on effect of IPI to NIVO on survival prolongation tends to differ according to the percentage of tumor cells expressing PDL1 (PD-L1 expression rate). In patients who have been confirmed to have a high PD-L1 expression rate, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy. • IPI should be administered intravenously over 90 minutes. Unresectable or metastatic RCC, or unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • IPI should be administered intravenously over 30 minutes.

7.R.5.1 Dosage and administration for NIVO and IPI

The applicant's explanation about the dosage and administration of NIVO as a monotherapy:

In view of the following points and other findings, the dosage and administration of NIVO as a monotherapy for the approved indications should be updated to include an infusion regimen of 480 mg every 4 weeks, in addition to the approved infusion regimen of 240 mg every 2 weeks.

- Simulations using the PPK models and exposure-response models for NIVO predicted no clear differences in the efficacy or safety of NIVO between infusion regimen of 480 mg every 4 weeks and the approved regimen of 240 mg every 2 weeks [see Section 6.1].
- No clear differences have been found in the safety profiles of NIVO across the approved cancer types (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg, dated January 9, 2020"). This suggests that NIVO, also when administered at 480 mg every 4 weeks, is unlikely to show safety profiles that clearly differ across the cancer types.
- Extension of the dosing intervals of NIVO is expected to offer clinical benefits, such as a possible reduction in the burdens on patients and health professionals.

The applicants' explanation about the rationale for the proposed dosage and administration for MSI-High colorectal cancer, "NIVO 240 mg and IPI 1 mg/kg, intravenously administered every 3 weeks for 4 doses":

In Study 142, the dosage regimen of NIVO/IPI therapy was determined to be "NIVO 3 mg/kg and IPI 1 mg/kg intravenously administered every 3 weeks for 4 doses each, followed by NIVO 3 mg/kg intravenously administered 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, Opdivo Intravenous Infusion 240 mg dated July 26, 2018") and other data. The results of the study showed the clinical usefulness of NIVO/IPI therapy for MSI-High colorectal cancer. Taking account of the study results, including the results of the PPK analyses for NIVO (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg dated July 26, 2018"), "NIVO 240 mg and IPI 1 mg/kg infused every 3 weeks for 4 doses each" has been proposed as the dosage and administration of NIVO/IPI therapy for MSI-High colorectal cancer.

Meanwhile, NIVO monotherapy or NIVO/IPI therapy should be chosen based on a good understanding of clinical study results and a consideration of individual patient condition, when NIVO is administered to patients with MSI-High colorectal cancer. Accordingly, the "Precautions Concerning Dosage and Administration" section for NIVO will contain the following precautionary statement.

- The dosage regimen of NIVO should be chosen based on a good understanding of the efficacy and safety of NIVO, after being familiar with the "Clinical Studies" section.

PMDA's view:

PMDA accepted the applicant's explanation, in general. However, the precaution to choose the dosage regimen of NIVO based on a good understanding of the efficacy and safety of NIVO, after being familiar with the "Clinical Studies" section is not a matter of special note, and is unnecessary to be included in the "Precautions Concerning Dosage and Administration" section.

As described above, the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections for NIVO and IPI should contain the following statements for the present application for partial changes.

NIVO:

- Dosage and administration

  Malignant melanoma:

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

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

  Unresectable or metastatic RCC:

  The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

  When administered in combination with IPI to chemotherapy-naïve patients with unresectable or metastatic RCC, the usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

  Unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy:

  The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

  When administered in combination with IPI, the usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks.

  Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, 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, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy:

  The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.

- Precautions concerning dosage and administration

  All indications:

  NIVO should be administered intravenously over ≥30 minutes.

IPI:

- Dosage and administration

  Unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy:

  In combination therapy with NIVO, the usual adult dosage is 1 mg/kg (body weight) of IPI administered intravenously every 3 weeks for a total of 4 doses.

- Precautions concerning dosage and administration

  All indications:

  The criteria for interruption or discontinuation of treatment in the event of adverse reactions (omitted, since they are identical to those at the previous approval)

  Unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy

  IPI should be administered intravenously over 30 minutes.

