Report on the Deliberation Results

August 7, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Yervoy Injection 50 mg (for intravenous use)
Non-proprietary Name	Ipilimumab (Genetical Recombination) (JAN*)
Applicant	Bristol-Meyers Squibb K.K.
Date of Application	January 15, 2018

Results of Deliberation

In its meeting held on August 3, 2018, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 5 years and 10 months.

Conditions of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

July 26, 2018
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)
Applicant	Bristol-Meyers Squibb K.K.
Date of Application	January 15, 2018
Dosage Form/Strength	Injection: One 10 mL vial contains 50 mg of ipilimumab (genetical recombination).
Application Classification	Prescription drug, (4) Drugs with a new indication, (6) Drugs with new dosages
Items Warranting Special Mention	Priority review (PSEHB/PED Notification No. 0320-4 dated March 20, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that nivolumab (genetical recombination) in combination with ipilimumab (genetical recombination) has efficacy in the treatment of unresectable or metastatic renal cell carcinoma, 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. The following events should be further evaluated through post-marketing surveillance: colitis, diarrhoea, gastrointestinal perforation; and hepatic function disorder, cholangitis sclerosing.

Indication(s)

1. Unresectable malignant melanoma
2. <u>Unresectable or metastatic renal cell carcinoma</u>

(Underline denotes additions.)

Dosage and Administration

1. <u>Unresectable malignant melanoma</u>

~~Chemotherapy-naïve patients:~~

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

~~Chemotherapy-treated patients:~~

~~The usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 times.~~

2. Unresectable or metastatic renal cell carcinoma

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 times.

(Single underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of May 25, 2018 after the present application.)

Condition of Approval

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

Attachment

Review Report (1)

June 15, 2018

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

Product Submitted for Approval

(a) Brand Name	(a) Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg (b) Opdivo Intravenous Infusion 240 mg
Non-proprietary Name	Nivolumab (Genetical Recombination)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	(a) December 22, 2017, January 15, 2018[1] (b) January 31, 2018, March 27, 2018[1]
Dosage Form/Strength	(a) Injection: Each vial of 2 mL contains 20 mg of nivolumab (genetical recombination). Each vial of 10 mL contains 100 mg of nivolumab (genetical recombination). (b) Injection: Each vial of 24 mL contains 240 mg of nivolumab (genetical recombination).
Proposed Indication(s)	1. Treatment of ~~unresectable~~ malignant melanoma 2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer 3. Treatment of unresectable or metastatic renal cell carcinoma 4. Treatment of relapsed or refractory classical Hodgkin lymphoma 5. Treatment of recurrent or distant metastatic head and neck cancer 6. Treatment of unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy 7. Treatment of unresectable, advanced or metastatic malignant pleural mesothelioma (Underline denotes additions. Strikethrough denotes deletions.)

Proposed Dosage and Administration

1. Treatment of ~~unresectable~~ malignant melanoma, unresectable, advanced or recurrent non-small cell lung cancer, relapsed or refractory classical Hodgkin lymphoma, recurrent or distant metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed

[1] For (a) Opdivo Intravenous Infusion 20 mg and Opdivo Intravenous Infusion 100 mg, and for (b) Opdivo Intravenous Infusion 240 mg, partial change applications to add a new dosage and administration for combination therapy with nivolumab (genetical recombination) and ipilimumab (genetical recombination) for the treatment of renal cell carcinoma were filed on (a) January 15, 2018 and (b) March 27, 2018, respectively.

after cancer chemotherapy, or unresectable, advanced or metastatic malignant pleural mesothelioma

~~Chemotherapy-naïve patients with unresectable malignant melanoma:~~

The usual adult dosage of nivolumab (genetical recombination) is 240 mg~~3 mg/kg body weight~~ administered as an intravenous infusion every 2 weeks.

~~Chemotherapy-treated patients with unresectable malignant melanoma: The usual adult dosage of nivolumab (genetical recombination) is 3 mg/kg body weight administered as an intravenous infusion every 2 weeks, or 2 mg/kg body weight as an intravenous infusion every 3 weeks.~~

2. Treatment of ~~unresectable, advanced or recurrent non-small cell lung cancer,~~ unresectable or metastatic renal cell carcinoma~~, relapsed or refractory classical Hodgkin lymphoma, recurrent or distant metastatic head and neck cancer, and unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy~~

The usual adult dosage of nivolumab (genetical recombination) is 240 mg~~3 mg/kg body weight~~ administered as an intravenous infusion every 2 weeks.

In combination with ipilimumab (genetical recombination), the usual adult dosage of nivolumab (genetical recombination) is 3 mg/kg (body weight) administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks.

(Underline denotes additions. Strikethrough denotes deletions.)

(b) Brand Name Yervoy Injection 50 mg (for intravenous use)

Non-proprietary Name Ipilimumab (Genetical Recombination)

Applicant Bristol-Meyers Squibb K.K.

Date of Application January 15, 2018

Dosage Form/Strength Injection: One 10 mL vial contains 50 mg of ipilimumab (genetical recombination)

Proposed Indication(s)

1. Unresectable malignant melanoma
2. Unresectable or metastatic renal cell carcinoma

(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 times.

2. Unresectable or metastatic renal cell carcinoma

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 times.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Summary of the proposed products

Nivolumab (genetical recombination) (hereinafter referred to as "NIVO"), a human monoclonal antibody against human programmed cell death-1 (PD-1) belonging to the immunoglobulin (Ig) G4 subclass, was developed by Ono Pharmaceutical Co., Ltd. and by Medarex in the US (currently known as Bristol-Myers Squibb). NIVO is considered to bind to the extracellular domain of PD-1 (PD-1 ligand binding site) and block the interaction between PD-1 and PD-1 ligands, thereby enhancing the activation of cancer antigen-specific T cells and cytotoxic activation against cancer cells to inhibit tumor growth.

Ipilimumab (genetical recombination) (hereinafter referred to as "IPI") is a human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) developed by Medarex in the US (currently known as Bristol-Myers Squibb). IPI is considered to suppress 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) 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 indication of "unresectable malignant melanoma" in July 2014, "unresectable, advanced or recurrent non-small cell lung cancer" in December 2015, "unresectable or metastatic renal cell carcinoma" in August 2016, "relapsed or refractory classical Hodgkin lymphoma" in December 2016, "recurrent or distant metastatic head and neck cancer" in March 2017, and "unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy" in September 2017. IPI was approved for the indication of "unresectable malignant melanoma" in July 2015. The combination therapy with NIVO and IPI (NIVO/IPI therapy) for which a new dosage and administration for the treatment of renal cell carcinoma (RCC) has been proposed in the present partial application was approved for the treatment of unresectable malignant melanoma in May 2018.

NIVO was designated as an orphan drug in June 2013 and December 2017 with the intended indications of "malignant melanoma" and "malignant pleural mesothelioma," respectively (Drug Designation No. 308 of 2013 [*25 yaku*] and No. 406 of 2017 [*29 yaku*]).

1.2 Development history, etc.

1.2.1 NIVO monotherapy for malignant pleural mesothelioma

In Japan, a phase II study of NIVO monotherapy was initiated by ONO Pharmaceutical Co., Ltd. in [redacted] 20[redacted] in chemotherapy-treated[2] patients with unresectable, advanced or recurrent malignant pleural mesothelioma (Study 41). In Study 41, NIVO was administered at a fixed dosage (240 mg), rather than at the previously approved body weight-based dosage (3 mg/kg).

[2] Patients were eligible if they were resistant or intolerant to platinum-based antineoplastic therapy in combination with PEM and had received ≤2 prior therapies.

Primarily based on the results of Study 41, the applicant has filed partial change applications for NIVO to add an indication of malignant pleural mesothelioma and to change the dosage regimen from a body weight-based dosage (3 mg/kg) to the fixed dosage (240 mg) that was used in Study 41 for both the newly proposed and previously approved indications.

1.2.2 NIVO monotherapy for the adjuvant therapy of malignant melanoma

Outside Japan, a global phase III study of NIVO monotherapy was conducted by Bristol-Myers Squibb from March 2015 in patients with completely resected[3] stage[4] IIIb/c or IV malignant melanoma (Study 238).

In Japan, patient enrollment in Study 238 was initiated in [redacted] 20[redacted].

Primarily based on the results of Study 238, the applicant has filed a partial change application for NIVO to add an indication of adjuvant therapy for malignant melanoma.

1.2.3 NIVO in combination with IPI for the treatment of RCC

Outside Japan, Bristol-Myers Squibb conducted a phase I study of NIVO/IPI therapy and other treatment regimens from February 2012 in patients with unresectable or metastatic RCC (Study 016). Bristol-Myers Squibb also conducted a global phase III study of NIVO/IPI therapy from October 2014 in chemotherapy-naïve patients with unresectable or metastatic[5] clear cell RCC (Study 214).

In Japan, patient enrollment in Study 214 was initiated in [redacted] 20[redacted].

Primarily based on the results of Study 214, the applicants have filed a partial change application for NIVO to add a new dosage and administration for use in NIVO/IPI therapy for RCC, and a partial change application for IPI to add a new indication, and dosage and administration for use in NIVO/IPI therapy for RCC.

1.2.4 Approval status outside Japan

As of April 2018, the approval status outside Japan of the indications and dosage regimens of NIVO and IPI proposed in the present partial change applications are as described in (a) to (d) below:

(a) NIVO as a monotherapy has not been approved for the treatment of malignant pleural mesothelioma in any country/region.

(b) In the US and EU, approval applications for NIVO for the adjuvant treatment of malignant melanoma were filed in August and October 2017, respectively, primarily based on the results of Study 238. In addition, NIVO was approved in the US in December 2017 as "OPDIVO is indicated for the adjuvant treatment of patients with melanoma with the involvement of lymph nodes or metastatic disease who have undergone a complete resection," while the application is currently

[3] Patients who have undergone a complete resection of the tumors
[4] Disease stage was assessed according to the staging system of the American Joint Committee on Cancer (AJCC), seventh edition.
[5] Disease stage IV as per the AJCC staging system

under review in the EU. NIVO as a monotherapy has been approved for the adjuvant therapy of malignant melanoma in 2 countries.

(c) In the US and EU, approval applications for NIVO in combination with IPI for the treatment of RCC were filed in October and November 2017, respectively, primarily based on the results of Study 214. In the US, NIVO and IPI were approved in April 2018 as "OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC)"and as "YERVOY, in combination with nivolumab, is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC)." In the EU, the applications are currently under review. NIVO/IPI therapy for the treatment of RCC has been approved only in the US.

(d) The fixed dosages (e.g., 240 mg every 2 weeks) of NIVO have been approved in the US and EU.

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

The present application is for new indications and new dosage regimens for Opdivo Intravenous Infusion 20 mg and Opdivo Intravenous Infusion 100 mg, and is also for additional dosage form for Opdivo Intravenous Infusion 240 mg. Therefore, data relating to quality have been submitted. Opdivo Intravenous Infusion 240 mg is a drug product in which the same drug product as the approved NIVO products (Opdivo Intravenous Infusion 20 mg and Opdivo Intravenous Infusion 100 mg) and is filled in a vial with a different fill. Thus, the newly proposed NIVO product differs from the approved NIVO products only in the fill volume, container, and container closure system. This review report describes matters only with respect to the new indications and the new dosage regimens. However, PMDA found no particular issue on the additional dosage form as a result of its review.

With the addition of the new dosage regimens of NIVO, the maximum daily dose exceeds the approved maximum daily dose. Therefore, data relating to the safety of excipients have been submitted for the present partial change applications.

2.R Outline of the review conducted by PMDA

With the addition of the new dosage regimens, the amount of diethylenetriamine pentaacetic acid contained in each NIVO product exceeds the amount present in existing intravenous infusion formulations. Therefore, diethylenetriamine pentaacetic acid is categorized as a novel excipient.

Based on the data submitted, PMDA concluded that the proposed new dosage regimens of NIVO are less likely to cause safety problems associated with the novel excipient.

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

Although the present applications are for new indications and new dosage regimens, no new study data on the non-clinical pharmacology of NIVO or IPI were submitted, because the non-clinical pharmacology of NIVO and IPI had been evaluated at the previous approvals.

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

Although the present applications are for new indications and new dosage regimens, no new study data on the non-clinical pharmacokinetics of NIVO or IPI were submitted, because the non-clinical pharmacokinetics of NIVO and IPI had been evaluated at the previous approvals.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present applications are for new indications and new dosage regimens, no data relating to the toxicity of NIVO or IPI were submitted.

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

Although the present applications are for new indications and new dosage regimens, no new data on biopharmaceutic studies and associated analytical methods were submitted because the biopharmaceutic studies and associated analytical methods for NIVO and IPI had been evaluated at the initial approvals.

6.1 Clinical pharmacology

The applicants have submitted new data relating to clinical pharmacology for the present applications. However, PMDA concluded that there is no difference in the applicant's explanation about the pharmacokinetics of IPI between Japanese and non-Japanese, etc., as those evaluated in the initial approvals.

The pharmacokinetics of NIVO administered as a monotherapy in patients with cancer was evaluated in the following subsections.

6.1.1 Japanese phase II study (CTD 5.3.5.2-1 [malignant pleural mesothelioma], Study 41, ongoing since [redacted] 20[redacted] [data cutoff date, April 21, 2017])

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of NIVO in 34 chemotherapy-treated[2] patients with unresectable, advanced or recurrent malignant pleural mesothelioma. All 34 patients were included in the PK analyses. The patients received NIVO 240 mg administered every 2 weeks as an intravenous infusion over 30 minutes and serum NIVO concentrations were determined. The serum NIVO concentrations (mean ± standard deviation) before the dose on Days 1 of Cycles 2, 3, and 10 were 20.5 ± 6.02, 38.4 ± 12.5, and 60.9 ± 27.2 μg/mL, respectively. The serum NIVO concentrations before the dose on Day 1 of Cycle 18 (individual values) were 47.2 and 54.8 μg/mL.

6.1.2 Population pharmacokinetics (PPK) analyses

6.1.2.1 Assessment of exposure to NIVO administered at the body weight-based dosage and the fixed dosage

The following 3 PPK analyses, (a) to (c), were conducted.

(a) Serum concentrations of NIVO administered at an intravenous dose of 3 mg/kg or 240 mg every 2 weeks were assessed in Japanese patients with malignant melanoma, non-small cell lung cancer

(NSCLC), RCC, squamous cell carcinoma of the head and neck (SCCHN), classical Hodgkin lymphoma (cHL), or gastric cancer, who were enrolled in clinical studies included in the PPK analyses.[6] The exposure to NIVO at 240 mg was predicted to be higher than that at NIVO 3 mg/kg, but lower than the exposure observed at the dosage that had been demonstrated to be tolerable in Japanese patients (i.e., 10 mg/kg every 2 weeks [see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated June 18, 2014"]) (Table 1).

Table 1. Pharmacokinetic parameters of NIVO

Dosage regimen	C_{max} (μg/mL)	C_{mind14} (μg/mL)	C_{avgd14} (μg/mL)	$C_{max,ss}$ (μg/mL)	$C_{min,ss}$ (μg/mL)	$C_{avg,ss}$ (μg/mL)
3 mg/kg every 2 weeks*1	50.9 (21.3)	16.4 (24.7)	24.2 (20.5)	113 (26.4)	59.6 (38.9)	76.3 (33.2)
	51.6 (35.2, 70.8)	16.6 (10.7, 24.5)	24.3 (17.1, 33.9)	113 (75.0, 171)	62.1 (27.1, 107)	77.6 (42.1, 127)
240 mg every 2 weeks*1	72.6 (21.9)	23.3 (24.6)	34.4 (19.2)	161 (27.5)	84.7 (40.9)	108 (34.7)
	72.7 (51.1, 103)	23.5 (15.2, 34.6)	34.1 (25.1, 47.8)	159 (102, 254)	87.8 (41.5, 158)	109 (62.1, 187)
10 mg/kg every 2 weeks*2	191 (147, 219)	61.3 (51.2, 79.2)	90.8 (79.0, 114)	398 (331, 532)	217 (184, 313)	278 (237, 386)

*1, Upper row, geometric mean (coefficient of variation [%]); lower row, median (5% point, 95% point)
*2, The median (5% point, 95% point) estimated using the pharmacokinetic data from a Japanese phase I study (Study 01)

(b) Serum concentrations of NIVO administered at an intravenous dose of 3 mg/kg or 240 mg in combination with IPI 1 mg/kg every 3 weeks were assessed in Japanese patients with RCC who were enrolled in a global clinical study (Study 214).[7] The exposure to NIVO at 240 mg was predicted to be higher than that at 3 mg/kg (Table 2).

Table 2. Pharmacokinetic parameters of NIVO

Dosage regimen	Number of doses	C_{max} (μg/mL)	C_{min} (μg/mL)	C_{avg} (μg/mL)
3 mg/kg every 3 weeks	1	55.5 (19.0)	12.8 (35.6)	22.6 (22.7)
	4	79.7 (22.6)	25.6 (42.2)	40.5 (32.0)
240 mg every 3 weeks	1	67.9 (22.6)	15.7 (46.5)	27.6 (31.1)
	4	97.5 (30.8)	31.3 (54.2)	49.5 (43.1)

Geometric mean (coefficient of variation [%])

(c) Serum concentrations of NIVO administered at an intravenous dose of 1 mg/kg or 80 mg in combination with IPI 3 mg/kg every 3 weeks were assessed in patients with malignant melanoma who were enrolled in a Japanese clinical study (Study 17).[7] The exposure to NIVO at 80 mg was predicted to be higher than that at 1 mg/kg, but lower than the exposure observed when NIVO was administered at a dose exceeding the maximum tolerated dose (i.e., 3 mg/kg), in combination with IPI 3 mg/kg every 3 weeks (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated April 13, 2018") (Table 3).

[6] A PPK analysis using the pharmacokinetic data for NIVO (3939 patients, 21,098 sampling points) obtained from Japanese clinical studies (Studies 01, 02, 05, 06, 08, and 15), foreign clinical studies (Studies 001, 03, 09, 010, 017, 032, 037, 039, 057, 063, 066, 067, and 205), and global clinical studies (Studies 12, 025, 026, 141, and 275) (NONMEM version 7.3.0)
[7] A PPK analysis using the pharmacokinetic data for NIVO (6468 patients, 32,843 sampling points) obtained from Japanese clinical studies (Studies 01 and 02), foreign clinical studies (Studies 001, 03, 04, 09, 010, CA209012, 016, 017, 032, 037, 057, 063, 066, 067, 069, CA209142, CA209511, and CA209568), and global clinical studies (Studies 025, 026, 214, ONO-4538-20/CA209040, and ONO-4538-27/CA209227) (NONMEM version 7.3.0)

Table 3. Pharmacokinetic parameters of NIVO

Dosage regimen	Number of doses	C_{max} (μg/mL)	C_{min} (μg/mL)	C_{avg} (μg/mL)
1 mg/kg every 3 weeks*1	1	19.1 (21.4)	3.67 (34.6)	7.06 (21.5)
		19.0 (13.7, 26.8)	3.84 (1.64, 6.49)	7.42 (4.61, 9.90)
	4	25.5 (23.3)	6.82 (43.0)	11.7 (30.3)
		25.4 (17.3, 38.4)	7.21 (2.83, 13.0)	11.8 (6.40, 19.3)
80 mg every 3 weeks*1	1	26.9 (19.2)	5.17 (34.3)	9.95 (20.2)
		27.3 (19.7, 36.9)	5.68 (2.61, 8.72)	10.1 (6.83, 13.8)
	4	36.0 (21.7)	9.61 (43.1)	16.5 (29.9)
		35.3 (25.2, 49.9)	10.9 (4.39, 17.9)	17.1 (10.1, 26.0)
3 mg/kg every 3 weeks*2	1	57.4 (37.8, 73.5)	14.1 (13.2, 20.1)	23.2 (19.4, 28.8)
	4	83.4 (64.1, 117)	29.1 (27.5, 50.4)	43.6 (39.5, 64.2)

*1, Upper row, geometric mean (coefficient of variation [%]); lower row, median (5% point, 95% point)
*2, The median (5% point, 95% point) estimated using the pharmacokinetic data from a foreign phase Ib study (Study 04)

6.1.2.2 Assessment of the effects of infusion time on the pharmacokinetics of NIVO

Serum concentrations of NIVO administered as an intravenous infusion over 30 or 60 minutes at a dose of 3 mg/kg or 240 mg every 2 weeks were assessed in Japanese patients with malignant melanoma, NSCLC, RCC, SCCHN, cHL, or gastric cancer who were enrolled in the clinical studies used in the PPK analysis.[6] The assessment revealed no clear difference in exposure to NIVO between the infusion times of 30 minutes and 60 minutes (Table 4). Based on this result, the applicant explained that infusion time is unlikely to affect the pharmacokinetics of NIVO.