7.R.6 Post-marketing investigations

The applicants' explanation about their post-marketing surveillance plans for (a) the new indication (MSI-High colorectal cancer) and the new dosage and administration of NIVO/IPI therapy, and (b) the new dosage and administration of NIVO (480 mg every 4 weeks) for all of the approved indications:

(a) For reasons including the ones described below, conducting new post-marketing surveillance immediately after the approval of the present application in patients receiving NIVO/IPI therapy for MSI-High colorectal cancer is not necessary, and safety information will be collected through routine pharmacovigilance activities.
  - Some adverse events were more frequently reported in patients receiving NIVO/IPI therapy for MSI-High colorectal cancer in Study 142 than in those who were treated for the approved indications. However, all of the adverse events were known adverse events of NIVO or IPI, indicating that the safety profile of NIVO/IPI therapy in Study 142 does not clearly differ from those observed in patients receiving the therapy for the approved indications [see Section 7.R.3.1].
  - A certain amount of safety data on NIVO/IPI therapy in Japanese patients are available from the ongoing post-marketing surveillance for the approved indications (i.e., malignant melanoma and RCC), and the safety data have identified no new safety concerns.

(b) The results of simulations using exposure-response models for the safety of NIVO [see Section 6.1.2.2] and the safety profile of NIVO does not clearly differ across cancer types [see Section 7.R.3.1] suggest that the safety profile of NIVO is unlikely to differ between the new regimen of 480 mg every 4 weeks and the approved regimen of 240 mg every 2 weeks. Therefore, the ongoing post-marketing surveillance for NIVO in patients treated for the approved indications will also cover patients receiving NIVO 480 mg every 4 weeks to collect safety information.

PMDA's view:

PMDA concluded as follows, regarding post-marketing surveillances for the above (a) and (b).

(a) In view of the data, including that no new safety concerns have been identified in patients with MSI-High colorectal cancer, there is little necessity to conduct post-marketing surveillance immediately after the approval of the present application, and safety information may be collected through routine pharmacovigilance activities.
(b) Safety information on the use of NIVO administered at a dose of 480 mg every 4 weeks may be collected from the ongoing post-marketing surveillance, as proposed by the applicants.

7.2 Adverse events reported in the clinical study

Among the clinical study results submitted for the safety evaluation, death are presented in "Section 7.1.1 Evaluation data," whereas other major adverse events are detailed below.

7.2.1 Foreign phase II study (Study 142)

7.2.1.1 Combination therapy stage

Adverse events were reported in 118 of 119 patients (99.2%). Adverse events for which a causal relationship to the study drugs could not be ruled out were reported in 87 of 119 patients (73.1%). Table 8 presents the adverse events reported with a ≥10% incidence.

Table 8. Adverse events with a ≥10% incidence

SOC PT (MedDRA/J Ver.20.0/20.0J)	n (%) N = 119 Any grade	 Grade ≥3
All adverse events	118 (99.2)	67 (56.3)
Blood and lymphatic system disorders		
Anaemia	28 (23.5)	9 (7.6)
Endocrine disorders		
Hypothyroidism	17 (14.3)	1 (0.8)
Hyperthyroidism	14 (11.8)	0
Gastrointestinal disorders		
Diarrhoea	53 (44.5)	4 (3.4)
Nausea	31 (26.1)	1 (0.8)
Abdominal pain	26 (21.8)	4 (3.4)
Vomiting	24 (20.2)	2 (1.7)
Constipation	18 (15.1)	0
General disorders and administration site conditions		
Pyrexia	42 (35.3)	0
Fatigue	39 (32.8)	4 (3.4)
Asthenia	22 (18.5)	3 (2.5)
Investigations		
AST increased	24 (20.2)	12 (10.1)
ALT increased	21 (17.6)	9 (7.6)
Blood creatinine increased	15 (12.6)	1 (0.8)
Lipase increased	13 (10.9)	8 (6.7)
Weight decreased	12 (10.1)	0
Metabolism and nutrition disorders		
Decreased appetite	24 (20.2)	2 (1.7)
Musculoskeletal and connective tissue disorders		
Back pain	24 (20.2)	3 (2.5)
Arthralgia	17 (14.3)	1 (0.8)
Nervous system disorders		
Headache	20 (16.8)	2 (1.7)
Psychiatric disorders		
Insomnia	15 (12.6)	1 (0.8)
Respiratory, thoracic, and mediastinal disorders		
Cough	22 (18.5)	1 (0.8)
Dyspnoea	14 (11.8)	2 (1.7)
Skin and subcutaneous tissue disorders		
Pruritus	33 (27.7)	2 (1.7)
Rash	16 (13.4)	3 (2.5)
Dry skin	13 (10.9)	0