Table 4. Pharmacokinetic parameters of NIVO

Dosage regimen	Infusion time (minutes)	C_{max} (μg/mL)	$C_{max,ss}$ (μg/mL)	Dosage regimen	Infusion time (minutes)	C_{max} (μg/mL)	$C_{max,ss}$ (μg/mL)
3 mg/kg every 2 weeks	30	51.1 (21.3)	113 (26.4)	240 mg every 2 weeks	30	72.6 (21.9)	161 (27.5)
	60	50.9 (21.3)	113 (26.4)		60	72.3 (21.8)	160 (27.5)

Geometric mean (coefficient of variation [%])

6.1.3 Relationship between exposure and efficacy or safety

6.1.3.1 Relationship between exposure and efficacy

Based on the data collected from patients receiving NIVO for malignant melanoma, SQ-NSCLC, NSQ-NSCLC, or RCC 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,[8] an exposure-response model describing the relationship between exposure to NIVO (C_{avgd28}) and overall survival (OS) or response rate was established, and the following assessments were performed.

- Data from Japanese clinical studies in which NIVO was administered at a dose of 3 mg/kg every 2 weeks to patients with malignant melanoma, SQ-NSCLC, or NSQ-NSCLC (Studies 05, 06, and 08) were added to the model to compare OS and response rates between the dosage regimens of 3 mg/kg every 2 weeks and 240 mg every 2 weeks in Japanese patients. The results predicted no clear difference in OS or response rate between 3 mg/kg every 2 weeks and 240 mg every 2 weeks.

[8] Data from foreign clinical studies (Studies 03, 010, 017, 037, 057, 063, and 066) and a global clinical study (Study 025) were used.

- In a global clinical study in patients with RCC (Study 025), the OS and response rate observed when NIVO was administered at a dose of 3 mg/kg every 2 weeks or 240 mg every 2 weeks were assessed. The assessment predicted no clear difference in OS or response rate between 3 mg/kg every 2 weeks and 240 mg every 2 weeks. The hazard ratio (95% confidence interval [CI]) of OS and the odds ratio [95% CI] of the response rate for the overall study population vs. the Japanese subpopulation were 0.999 [0.900, 1.11] and 0.938 [0.776, 1.13], respectively. These results indicated no clear difference in OS or response rate between the overall study population and the Japanese subpopulation, suggesting that the results predicted from the overall study population of Study 025 can be extrapolated to Japanese patients.

6.1.3.2 Relationship between exposure and safety

The following assessments were performed regarding the relationship between exposure and safety.

- Based on the data collected from patients with malignant melanoma, SQ-NSCLC, NSQ-NSCLC, RCC, SCCHN, or cHL who received NIVO at a dose of 1 to 10 mg/kg intravenously every 2 weeks or at a dose of 0.3 to 10 mg/kg intravenously every 3 weeks,[9] an exposure-response model describing the relationship between exposure to NIVO (C_{avgd28}) and the incidence of adverse events leading to drug discontinuation, adverse events leading to death, Grade ≥3 adverse events, or Grade ≥2 immune-mediated adverse events was established. Using the resulting exposure-response model and the exposure to NIVO (C_{avgd28}) in Japanese patients,[10] the incidences of the above adverse events were assessed in Japanese patients with malignant melanoma, SQ-NSCLC, NSQ-NSCLC, RCC, SCCHN, or cHL who received NIVO at a dose of 3 mg/kg intravenously every 2 weeks or 240 mg intravenously every 2 weeks. The assessments predicted no clear differences in the incidences of these adverse events between the dosage regimens of 3 mg/kg every 2 weeks and 240 mg every 2 weeks in the Japanese patients.
- Based on the data from patients with RCC who received NIVO at a dose of 0.3 to 10 mg/kg intravenously every 2 or 3 weeks,[11] an exposure-response model describing the relationship between exposure to NIVO (daily C_{avg}) and the incidence of adverse events leading to drug discontinuation, adverse events leading to death, or Grade ≥2 immune-mediated adverse events was established. Using the resulting exposure-response model, the incidences of the above adverse events in Japanese patients with RCC who were enrolled in a global clinical study (Study 214) and received NIVO at a dose of 3 mg/kg or 240 mg intravenously, in combination with IPI 1 mg/kg every 3 weeks were assessed. The assessments predicted no clear differences in the incidences of these adverse events between the dosage regimens in the Japanese patients.
- Based on the data from patients with malignant melanoma who received NIVO at a dose of 0.3 to 3 mg/kg intravenously every 2 or 3 weeks,[12] an exposure-response model describing the relationship between exposure to NIVO (C_{avg} after the first dose) and the incidence of adverse events leading to

[9] Data from foreign clinical studies (Studies 03, 010, 017, 032, 037, 039, 057, 063, 066, and 205) and global clinical studies (Studies 025, 141, and 275) were used.
[10] Data from Japanese patients enrolled in Japanese clinical studies (Studies 01, 02, 05, 06, and 08) and global clinical studies (Studies 025, 026, 141, and 275) were used for estimation.
[11] Data from foreign clinical studies (Studies 03, 09, and 010) and global clinical studies (Studies 025 and 214) were used. Study 09 was excluded from the assessment of immune-mediated adverse events, because no immune mediated adverse events were reported.
[12] Data from foreign clinical studies (Studies 04, 037, 066, 067, and 069) were used.

drug discontinuation or adverse events leading to death was established. To the resulting exposure-response model, the data from a Japanese clinical study (Study 17) were added to assess the incidences of these adverse events in Japanese patients who received NIVO at a dose of 1 mg/kg or 80 mg intravenously, in combination with IPI 3 mg/kg every 3 weeks. The assessments predicted no clear differences in the incidences of these adverse events between the dosage regimens in the Japanese patients.

The applicant's explanation:

The use of the exposure-response models presented above is appropriate for predicting (a) the efficacy and safety of NIVO administered as a monotherapy at a dose of 3 mg/kg or 240 mg every 2 weeks, (b) the safety of NIVO administered at a dose of 3 mg/kg or 240 mg in combination with IPI 1 mg/kg every 3 weeks, and (c) the safety of NIVO administered at a dose of 1 mg/kg or 80 mg in combination with IPI 3 mg/kg every 3 weeks, in view of the following findings (a) to (c), respectively.

(a) In Japanese clinical studies in patients with malignant melanoma, SQ-NSCLC, or NSQ-NSCLC (Studies 05, 06, and 08), and a global clinical study in patients with RCC (Study 025), the predicted OS and response rate with NIVO 3 mg/kg every 2 weeks were generally consistent with the observed values. The predicted incidences of adverse events leading to drug discontinuation, adverse events leading to death, Grade ≥3 adverse events, and Grade ≥2 immune-mediated adverse events were also generally consistent with the observed values.

(b) In a global clinical study in patients with RCC (Study 214), the predicted incidence of Grade ≥2 immune-mediated adverse events with NIVO 3 mg/kg in combination with IPI 1 mg/kg every 3 weeks was generally consistent with the observed value in the Japanese subpopulation. The predicted incidences of adverse events leading to drug discontinuation and adverse events leading to deaths were generally consistent with the observed values in the overall study population, but tended to be lower than the observed values in the Japanese subpopulation. However, as the incorporation of race as a covariate into the exposure-response model did not improve the model, race is less likely to clearly affect the exposure-response relationship.

(c) In a Japanese clinical study in patients with malignant melanoma (Study 17), the incidences of adverse events leading to drug discontinuation and adverse events leading to death with NIVO 1 mg/kg in combination with IPI 3 mg/kg every 3 weeks were generally consistent with the observed values.

6.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the applicant's explanation about the clinical pharmacology of NIVO is acceptable.

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

7.1 Clinical efficacy and safety in the treatment of malignant pleural mesothelioma, and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results from a Japanese phase II study (Table 5).

Table 5. Clinical study on the efficacy and safety of NIVO/IPI therapy

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation data	Japan	Study 41	II	Chemotherapy-treated patients with unresectable, advanced or recurrent malignant pleural mesothelioma	34	Intravenous NIVO 240 mg every 2 weeks	Efficacy Safety

A summary of the clinical study is presented below. Common adverse events other than deaths reported in the study are detailed in Section "7.6 Adverse events reported in clinical studies." Clinical pharmacokinetic data are detailed in Section "6.1 Clinical pharmacology."

7.1.1 Evaluation data

7.1.1.1 Japanese clinical study

7.1.1.1.1 Japanese phase II study (CTD 5.3.5.2-1, Study 41, ongoing since [redacted] 20[redacted] [data cutoff date, April 21, 2017])

An open-label, uncontrolled study was conducted at 15 sites in Japan to evaluate the efficacy and safety of NIVO in chemotherapy-treated patients[2] with unresectable, advanced or recurrent malignant pleural mesothelioma (target sample size: 32 subjects).

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

A total of 34 enrolled patients were treated with NIVO, and included in both the efficacy analysis set and the safety analysis set.

Table 6 shows the response rate, as assessed centrally using modified RECIST,[13] which was the primary endpoint. The lower bound of the 95% CI for the response rate exceeded the predefined threshold response rate (5.0%).[14]

Table 6. Best overall response and response rate
(Modified RECIST; efficacy analysis set; central assessment [data cutoff date, April 21, 2017])

Best overall responses	n (%)
	N = 34
CR	0
PR	10 (29.4)
SD	13 (38.2)
PD	9 (26.5)
NE	2 (5.9)
Response (CR + PR) (Response rate [95%CI*])	10 (29.4 [16.8, 46.2])

* Wilson method

There were no deaths during the treatment period or within 28 days of the last dose of NIVO.

[13] For a pleural lesion, the longest tumor diameter (thickness) perpendicular to the chest wall or mediastinum was measured as the longest diameter.
[14] The clinically significant response rate in the target patient population of Study 41 was predefined at 5.0%.

7.1.R Outline of the review conducted by PMDA on the treatment of malignant pleural mesothelioma

7.1.R.1 Efficacy

As a result of its review described below, PMDA concluded that a certain level of efficacy of NIVO monotherapy was demonstrated in chemotherapy-treated patients with unresectable, advanced or recurrent malignant pleural mesothelioma.