Serious adverse events were reported in 57 of 119 patients (47.9%). Serious adverse events reported by ≥2 patients were pyrexia in 4 patients (3.4%), colitis, small intestinal obstruction, malignant neoplasm progression, and acute kidney injury in 3 patients (2.5%) each, and anaemia, abdominal pain, diarrhoea, intestinal obstruction, large intestinal obstruction, bile duct obstruction, transaminases increased, and back pain in 2 patients (1.7%) each. A causal relationship to the study drugs could not be ruled out for the pyrexia and colitis in 3 patients each, acute kidney injury, anaemia, abdominal pain, and transaminases increased in 2 patients each, and diarrhoea in 1 patient.

Adverse events led to drug discontinuation in 17 of 119 patients (14.3%). The adverse events that led to drug discontinuation in ≥2 patients were AST increased, autoimmune hepatitis, and acute kidney injury in 2 patients

(1.7%) each. A causal relationship to the study drugs could not be ruled out for the autoimmune hepatitis and acute kidney injury in 2 patients each, and AST increased in 1 patient.

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 and CTD 5.3.5.2-1.2) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals, and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that NIVO/IPI therapy has a certain level of efficacy in the treatment of unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy, and that the NIVO/IPI therapy has acceptable safety in view of its benefits. NIVO/IPI therapy is clinically meaningful because it offers a new treatment option for patients with such disease condition. PMDA has also concluded that updating the dosage and administration of nivolumab (genetical recombination) to include regimen with 480 mg every 4 weeks is appropriate. The efficacy, dosage and administration, post-marketing investigations, etc. for NIVO and IPI need to be further investigated.

PMDA has concluded that nivolumab administered alone or in combination with ipilimumab may be approved if nivolumab administered alone or in combination with ipilimumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 26, 2020

Products Submitted for Approval

(a)	**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	November 12, 2019; November 27, 2019[10)]
(b)	**Brand Name**	Yervoy Injection 50 mg (for intravenous use)
	Non-proprietary Name	Ipilimumab (Genetical Recombination)
	Applicant	Bristol-Myers Squibb K.K.
	Date of Application	November 12, 2019

List of Abbreviations See Appendix

1. Content of the Review

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

1.1 Efficacy

As a result of its review, described in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that the combination therapy with nivolumab (genetical recombination) (hereinafter, referred to as "NIVO") and ipilimumab (genetical recombination) (hereinafter, referred to as "IPI") ("NIVO/IPI therapy") has demonstrated 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, taking into account the molecular pathogenesis of MSI-High colorectal cancer [see Section 7.R.2.1] and available data including the overall response rates [95% confidence intervals [CIs]] (the primary endpoint), as assessed by investigator using RECIST Ver. 1.1, of 54.6 [45.2, 63.8]% (65 of 119 patients) observed in a foreign phase II study in patients with such disease condition (Study 142).

10) (a) An application for partial change was filed on November 12, 2019 to add a new dosage and administration for combination therapy with nivolumab (genetical recombination) and ipilimumab (genetical recombination) for microsatellite instability-high (MSI-High) colorectal cancer. (b) An application for partial change was filed on November 27, 2019 to update the dosage and administration of nivolumab (genetical recombination) to include an infusion regimen of 480 mg every 4 weeks, for all of the approved indications.

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

1.2 Safety

As a result of its review, described in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that NIVO/IPI therapy for chemotherapy-treated patients with unresectable, advanced or recurrent MSI-High colorectal cancer requires particular attention to the onset of myocarditis associated with IPI, in addition to the adverse events identified as requiring attention at the regulatory reviews for the approved indications for (a) NIVO and (b) IPI.