7.1.R.1.1 Efficacy endpoints and evaluation results

The applicant's explanation about the primary endpoint in Study 41 and the efficacy of NIVO in the treatment of chemotherapy-treated patients with unresectable, advanced or recurrent malignant pleural mesothelioma:

Response rate was selected as the primary endpoint since achieving response that leads to the improvement of clinical symptoms associated with disease progression is clinically significant in the target patient population of Study 41.

In Study 41, the response rate [95% CI], the primary endpoint as assessed centrally using modified RECIST was 29.4 [16.8, 46.2]) and the lower bound of the 95% CI exceeded the predefined threshold response rate [see Section 7.1.1.1.1]. Based on this result, and in view of the following points, the efficacy of NIVO can be expected in the treatment of chemotherapy-treated patients with unresectable, advanced or recurrent malignant pleural mesothelioma.

- The prognosis of chemotherapy-treated patients with unresectable, advanced or recurrent malignant pleural mesothelioma is poor and there is no established standard therapy that has been demonstrated to prolong OS.
- The response rate (the primary endpoint) observed in Study 41 is clinically significant.

PMDA's view:

As the relationship between OS, the true endpoint to assess the efficacy of anti-cancer treatments, and response rate is unclear in patients with unresectable, advanced or recurrent malignant pleural mesothelioma, it is difficult to assess the life-prolongation effect of NIVO in such a patient population based on the response rate, which was the primary endpoint in Study 41. Nevertheless, the applicant's explanation about the efficacy of NIVO is understandable. PMDA therefore concluded that the response rate and other results of Study 41 had demonstrated a certain level of efficacy of NIVO in the treatment of chemotherapy-treated patients with unresectable, advanced or recurrent malignant pleural mesothelioma.

7.1.R.2 Safety [for adverse events, see Section "7.6 Adverse events reported in clinical studies"]

PMDA's view:

As a result of the following review, PMDA concluded that special attention should be paid to the following adverse events when NIVO is administered to chemotherapy-treated patients with

unresectable, advanced or recurrent malignant pleural mesothelioma. These events[15] were identified as requiring attention at the regulatory reviews for the approved indications of NIVO. Thus it is necessary to continue to carefully watch for the possible occurrence of these events.

Although attention should be paid to the above events, NIVO is tolerable in patients with malignant pleural mesothelioma, provided that physicians with sufficient knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions, including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions, and drug interruption of NIVO.

7.1.R.2.1 Safety profile

The applicant's explanation about the safety profile of NIVO based on the safety data from Study 41:
Table 7 shows a safety summary for Study 41.

Table 7. Safety summary (Study 41)

	n (%)
	N = 34
All adverse events	32 (94.1)
Grade ≥3 adverse events	13 (38.2)
Adverse events leading to death	0
Serious adverse events	11 (32.4)
Adverse events leading to drug discontinuation	2 (5.9)
Adverse events leading to drug interruption	11 (32.4)

The adverse events of any grade reported with a ≥5% incidence were viral upper respiratory tract infection (8 patients [23.5%]), pyrexia (6 patients [17.6%]), diarrhoea and stomatitis (5 patients [14.7%] each), nausea, lipase increased, weight decreased, arthralgia, and rash (4 patients [11.8%] each), malaise, decreased appetite, and amylase increased (3 patients [8.8%] each), and hypothyroidism, vomiting, fatigue, lymphocyte count decreased, hypophosphataemia, myalgia, dyspnoea, and rash maculo-papular (2 patients [5.9%] each). The Grade ≥3 adverse events reported with a ≥5% incidence were diarrhoea and lipase increased (2 patients [5.9%] each). The adverse events leading to drug interruption with a ≥5% incidence were diarrhoea (3 patients [8.8%]) and lipase increased (2 patients [5.9%]). There were neither serious adverse events nor adverse events leading to drug discontinuation, with a ≥5% incidence.

The applicant's explanation about the differences in the safety profile of NIVO between patients receiving NIVO for malignant pleural mesothelioma and those for the approved indications:
Table 8 shows comparisons of the incidences of adverse events in the clinical studies described in (a) to (h) below.
(a) A Japanese phase II study in patients with malignant pleural mesothelioma (Study 41)

[15] ILD; hepatic function disorder; abnormal thyroid function; infusion reaction; skin disorder; colitis, severe diarrhoea; myasthenia gravis, myocarditis, rhabdomyolysis, myositis; neurological disorder; renal disorder; venous thrombosis and embolism; adrenal disorder; encephalitis; type 1 diabetes mellitus; immune thrombocytopenic purpura; and cardiac disorder (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated August 22, 2017," etc.)

(b) The NIVO group of a global phase III study in patients with resected malignant melanoma (Study 238)
(c) The NIVO groups of foreign phase III studies in patients with unresectable malignant melanoma (Studies 066 and 037)
(d) The NIVO groups of foreign phase III studies in patients with NSCLC (Studies 017 and 057)
(e) The NIVO group of a global phase III study in patients with RCC (Study 025)
(f) A Japanese phase II study (Study 15) and a foreign phase II study (Study 205) in patients with cHL
(g) The NIVO group of a global phase III study in patients with head and neck cancer (Study 141)
(h) The NIVO group of a global phase III study in patients with gastric cancer (Study 12)

Table 8. Safety summary in patients with malignant pleural mesothelioma, malignant melanoma, NSCLC, RCC, cHL, head and neck cancer, or gastric cancer*

	n (%)							
	Malignant pleural mesotheliom a	Resected malignant melanoma	Unresectabl e malignant melanoma	NSCLC	RCC	cHL	Head and neck cancer	Gastric cancer
	N = 34	N = 452	N = 474	N = 418	N = 406	N = 260	N = 236	N = 330
All adverse events	32 (94.1)	438 (96.9)	457 (96.4)	407 (97.4)	397 (97.8)	255 (98.1)	229 (97.0)	300 (90.9)
Grade ≥3 adverse events	13 (38.2)	115 (25.4)	218 (46.0)	222 (53.1)	230 (56.7)	83 (31.9)	143 (60.6)	153 (46.4)
Adverse events leading to death	0	1 (0.2)	44 (9.3)	65 (15.6)	23 (5.7)	5 (1.9)	54 (22.9)	35 (10.6)
Serious adverse events	11 (32.4)	79 (17.5)	206 (43.5)	195 (46.7)	194 (47.8)	55 (21.2)	127 (53.8)	131 (39.7)
Adverse events leading to drug discontinuation	2 (5.9)	44 (9.7)	48 (10.1)	62 (14.8)	72 (17.7)	13 (5.0)	51 (21.6)	23 (7.0)
Adverse events leading to drug interruption	11 (32.4)	128 (28.3)	146 (30.8)	118 (28.2)	177 (43.6)	85 (32.7)	56 (23.7)	63 (19.1)

*, Patients received NIVO at an intravenous dose of 240 mg every 2 weeks for malignant pleural mesothelioma, or at an intravenous dose of 3 mg/kg every 2 weeks for other indications.

The Grade ≥3 adverse events with a ≥3% higher incidence in patients with malignant pleural mesothelioma than in those with any other type of cancer was diarrhoea (5.9% in the malignant pleural mesothelioma group, 1.5% in the unresectable malignant melanoma group, 1.2% in the NSCLC group, 1.2% in the RCC group, 0.4% in the cHL group, 0.8% in the head and neck cancer group, and 1.2% in the gastric cancer group). The adverse events leading to drug interruption with a ≥3% higher incidence in patients with malignant pleural mesothelioma than in those with any other type of cancer were diarrhoea (8.8%, 2.1%, 2.6%, 3.7%, 2.7%, 0.4%, 1.2%) and lipase increased (5.9%, 1.1%, 0%, 0.2%, 1.9%, 0.4%, 0%). There were no adverse events of any grade with a ≥10% higher incidence, or serious adverse events or adverse events leading to drug discontinuation with a ≥3% higher incidence in patients with malignant pleural mesothelioma than in those with any other type of cancer.

There were no adverse events that did not occur in patients treated with NIVO for the approved indications, but were newly reported in Study 41.

Based on the above, there are some adverse events that were more frequently reported in patients receiving NIVO for malignant pleural mesothelioma than in those for the approved indications. However, no clear differences were noted in the incidence of serious adverse events and other categories of adverse events between these patient populations. Therefore, the safety of NIVO does not differ between the treatment of malignant pleural mesothelioma and the approved indications.

PMDA's view:
Some adverse events were more frequently reported in patients receiving NIVO for malignant pleural mesothelioma in Study 41 than in those for the approved indications. However, all of these adverse events were known adverse events of NIVO. PMDA therefore concluded that NIVO therapy is also tolerable in patients with malignant pleural mesothelioma, provided that physicians with sufficient knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions, including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions, and drug interruption of NIVO.

7.1.R.3 Clinical positioning and indications

The proposed indication of NIVO in the present application for malignant pleural mesothelioma was "treatment of unresectable, advanced or metastatic malignant pleural mesothelioma" and the following precautionary statements were proposed for the "Precautions for Indications" section of the package insert.

- The efficacy and safety of NIVO have not been established in chemotherapy-naïve patients.
- The efficacy and safety of NIVO in adjuvant chemotherapy have not been established.
- Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, and a thorough understanding of the efficacy and safety of NIVO.

As a result of its review, described in Sections "7.1.R.1 Efficacy" and "7.1.R.2 Safety" and the following subsections, PMDA concluded that the indication of NIVO for malignant pleural mesothelioma should be "treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy," provided that the following precautionary advice is given in the "Precautions for Indications" section.

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

7.1.R.3.1 Intended population of NIVO

Among major foreign and Japanese clinical practice guidelines and standard textbooks on oncology, the following guidelines include a statement about NIVO therapy for malignant pleural mesothelioma:

- NCCN guidelines (malignant pleural mesothelioma) (version 2.2018)
  NIVO monotherapy is recommended as a second-line or subsequent therapy option for malignant pleural mesothelioma.

PMDA asked the applicant to explain the clinical positioning and indication of NIVO in the treatment of unresectable, advanced or recurrent malignant pleural mesothelioma.

The applicant's explanation:

Based on the results of Study 41, NIVO can be positioned as a therapeutic option for unresectable, advanced or recurrent malignant pleural mesothelioma that has become resistant or intolerant to platinum-based and other chemotherapies. Therefore, the proposed indication was "treatment of unresectable, advanced or metastatic malignant pleural mesothelioma" and a precautionary statement to the effect that the efficacy and safety of NIVO have not been established in the treatment of chemotherapy-naïve patients with unresectable, advanced or recurrent malignant pleural mesothelioma was proposed for the "Precautions for Indications" section. A global phase III study (Study CA209743)[16] is ongoing as a confirmatory study of NIVO therapy for malignant pleural mesothelioma.

PMDA's view:

PMDA accepted the applicant's explanation in general. However, as NIVO will be administered to patients requiring second-line or subsequent treatments, which corresponds to the target patient population of Study 41, the intended population of NIVO should be clearly specified as patients with malignant pleural mesothelioma that has progressed after cancer chemotherapy. For that purpose, the indication of NIVO should be "treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy," and the following precautionary advice should be included in the "Precautions for Indications" section.

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

There is little need to include the precautionary statements (a) and (b) below, proposed by the applicant for the "Precautions for Indications" section, because (a) adjuvant therapy for malignant pleural mesothelioma is not recommended as a standard treatment in either foreign or Japanese clinical practice guidelines, and because (b) it does not include information for which there is a particular necessity for caution.

(a) The efficacy and safety of NIVO in adjuvant chemotherapy have not been established.
(b) Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, and a thorough understanding of the efficacy and safety of NIVO.

7.1.R.3.2 Efficacy and safety of NIVO by PD-L1 expression status, and the intended population

NIVO is an antibody against human PD-1. PMDA therefore asked the applicant to explain the efficacy and safety of NIVO by PD-L1 expression status,[17] and to identify the intended population of NIVO.

The applicant's explanation:

[16] An open-label, randomized, comparative study to compare the efficacy and safety of NIVO/IPI therapy with those of platinum-based anti-neoplastic therapy in combination with PEM in chemotherapy-naïve patients with unresectable, advanced or recurrent malignant pleural mesothelioma (target sample size, 600) (Patient enrollment will end in [redacted] of 20[redacted] and the results of the primary analyses of the co-primary endpoints, PFS and OS, will be obtained in 20[redacted] and 20[redacted], respectively).

[17] Percentage of cells expressing PD-L1 in the tumor tissues

In Study 41, PD-L1 expression was assessed using the Dako-developed "PD-L1 immunohistochemistry (IHC) 28-8 pharmDx" assay. The (a) efficacy and (b) safety of NIVO by PD-L1 expression status (cutoff values: 1%, 5%, and 10%) are summarized below.

(a) Efficacy:

Table 9 shows the response rates by PD-L1 expression status (cutoff values; 1%, 5%, and 10%) in patients with evaluable PD-L1 data (94.1%, 32 of 34 patients) (data cutoff date, April 21, 2017).

As one or more responders were present in both the PD-L1-positive and -negative populations at all of the cutoff values, the efficacy of NIVO can be expected, regardless of PD-L1 expression status.

Table 9. Efficacy by PD-L1 expression status (Study 41)

Percentage of cells with PD-L1	Responders/N	Response rate [95%CI*](%)
<1%	1/12	8.3 [1.5, 35.4]
≥1%	8/20	40.0 [21.9, 61.3]
<5%	3/19	15.8 [5.5, 37.6]
≥5%	6/13	46.2 [23.2, 70.9]
<10%	5/22	22.7 [10.1, 43.4]
≥10%	4/10	40.0 [16.8, 68.7]

* Wilson method

(b) Safety:

Table 10 shows the safety results in Study 41 by PD-L1 expression status.

Although the results should be interpreted carefully due to the small number of patients, the safety of NIVO did not differ significantly between the PD-L1-positive and -negative populations at any of the cutoff values. Therefore, NIVO is considered to be tolerable, regardless of PD-L1 expression status.

Table 10. Safety summary by PD-L1 expression status (Study 41)

	n/N (%)	
PD-L1 expression rate	<1%	≥1%
All adverse events	11/12 (91.7)	19/20 (95.0)
Grade ≥3 adverse events	4/12 (33.3)	8/20 (40.0)
Serious adverse events	3/12 (25.0)	8/20 (40.0)
PD-L1 expression rate	<5%	≥5%
All adverse events	17/19 (89.5)	13/13 (100)
Grade ≥3 adverse events	7/19 (36.8)	5/13 (38.5)
Serious adverse events	5/19 (26.3)	6/13 (46.2)
PD-L1 expression rate	<10%	≥10%
All adverse events	20/22 (90.9)	10/10 (100)
Grade ≥3 adverse events	7/22 (31.8)	5/10 (50.0)
Serious adverse events	6/22 (27.3)	5/10 (50.0)

Based on the results of reviews on the above (a) and (b), NIVO can be recommended as a therapeutic option for patients with unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy, regardless of PD-L1 expression status.

PMDA's view:

PMDA accepted the applicant's explanation in general. However, the applicant should continue to collect information on possible predictors of response to NIVO, other than PD-L1 expression, and appropriately provide any new findings to healthcare professionals.

7.2 Clinical efficacy and safety in the adjuvant therapy of malignant melanoma, and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results from a global phase III study (Table 11).

Table 11. Summary of a clinical study on the efficacy and safety of NIVO

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation data	Global	238*	III	Patients with completely resected stage IIIb/c or IV malignant melanoma	906 (a) 453 (b) 453	(a) Intravenous NIVO 240 mg every 2 weeks (b) Intravenous IPI 10 mg/kg every 3 weeks for 4 doses, then every 12 weeks at Week 24 onward	Efficacy Safety

*, Study 238 was a double-blind study in which the respective placebos for NIVO and IPI were administered according to the dosing schedule for the active drugs, to maintain the blind.

A summary of the clinical study is presented below. Common adverse events other than deaths reported in the study are detailed in Section "7.6 Adverse events reported in clinical studies."

7.2.1 Evaluation Data

7.2.1.1 Global clinical study

7.2.1.1.1 Global phase III study (CTD 5.3.5.1-1, Study 238, ongoing since March 2015 [data cutoff date, June 12, 2017])

A double-blind, randomized, comparative study was conducted at 130 sites in 25 countries/regions including Japan, to compare the efficacy and safety of NIVO with those of IPI in patients with resected stage[3] IIIb/c or IV malignant melanoma[4] (target sample size, 800 subjects).

Patients received NIVO 3 mg/kg intravenously every 2 weeks, or IPI 10 mg/kg intravenously every 3 weeks for 4 doses then every 12 weeks starting at Week 24. The treatment was continued for a maximum duration of 1 year, until either recurrence occurred or a withdrawal criterion was met.

All 906 enrolled and randomized patients (453 in the NIVO group and 453 in the IPI group) were included in the intention-to-treat (ITT) population and used for the efficacy analyses. Of these 906 patients, 1 did not receive the study drug, and the remaining 905 (452 in the NIVO group and 453 in the IPI group) were included in the safety analysis set.

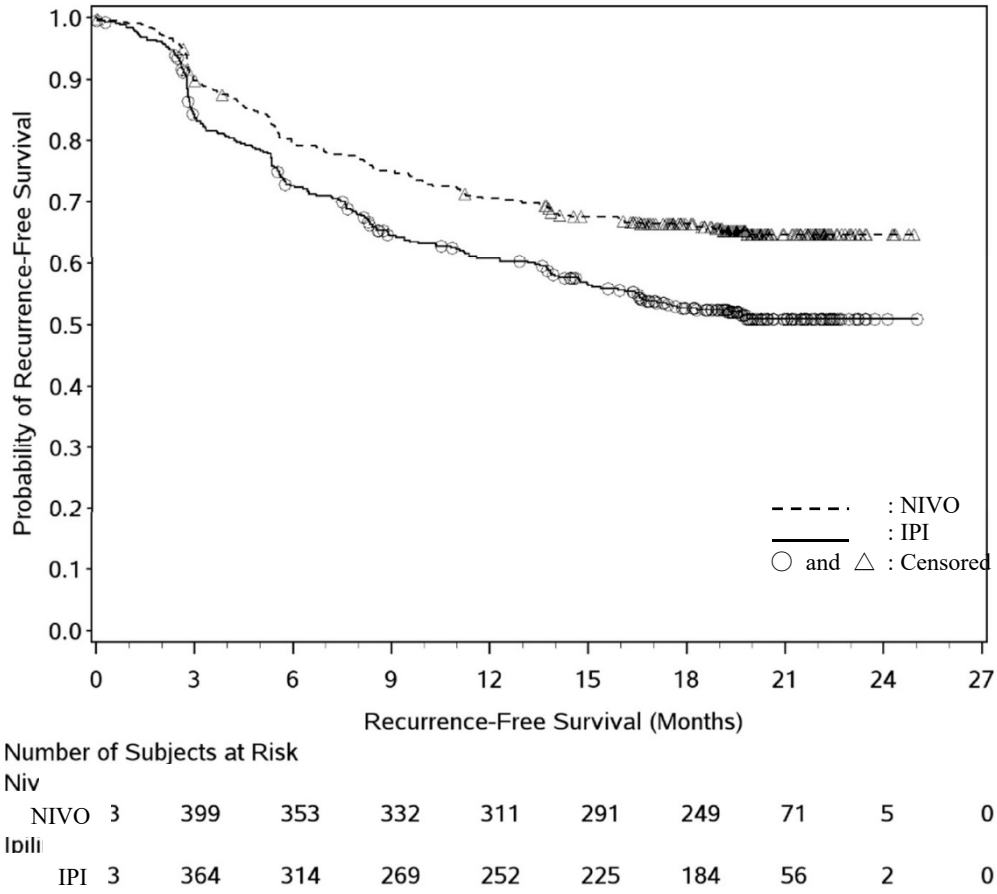
The primary endpoint was recurrence-free survival (RFS),[18] as assessed by the investigator. The primary analysis was originally planned to be conducted when 507 RFS events had occurred. However, [redacted], the study protocol was amended to perform the primary analysis when 450 events had occurred, and an interim analysis to allow early termination for good response when approximately 350 events had occurred (Protocol version [redacted] [dated [redacted] 20[redacted]]). A Lan-DeMets α spending function of the O'Brien-Fleming type was used to adjust the probability of a type I error associated with the interim analysis.

The interim efficacy analysis was performed (data cutoff date, June 12, 2017) when 360 RFS events had occurred. The results of the interim RFS analysis (Table 12) and Kaplan-Meier curves for RFS (Figure 1) are shown below.