(a) 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 thrombosis and embolism; adrenal disorder; encephalitis; type 1 diabetes mellitus; serious blood disorder; cardiac disorder; tuberculosis; and pancreatitis

(b) Diarrhoea, colitis, and gastrointestinal perforation; skin disorder; liver disorder; hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency; peripheral neuropathy; renal disorder; ILD; myositis; and infusion reaction

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

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 Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the indications of NIVO and IPI should be "unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy," as proposed by the applicants, and that the following cautionary statements should be included in the "Precautions Concerning Indications" sections for NIVO and IPI.

NIVO:

- The efficacy and safety of NIVO have not been established in patients who have not received prior treatments with a fluoropyrimidine, L-OHP, and CPT-11.
- NIVO should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic or medical device should be used in the test.
- The efficacy and safety of NIVO as an adjuvant therapy have not been established.

- Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of NIVO, after fully understanding the "Clinical Studies" section and carefully considering the choice of alternative therapies.

IPI:

- The efficacy and safety of IPI have not been established in patients who have not received prior treatments with a fluoropyrimidine, L-OHP, and CPT-11.
- IPI should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An *in vitro* diagnostic or medical device that is approved to assist assessment of patient eligibility for NIVO therapy for MSI-High colorectal cancer should be used in the test.
- The efficacy and safety of IPI as an adjuvant therapy have not been established.
- Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of IPI, after fully understanding the "Clinical Studies" section and carefully considering the choice of alternative therapies.

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

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

1.4 Dosage and administration

As a result of its review, described in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the statements presented in the table below should be included in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections for NIVO and IPI. (Underline denotes changes for the present application for partial changes.)

	Dosage and administration	Precautions concerning dosage and administration
NIVO	Malignant melanoma: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. In combination therapy with IPI for unresectable malignant melanoma, the usual adult dosage of NIVO is 80 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable or metastatic RCC: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. • When administered in combination with IPI to chemotherapy-naïve patients with unresectable or metastatic RCC, the usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks. When administered in combination with IPI, the usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks or 480 mg as an intravenous infusion every 4 weeks. Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, 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, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy: • The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks or 480 mg administered as an intravenous infusion every 4 weeks.	All indications: • NIVO should be administered intravenously over ≥30 minutes. Unresectable or metastatic RCC: • The efficacy and safety of NIVO 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 NSCLC, relapsed or refractory cHL, 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, or unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy: • The efficacy and safety of NIVO in combination with other antineoplastic drugs have not been established. Malignant melanoma: • When administered in combination with IPI to patients with unresectable malignant melanoma, the necessity of the combination therapy should be carefully determined based on a careful review 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 NIVO. The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy.
IPI	Unresectable malignant melanoma: • The usual adult dosage is 3 mg/kg (body weight) of IPI administered intravenously every 3 weeks for a total of 4 doses. IPI should not be used in combination with antineoplastic agents other than NIVO. Unresectable or metastatic RCC, or unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • In combination therapy with NIVO, the usual adult dosage is 1 mg/kg (body weight) of IPI administered intravenously every 3 weeks for a total of 4 doses.	All indications: • The criteria for interruption or discontinuation of treatment in the event of adverse reactions (omitted, since they are identical to those at the previous approval) Unresectable malignant melanoma: • When administered in combination with NIVO, the necessity of the combination therapy should be carefully determined based on a careful review of the "Clinical Studies" section, particularly regarding the characteristics, such as prior treatments, of patients enrolled in the clinical studies and a thorough understanding of the efficacy and safety of IPI. The add-on effect of IPI to NIVO on survival prolongation tends to differ according to the percentage of tumor cells expressing PDL1 (PD-L1 expression rate). In patients who have been confirmed to have a high PD-L1 expression rate, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy. • IPI should be administered intravenously over 90 minutes. Unresectable or metastatic RCC, or unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy: • IPI should be administered intravenously over 30 minutes.