Table 12. Interim RFS analysis (investigator assessment, ITT population [data cutoff, June 12, 2017])

	NIVO	IPI
N	453	453
Number of events (%)	154 (34.0)	206 (45.5)
Median [95% CI] (months)	— [—,—]	— [16.56, —]
Hazard ratio [97.56% CI][*1]	0.65 [0.51, 0.83]	
P-value (2-sided)[*2]	<0.0001	

—, Not evaluable; *1, Cox regression stratified by PD-L1 expression status[17] (≥5%, <5%, or unknown) and disease stage (IIIb/c, IV [M1a/M1b], IV [M1c]); *2, Log-rank test stratified by PD-L1 expression status[17] (≥5%, <5%, or unknown) and disease stage (IIIb/c, IV [M1a/M1b], IV [M1c]) with a 2-sided significance level of 0.0244



[18] Defined as the time between the date of randomization and the date of (a) first recurrence (local recurrence, regional lymph node metastasis, or distant metastasis), (b) new primary melanoma, or (c) death, whichever occurs first

Figure 1. Kaplan-Meier curves for interim RFS analysis
(investigator assessment, ITT population [data cutoff date, June 12, 2017])

There were no deaths during the treatment period or within 30 days after the last dose.

7.2.R Outline of the review conducted by PMDA for the adjuvant therapy of malignant melanoma

7.2.R.1 Efficacy

PMDA evaluated the efficacy of NIVO in Japanese patients, concerning the consistency between the overall study population and the Japanese subpopulation of Study 238, according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012), and concluded that the efficacy of NIVO had been demonstrated in patients with resected stage IIIb/c or IV malignant melanoma, based on the discussion below.

7.2.R.1.1 Selection of control group

The applicant's rationale for the selection of IPI as the comparator in Study 238:
When Study 238 was planned, there were no established standard treatments for the target patient population of the study. However, IPI was selected as the comparator for Study 238, based on a report that demonstrated the superiority of IPI to placebo (*J Clin Oncol.* 2014;32:18_suppl, LBA9008).

PMDA accepted the applicant's explanation.

7.2.R.1.2 Efficacy endpoints

The applicant's explanation about the appropriateness of selecting RFS as the primary endpoint in Study 238:
The prolongation of RFS,[18] as defined in Study 238, is clinically significant in patients with malignant melanoma who have undergone complete resection, because delayed recurrence can lead to the long-term maintenance of patient physical functions and quality of life. Therefore, the selection of RFS as the primary endpoint in Study 238 is appropriate.

PMDA's view:
As patients with malignant melanoma who have undergone a complete resection receive postoperative treatments to prolong their survival, OS would be the appropriate primary endpoint for Study 238. However, the applicant's explanation that the prolongation of RFS has a certain level of clinical significance in such patients is understandable. In view of the applicant's explanation and for other reasons, PMDA concluded that evaluating the efficacy of NIVO based on RFS data is acceptable.

7.2.R.1.3 Efficacy evaluation results

In Study 238, NIVO was superior to IPI in the primary endpoint, RFS as assessed by the investigator [see Section 7.2.1.1.1]. The results of the interim RFS analysis (Table 13) and Kaplan-Meier curves

(Figure 2) for RFS, as assessed by the investigator in the Japanese subpopulation of Study 238, are shown below.

Table 13. Interim RFS analysis in the Japanese subpopulation (investigator assessment, ITT population, data cutoff date, June 12, 2017)

	NIVO	IPI
N	18	10
Number of events (%)	9 (50.0)	7 (70.0)
Median [95% CI] (months)	19.84 [2.83, —]	10.10 [1.25, —]
Hazard ratio [97.56% CI][*1]	0.66 [0.19, 2.24]	
P-value (2-sided)[*2]	0.4390	

—, Not evaluable; *1, Cox regression stratified by PD-L1 expression status[17] (≥5%, <5%, or unknown) and disease stage (IIIb/c, IV [M1a/M1b], IV [M1c]); *2, Log-rank test stratified by PD-L1 expression status[17] (≥5%, <5%, or unknown) and disease stage (IIIb/c, IV [M1a/M1b], IV [M1c])

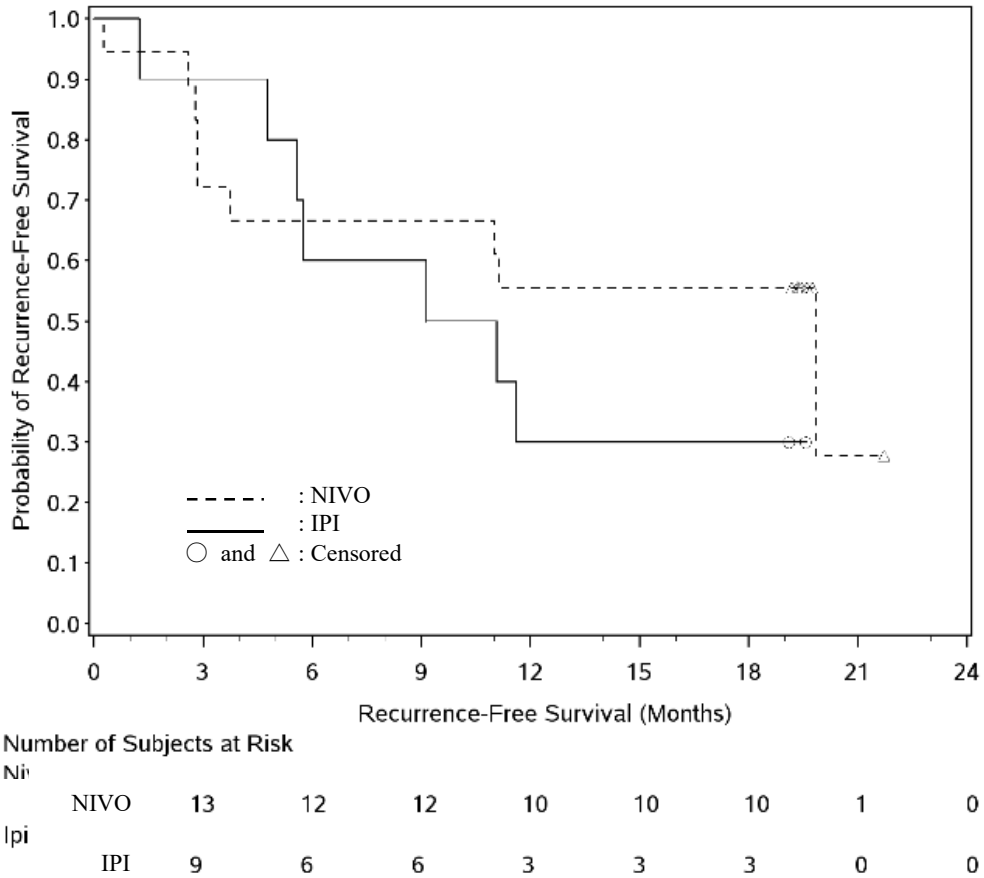


Figure 2. Kaplan-Meier curves for the interim RFS analysis in the Japanese subpopulation (investigator assessment, ITT population, data cutoff date, June 12, 2017)

PMDA's view:

Considering that NIVO was demonstrated to prolong OS in a foreign double-blind, randomized, phase III study in patients with unresectable malignant melanoma (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated January 22, 2016"), PMDA concluded that the efficacy of NIVO has been demonstrated in patients with resected stage IIIb/c or IV malignant melanoma, in view of the following results.

- In Study 238, NIVO was superior to IPI in the primary endpoint, RFS as assessed by the investigator, and the observed RFS prolongation was clinically significant.
- Although the sample size of the Japanese subpopulation in Study 238 and the number of events occurring in that subpopulation were limited and insufficient to appropriately evaluate the efficacy of NIVO in Japanese patients, based only on the results from that subpopulation, the RFS in the Japanese subpopulation did not tend to clearly differ from that in the overall study population.

7.2.R.2 Safety [for adverse events, see "7.6 Adverse events reported in clinical studies"]

PMDA's view:

Based on the review described in the following subsections, special attention should be also paid to the events[15] that were identified as requiring attention at the regulatory reviews for the previously approved indications, when administrating NIVO to patients with resected stage IIIb/c or IV malignant melanoma.

PMDA's view:

Although attention should be paid to the above events, NIVO is tolerable in patients with resected stage IIIb/c or IV malignant melanoma, provided that physicians with sufficient knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions, including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions, and drug interruption of NIVO.

7.2.R.2.1 Safety profile

The applicant's explanation about the safety profile of NIVO based on the safety data from Study 238.

Table 14 shows a safety summary for Study 238.

Table 14. Safety Summary (Study 238)

	n (%)	
	NIVO N = 452	IPI N = 453
All adverse events	438 (96.9)	446 (98.5)
Grade ≥3 adverse events	115 (25.4)	250 (55.2)
Adverse events leading to death	1 (0.2)	1 (0.2)
Serious adverse events	79 (17.5)	183 (40.4)
Adverse events leading to drug discontinuation	44 (9.7)	193 (42.6)
Adverse events leading to drug interruption	128 (28.3)	222 (49.0)

The adverse events of any grade reported with a ≥5% higher incidence in the NIVO group than in the IPI group were arthralgia (19.2% [87 of 452 patients] in the NIVO group, 13.0% [59 of 453 patients] in the IPI group), myalgia (13.9% [63 of 452 patients], 6.8% [31 of 453 patients]), and viral upper respiratory tract infection (11.5% [52 of 452 patients], 5.5% [25 of 453 patients]). No Grade ≥3 adverse events, serious adverse events, or adverse events leading to drug discontinuation or drug interruption were reported with a ≥2% higher incidence in the NIVO group than in the IPI group.

The applicant's explanation about the differences in the safety profile of NIVO between patients treated for resected malignant melanoma and those treated for the previously approved indications:

Table 8 shows the results that compare the incidences of adverse events between patients in the NIVO group of Study 238 and patients who received NIVO for the previously approved indications [see Section 7.1.R.2.1].

The adverse event of any grade reported with a ≥10% higher incidence in patients with resected malignant melanoma than in any of the other patient populations was diarrhoea (resected malignant melanoma, 36.9%; unresectable malignant melanoma, 26.4%; NSCLC, 15.6%; RCC, 23.6%; cHL, 25.8%; head and neck cancer, 14.8%; gastric cancer, 17.6%). No Grade ≥3 adverse events, serious adverse events, or adverse events leading to drug discontinuation or drug interruption were reported with a ≥3% higher incidence in patients with resected malignant melanoma than in any of the other patient populations.

There were no adverse events that did not occur in patients treated with NIVO for the approved indications, but were newly reported in the NIVO group of Study 238.

The above comparisons revealed no clear differences in the incidences of clinically notable adverse events (e.g., serious adverse events) between patients treated with NIVO for resected malignant melanoma and those treated for the previously approved indications, although some adverse events occurred more frequently in patients with resected malignant melanoma. Thus, the safety of NIVO does not differ between patients treated for resected malignant melanoma and those treated for the previously approved indications.

PMDA's view and conclusion:
Some adverse events occurred more frequently in the NIVO group than in the IPI group in Study 238, and some adverse events developed more frequently in patients treated for resected malignant melanoma than in those treated for the previously approved indications. However, all of these adverse events were known adverse events of NIVO. In consideration of these findings, PMDA concluded that NIVO is also tolerable in patients with resected malignant melanoma, provided that physicians with sufficient knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions, including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions, and drug interruption of NIVO.

7.2.R.2.2 Differences in the safety between Japanese and non-Japanese patients

The applicant's explanation:
Table 15 shows a safety summary in Japanese and non-Japanese patients receiving NIVO in Study 238.

Table 15. Safety summary (Study 238)

	n (%)	
	Japanese N = 18	Non-Japanese N = 434
All adverse events	15 (83.3)	423 (97.5)
Grade ≥3 adverse events	0	115 (26.5)
Adverse events leading to death	0	1 (0.2)
Serious adverse events	1 (5.6)	78 (18.0)
Adverse events leading to drug discontinuation	0	44 (10.1)
Adverse events leading to drug interruption	3 (16.7)	125 (28.8)

The adverse event of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients was viral upper respiratory tract infection (Japanese, 33.3% [6 of 18 patients]; non-Japanese, 10.6% [46 of 434 patients]). The serious adverse event with a ≥3% higher incidence in Japanese patients than in non-Japanese patients was diarrhoea (5.6% [1 of 18 patients], 0.7% [3 of 434 patients]). The adverse events leading to drug interruption with a ≥3% higher incidence in Japanese patients than in non-Japanese patients were hypothyroidism (5.6% [1 of 18 patients], 1.8% [8 of 434 patients]), hyperthyroidism (5.6% [1 of 18 patients], 1.6% [7 of 434 patients]), and rash maculo-papular (5.6% [1 of 18 patients], 0%).

PMDA's view:

Because of the small number of Japanese patients who have received NIVO for the adjuvant therapy of malignant melanoma, there are limitations in comparing the safety of NIVO between Japanese and non-Japanese patients based only on the results of Study 238. Nevertheless, PMDA concluded that NIVO is tolerable in Japanese patients with resected malignant melanoma, as in non-Japanese patients, since all of the adverse events with a higher incidence in Japanese patients than in non-Japanese patients in Study 238 were Grade ≤2 in severity.

7.2.R.3 Clinical positioning and indications

The applicant has proposed to change the indication of NIVO for malignant melanoma from the approved indication of "unresectable malignant melanoma" to "malignant melanoma," and to include the following statement in the "Precautions for Indications" section:

- Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, and a thorough understanding of the efficacy and safety of NIVO.

As a result of its review, described in Sections "7.2.R.1 Efficacy," "7.2.R.2 Safety," and following subsections, PMDA concluded that the proposed indication and the proposed statement for the "Precautions for Indications" section are acceptable.

7.2.R.3.1 Intended population of NIVO

Among major foreign and Japanese clinical practice guidelines and standard textbooks on oncology, NIVO therapy as an adjuvant therapy for malignant melanoma was mentioned as follows:

- NCCN guidelines (malignant melanoma) (version 2.2018)
  NIVO is strongly recommended as one of adjuvant therapies for resected stage IIIb/c or IV malignant melanoma.
- US National Cancer Institute Physician Data Query (NIC PDQ) (dated March 22, 2018)
  The results of Study 238 demonstrated the efficacy of NIVO in the treatment of resected stage IIIb/c or IV malignant melanoma in an adjuvant setting.

PMDA asked the applicant to explain the clinical positioning and indication of NIVO in patients who have undergone a complete resection of malignant melanoma:

The applicant's explanation:
NIVO can be positioned as a therapeutic option of adjuvant therapy for patients with resected stage IIIb/c or IV malignant melanoma, based on the results of Study 238. The use of NIVO in patients with different stages of malignant melanoma from those enrolled in Study 238 is considered as follows:

- NIVO can also be recommended in the treatment of patients with resected stage IIIa malignant melanoma, because its pathology resembles that of stage IIIb/c or IV malignant melanoma, the target disease of Study 238.
- NIVO cannot be recommended in the treatment of patients with stage I or II malignant melanoma, because there are no data demonstrating the clinical usefulness of NIVO in such patients.

Nevertheless, taking into consideration that NIVO is administered by physicians with sufficient knowledge and experience in cancer chemotherapy, the applicant has proposed to change the indication of NIVO for malignant melanoma from the approved indication of "unresectable malignant melanoma" to "malignant melanoma," provided that the disease stages of the patients enrolled in Study 238 are specified in the "Clinical Studies" section of the package insert and the following precautionary advice is given in the "Precautions for Indications" section.

- Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, and a thorough understanding of the efficacy and safety of NIVO.

PMDA accepted the applicant's explanation.

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

NIVO is an antibody against human PD-1. PMDA therefore asked the applicant to explain the efficacy and safety of NIVO by the expression status of PD-L1,[17] a ligand of PD-1, and to identify the intended population of NIVO.

The applicant's explanation:
In Study 238, PD-L1 expression levels were assessed using the Dako-developed IHC 28-8 assay (verified version), to randomize patients with stratification by PD-L1 expression status [see Section 7.2.1.1.1]. The (a) efficacy and (b) safety of NIVO by PD-L1 expression status (cutoff values; 1%, 5%, and 10%) are summarized below.

(a) Efficacy:

The RFS data (Table 16) and Kaplan-Meier curves for RFS (Figure 3) by PD-L1 expression status (cutoff values; 1%, 5%, and 10%) in patients with evaluable PD-L1 data are shown below (NIVO group, 427 of 453 patients [94.3%]; IPI group, 440 of 453 patients [97.1%]) (data cutoff date, June 12, 2017).

As an improvement in RFS in the NIVO group compared with that in the IPI group was found in both PD-L1-positive and -negative populations at all of the cutoff values, the efficacy of NIVO can be expected, regardless of PD-L1 expression status.

Table 16. Efficacy by PD-L1 expression status (NIVO group vs. IPI group in Study 238)

Percentage of cells with PD-L1	Treatment	N	RFS		
			Median [95% CI] (months)	Hazard ratio[*1] [95% CI]	P-value for the interaction[*2]
<1%	NIVO	140	— [12.85, —]	0.82 [0.59, 1.16]	0.0794
	IPI	133	14.95 [9.4, —]		
≥1%	NIVO	287	— [—, —]	0.56 [0.42, 0.73]	
	IPI	307	— [17.54, —]		
<5%	NIVO	275	— [—, —]	0.71 [0.56, 0.91]	0.1765
	IPI	286	15.9 [10.38, -]		
≥5%	NIVO	152	— [—, —]	0.50 [0.32, 0.78]	
	IPI	154	— [—, —]		
<10%	NIVO	321	— [—, —]	0.71 [0.56, 0.89]	0.1429
	IPI	335	17.08 [13.73, —]		
≥10%	NIVO	106	— [—, —]	0.45 [0.26, 0.77]	
	IPI	105	— [19.29, —]		

—, Not evaluable; *1, Cox regression; *2, Cox regression with (a) treatment group, (b) PD-L1 expression status, and (c) interaction between treatment group and PD-L1 expression status as covariates

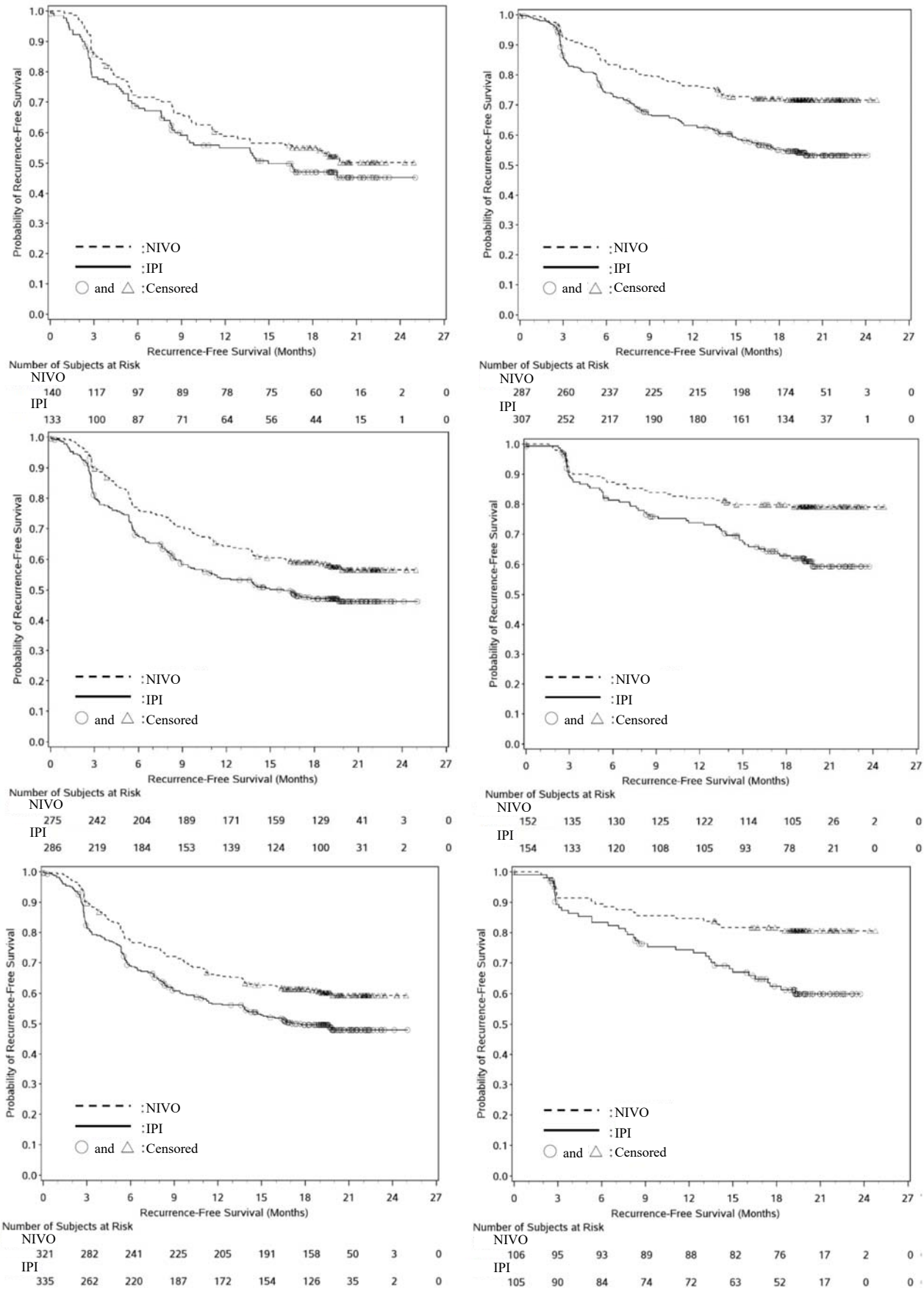


Figure 3. Kaplan-Meier curves of RFS by PD-L1 expression status (data cutoff date, June 12, 2017)
(Upper left, PD-L1 expression <1%; upper right, ≥1%; middle left, <5%; middle right, ≥5%; lower left, <10%; lower right, ≥10%)