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

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

1.5 Risk management plans (draft)

As a result of its review described in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA has concluded that (a) safety information regarding the new indication and the new dosage and administration of NIVO/IPI therapy for MSI-High colorectal cancer may be collected through routine pharmacovigilance activities, and that (b) safety information regarding the new dosage and administration of NIVO, "480 mg every 4 weeks," for all of the approved indications may be collected through the ongoing post-marketing surveillance or other activities for the approved indications, as proposed by the applicants.

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

In view of the discussion above, PMDA has concluded that the risk management plans (draft) for NIVO and IPI should include the safety specifications presented in Tables 9 and 11, and that the applicants should conduct the additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Tables 10 and 12.

Table 9. Safety and efficacy specifications in the risk management plan for NIVO (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Interstitial lung disease (ILD) • Myasthenia gravis, myocarditis, myositis, rhabdomyolysis • Colitis, enteritis, severe diarrhoea • Type 1 diabetes mellitus • Hepatic failure, hepatic function disorder, hepatitis, sclerosing cholangitis • Endocrine disorder (thyroid dysfunction, pituitary dysfunction, adrenal disorder) • Neurological disorder • Renal disorder • Encephalitis • Severe skin disorder • Venous thromboembolism • Infusion reaction • Serious blood disorder • Haemophagocytic syndrome • Tuberculosis • Use in patients with a history of organ transplant (including haematopoietic stem cell transplant) • Pancreatitis	• Excessive immune response • Embryonic/fetal toxicity • Cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles) • Aplasia pure red cell • Increased risk of severe comorbidities associated with allogenic haematopoietic stem cell transplant after NIVO therapy (Haematological malignancy) • Tumour haemorrhage • Fistula	None
Efficacy specification (for the present application for partial changes)		
None		

No changes are made for the preset application for partial changes.
Wavy line denotes important identified risks or important potential risks that were added after the present application for partial changes.

Table 10. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan for NIVO (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 (NIVO/IPI therapy) • Specified use-results survey in patients with unresectable or metastatic RCC (NIVO/IPI 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 ONO-4538-05, 06, 08, 03, 12, 41, 24, 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 clinical studies (extension studies of Studies ONO-4538-05, 06, 08, 03, and 12)	• Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

Underlines indicate activities to be performed after the new dosage and administration is added.

Table 11. Safety and efficacy specifications in the risk management plan for IPI (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Diarrhoea, colitis, gastrointestinal perforation • Liver disorder • Skin disorder • Hypophysitis, hypopituitarism, hypothyroidism, adrenal insufficiency • Neuropathy Peripheral • Renal disorder • ILD • Infusion reaction • Myositis • Myocarditis	• Excessive immune response • Reproductive and developmental toxicity • Sepsis	None
Efficacy specification (for the present application for partial changes)		
None		

Underline denotes specification added in the present application for partial changes.

Table 12. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan for IPI (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Specified use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Specified use-results survey in patients with unresectable malignant melanoma (NIVO/IPI therapy) • Specified use-results survey in patients with unresectable or metastatic RCC (NIVO/IPI therapy)	• Specified use-results survey in patients with unresectable malignant melanoma (all-case surveillance)	• Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

Underlines denote activities to be performed after the new indication is added.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that NIVO and IPI may be approved for the proposed indication and dosage and administration as follows, with the approval conditions shown below, provided that the necessary precautionary statements are included in the package inserts, and information on the proper use of the products is properly disseminated after the market launch, and provided that the products are used under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy, at medical institutions capable of emergency response. The re-examination periods for the present application are as follows.

NIVO:

- Malignant melanoma (The re-examination period is the reminder of the ongoing re-examination period [until July 3, 2024].)
- Unresectable, advanced or recurrent NSCLC (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)
- Unresectable or metastatic RCC (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)
- Recurrent or refractory cHL (The re-examination period is the remainder of the ongoing re-examination period [until December 1, 2026].)
- Recurrent or metastatic head and neck cancer (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)
- Unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)
- Unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy (The re-examination period is the remainder of the ongoing re-examination period [until August 20, 2028].)
- Unresectable, advanced or recurrent MSI-High colorectal cancer (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)
- Unresectable, advanced or recurrent esophageal cancer that has progressed after cancer chemotherapy (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)

IPI:

- Unresectable, advanced or recurrent MSI-High colorectal cancer that has progressed after cancer chemotherapy (The re-examination period is the remainder of the ongoing re-examination period [until June 20, 2024].)

(Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, Opdivo Intravenous Infusion 240 mg)

Indications (Double-underline denotes additions made as of February 21, 2020, after the present application for partial changes.)

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

Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of February 21, 2020, after the present application for partial changes. Double-strikethrough denotes deletions made as of February 21, 2020, after the present application for partial changes.)

~~1.~~ Malignant melanoma:

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

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

~~2.~~ Unresectable or metastatic renal cell carcinoma:

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

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

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

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

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

~~3.~~ 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 or 480 mg administered as an intravenous infusion every 4 weeks.

Approval Condition

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

Warnings (No change)

1. Opdivo should be administered only to eligible patients under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities to respond to emergencies. Before the start of treatment, 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. Opdivo may cause interstitial lung disease, resulting in fatal outcomes in some cases. 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 abnormalities being found, the administration of Opdivo should be discontinued and appropriate actions such as the introduction of corticosteroid therapy should be taken.

Contraindication (No change)

Patients with a history of hypersensitivity to the ingredients of Opdivo

Precautions Concerning Indications (Underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of February 21, 2020, after the present application for partial changes. Double-strikethrough denotes deletions made as of February 21, 2020, after the present application for partial changes.)

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 treatments with a fluoropyrimidine, oxaliplatin, and irinotecan hydrochloride hydrate.
7. Opdivo should be administered to patients with a MSI-High cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An approved *in vitro* diagnostic or medical device should be used in the test.
8. Eligible patients should 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:

~~6~~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 as an 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:

~~7~~11. Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of Opdivo, after fully understanding the "Clinical Studies" section.

Note) International Metastatic RCC Database Consortium

Precautions Concerning Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of February 21, 2020, after the present application for partial changes.)

All indications:

1. Opdivo should be administered intravenously over ≥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 "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.

Yervoy Injection 50 mg (for intravenous use)

Indications (Underline denotes additions.)

○ Unresectable malignant melanoma

○ Unresectable or metastatic renal cell carcinoma

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

Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions.)

~~1.~~ Unresectable malignant melanoma:

The usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 doses. Ipilimumab (genetical recombination) should not be used in combination with antineoplastic agents other than nivolumab (genetical recombination).

~~2.~~ Unresectable or metastatic renal cell carcinoma, or unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy:
In combination therapy with nivolumab (genetical recombination), the usual adult dosage is 1 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 doses.

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

Warnings (No change)

1. Yervoy should be administered only to eligible patients under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities to respond to emergencies. Before the start of treatment, 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. Yervoy may cause serious diarrhoea, colitis, or gastrointestinal perforation. These events occurred a few months after the completion of treatment and resulted in fatal outcomes in some cases. Patients should be closely monitored after the completion of treatment, as well as during treatment with Yervoy. In the event of abnormalities being found, appropriate measures, including corticosteroid therapy, should be taken.

Contraindication (No change)
Patients with a history of severe hypersensitivity to any ingredient of Yervoy

Precautions Concerning Indications (Underline denotes additions. Strikethrough denotes deletions.)

All indications:

~~1. Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of Yervoy, after fully understanding the "Clinical Studies" section. In particular when administering Yervoy as a monotherapy to chemotherapy-naïve patients with unresectable malignant melanoma, other therapeutic options should also be carefully considered.~~

~~2~~1. The efficacy and safety of Yervoy as an adjuvant therapy have not been established.

Unresectable malignant melanoma:

2. Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of Yervoy, after fully understanding the "Clinical Studies" section. In particular when administering Yervoy as a monotherapy to chemotherapy-naïve patients with unresectable malignant melanoma, other therapeutic options should also be carefully considered.

Unresectable or metastatic renal cell carcinoma:

3. The use of Yervoy should be limited to IMDC[Note)] intermediate- or poor-risk patients.
4. Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of Yervoy, after fully understanding the "Clinical Studies" section.

Note) International Metastatic RCC Database Consortium

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

5. The efficacy and safety of Yervoy have not been established in patients who have not received prior treatments with a fluoropyrimidine, oxaliplatin, and irinotecan hydrochloride hydrate.
6. Yervoy should be administered to patients with a microsatellite instability-high (MSI-High) cancer confirmed by tests performed by a highly experienced pathologist or at a laboratory facility. An *in vitro* diagnostic or medical device that is approved to assist assessment of patient eligibility for nivolumab (genetical recombination) therapy for MSI-High colorectal cancer should be used in the test.
7. Eligible patients should be selected by physicians with adequate knowledge in the efficacy and safety of Yervoy, after fully understanding the "Clinical Studies" section and carefully considering the choice of alternative therapies.

Precautions Concerning Dosage and Administration (Underline denotes additions.)

All indications:

1. In the event of adverse reactions, treatment should be interrupted or discontinued according to the following criteria:

Criteria for interruption or discontinuation of treatment

Adverse reactions	Actions
• Grade 2 adverse reactions (excluding endocrine or skin disorder) • Grade 3 skin disorder • Symptomatic endocrine disorder	Interrupt treatment until the event resolves to Grade ≤1 or baseline. For endocrine disorder, interrupt treatment until symptoms resolve. If the event fails to meet any of these criteria, discontinue treatment.
• Grade ≥3 adverse reactions (excluding endocrine or skin disorder) • Grade ≥2 eye disorder for which local immunosuppressive therapy is ineffective • Grade 4 skin disorder	Discontinue treatment.

Events are graded according to the NCI-CTCAE Ver. 4.0.

Unresectable malignant melanoma:

2. When administered in combination with nivolumab (genetical recombination), the necessity of the combination therapy should be carefully determined based on a careful review of the "Clinical Studies" section, particularly regarding the characteristics, such as prior treatments, of patients enrolled in the clinical studies and a thorough understanding of the efficacy and safety of Yervoy. The add-on effect of Yervoy to nivolumab (genetical recombination) 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, nivolumab (genetical recombination) monotherapy should also be carefully considered before initiating nivolumab (genetical recombination)/Yervoy therapy.
3. Yervoy should be administered intravenously over 90 minutes.

Unresectable or metastatic renal cell carcinoma, or unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after cancer chemotherapy:

4. Yervoy should be administered intravenously over 30 minutes.

Appendix

List of Abbreviations

ALT	alanine aminotransferase
application for partial change	application for partial change approval
AST	aspartate aminotransferase
bevacizumab	bevacizumab (genetical recombination)
$C_{avg,d28}$	average serum concentration over the first 28 days of treatment
$C_{avg,ss}$	average serum concentration at steady state
cHL	classical Hodgkin lymphoma
CI	confidence interval
$C_{max,ss}$	maximum serum concentration at steady state
C_{max1}	maximum serum concentration after the first dose
$C_{min,d28}$	minimum serum concentration at day 28
$C_{min,ss}$	trough serum concentration at steady state
CPT-11	irinotecan hydrochloride hydrate
CR	complete response
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
dMMR	mismatch repair deficient
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IPI	Ipilimumab (genetical recombination)
IRRC	independent radiology review committee
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 (rectal cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Rectal Cancer
NE	not evaluable
NIVO	Nivolumab (genetical recombination)
NIVO/IPI	a combination of nivolumab (genetical recombination) and ipilimumab (genetical recombination)
NSCLC	non-small cell lung cancer
NSQ-NSCLC	non-squamous cell non-small cell lung cancer
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease

PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
pembrolizumab	pembrolizumab (genetical recombination)
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PMS2	postmeiotic segregation increased 2
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
QD	quaque die
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
Q4W	quaque 4 weeks
regorafenib	regorafenib hydrate
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SOC	system organ class
SQ-NSCLC	squamous cell non-small cell lung cancer
Study 067	Study CA209067
Study 142	Study CA209142
Study 17	Study ONO-4538-17
Study 214	Study ONO-4538-16/CA209214