(b) Safety:

Table 17 shows the safety data by PD-L1 expression status in Study 238.

Although the results should be interpreted carefully due to the small number of patients, the safety of NIVO did not differ significantly between PD-L1-positive and -negative populations, at any of the cutoff values. Therefore, NIVO is tolerable in patients with resected malignant melanoma, regardless of PD-L1 expression status.

Table 17. Safety summary by PD-L1 expression status (Study 238)

	n/N (%)			
	NIVO	IPI	NIVO	IPI
PD-L1 expression rate	<1%		≥1%	
All adverse events	135/140 (96.4)	129/133 (97.0)	280/286 (97.9)	304/307 (99.0)
Grade ≥3 adverse events	36/140 (25.7)	69/133 (51.9)	75/286 (26.2)	173/307 (56.4)
Serious adverse events	23/140 (16.4)	50/133 (37.6)	55/286 (19.2)	127/307 (41.4)
PD-L1 expression rate	<5%		≥5%	
All adverse events	267/274 (97.4)	280/286 (97.9)	148/152 (97.4)	153/154 (99.4)
Grade ≥3 adverse events	70/274 (25.5)	147/286 (51.4)	41/152 (27.0)	95/154 (61.7)
Serious adverse events	51/274 (18.6)	109/286 (38.1)	27/152 (17.8)	68/154 (44.2)
PD-L1 expression rate	<10%		≥10%	
All adverse events	311/320 (97.2)	329/335 (98.2)	104/106 (98.1)	104/105 (99.0)
Grade ≥3 adverse events	76/320 (23.8)	172/335 (51.3)	35/106 (33.0)	70/105 (66.7)
Serious adverse events	56/320 (17.5)	126/335 (37.6)	22/106 (20.8)	51/105 (48.6)

Based on the above findings (a) and (b), NIVO can be recommended as a therapeutic option for patients with resected stage IIIb/c or IV malignant melanoma, regardless of PD-L1 expression status.

PMDA's view:

The applicant's explanation is acceptable in general. However, the applicant should continue to collect information on possible predictors of response to NIVO, including PD-L1 expression, and appropriately provide any new findings to healthcare professionals.

7.3 Clinical efficacy and safety in the treatment of RCC, and outline of the review conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results from 2 clinical studies in patients with RCC, a global phase III study and a foreign phase I study (Table 18). The applicant also submitted the results of 2 clinical studies, a foreign phase Ib study and a foreign phase II study, as reference data (Table 18).

Table 18. Clinical studies on the efficacy and safety

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation Data	Global	Study 214	III	Chemotherapy-naïve patients with unresectable or metastatic clear cell RCC	1096 (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 weeks off, of each 6-week cycle	Efficacy Safety
	Foreign	Study 016	I	Patients with unresectable or metastatic RCC	153 (a) 100 (b) 33 (c) 20	(a) Arm I: Intravenous NIVO 1 or 3 mg/kg and intravenous IPI 1 or 3 mg/kg[19] every 3 weeks for 4 doses each, followed by intravenous NIVO 3 mg/kg every 2 weeks (b) Arm S: Intravenous NIVO 2 or 5 mg/kg every 3 weeks in combination with oral sunitinib 50 mg once daily[20] (c) Arm P: Intravenous NIVO 2 or 5 mg/kg every 3 weeks in combination with oral pazopanib 800 mg once daily	Safety Tolerability
Reference data	Foreign	Study 09	Ib	Patients with unresectable or metastatic clear cell RCC	91* (a) 67 (b) 24	(a) Intravenous NIVO 0.3, 2, or 10 mg/kg every 3 weeks (b) Intravenous NIVO 10 mg/kg every 3 weeks	Safety Tolerability
		Study MDX-010-11	II	Patients with unresectable or metastatic clear cell RCC	61 (a) 21 (b) 40	(a) A single dose of intravenous IPI 3 mg/kg, followed by intravenous IPI 1 mg/kg every 3 weeks (b) Intravenous IPI 3 mg/kg every 3 weeks	Efficacy Safety

*, Patients who have received prior anti-neoplastic drugs with antiangiogenic effects (a) and those who have no history of such prior treatment (b)

A summary of the clinical studies is presented below. Major adverse events other than deaths reported in these studies are detailed in "7.6 Adverse events reported in clinical studies."

7.3.1 Evaluation Data

7.3.1.1 Global clinical study

7.3.1.1.1 Global phase III study (CTD 5.3.5.1-2.1, Study 214, ongoing since October 2014 [data cutoff date, August 7, 2017])

An open-label, randomized, comparative study was conducted at 174 sites in 28 countries/regions, including Japan, to compare the efficacy and safety of NIVO/IPI therapy with those of sunitinib in chemotherapy-naïve patients with unresectable or metastatic[5] clear cell RCC (target sample size, approximately 1070 subjects).

Patients 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 (NIVO/IPI group), or an oral dose of sunitinib 50 mg once daily for 4 weeks, followed by 2 weeks off, in each 6-week cycle (sunitinib group). The treatment was continued until either disease progression occurred or a withdrawal criterion was met.

[19] A group receiving NIVO 3 mg/kg in combination with IPI 1 mg/kg (Arm I-1), 47 patients; a group receiving NIVO 1 mg/kg in combination with IPI 3 mg/kg (Arm I-3), 47 patients; and a group receiving NIVO 3 mg/kg in combination with IPI 3 mg/kg (Arm IN-3), 6 patients

[20] Sunitinib was administered orally once daily for 4 weeks, followed by a 2-week withdrawal, in each 6-week cycle.

Patients in both groups were allowed to continue the study treatment after the initial disease progression until disease progression occurs again, if they are obtaining clinical benefits without intolerable toxicity.

All 1096 enrolled and randomized patients (550 in the NIVO/IPI group and 546 in the sunitinib group) were included in the efficacy analysis set. Of these 1096 patients, 14 did not receive the study treatment, and the remaining 1082 (547 in the NIVO/IPI group and 535 in the sunitinib group) were included in the safety analysis set.

The coprimary endpoints at the start of the study were OS and progression-free survival (PFS), as assessed by the Independent Radiology Review Committee (IRRC) using RECIST version 1.1 in patients who were categorized as having intermediate or poor risk, as per the International Metastatic RCC Database Consortium (IMDC) criteria.[21] However, [redacted], the protocol was amended to add another primary endpoint, namely the response rate, as assessed by the IRRC using RECIST version 1.1 in the intermediate- or poor-risk patients (Protocol version [redacted], dated [redacted], 20[redacted]). Multiplicity arising from the 3 primary endpoints was adjusted by splitting the significance level, as follows: 0.04 for OS, 0.009 for PFS, and 0.001 for response rate. Primary endpoint(s) showing a statistically significant difference between the treatments groups were also analyzed for the overall study population, including favorable-risk patients.

PFS was originally planned to be analyzed when a total of 591 events had occurred. However, [redacted], the statistical analysis plan was amended to conduct the PFS analysis when 465 events had occurred (Statistical analysis plan version [redacted], dated [redacted], 20[redacted]). For OS, the interim analysis was planned to be performed at the time of the final PFS analysis. An α spending function of the O'Brien-Fleming type was used to adjust the probability of a type I error associated with the interim OS analysis.

The interim OS analysis,[22] performed at the time of the final PFS analysis, demonstrated a statistically significant difference in OS between the NIVO/IPI group and the sunitinib group, and the study was terminated. The results of the interim OS analysis (Table 19) and Kaplan-Meier curves for OS (Figure 4) are shown below.

[21] Patients who met none of the factors (a) to (f) below were categorized as being at "favorable risk," patients who met 1 or 2 factors at "intermediate risk", and patients who met 3 or more factors at "poor risk."
(a) <1 year from the time of the initial diagnosis of RCC to randomization for Study 214
(b) Karnofsky performance status <80%
(c) Hemoglobin level < lower limit of normal
(d) Corrected calcium level >10 mg/dL
(e) Neutrophil t count > upper limit of normal
(f) Platelet count > upper limit of normal

[22] At the final PFS analysis (i.e., at the interim OS analysis), 456 PFS events and 328 OS events had occurred.

Table 19. Interim OS analysis (IMDC intermediate- or poor-risk patients, data cutoff date, August 7, 2017)

	NIVO/IPI	Sunitinib
N	425	422
Number of events (%)	140 (32.9)	188 (44.5)
Median [95% CI] (months)	— [28.16, —]	25.95 [22.08, —]
Hazard ratio [99.8% CI][*1]	0.63 [0.44, 0.89]	
P-value (2-sided)[*2]	<0.0001	

—, Not evaluable; *1, Cox regression stratified by IMDC score (0, 1 to 2, 3 to 6) and region (US, Canada/Western Europe/Northern Europe, others); *2, Log-rank test stratified by IMDC score (0, 1 to 2, 3 to 6) and region (US, Canada/Western Europe/Northern Europe, others) with a 2-sided significance level of 0.002

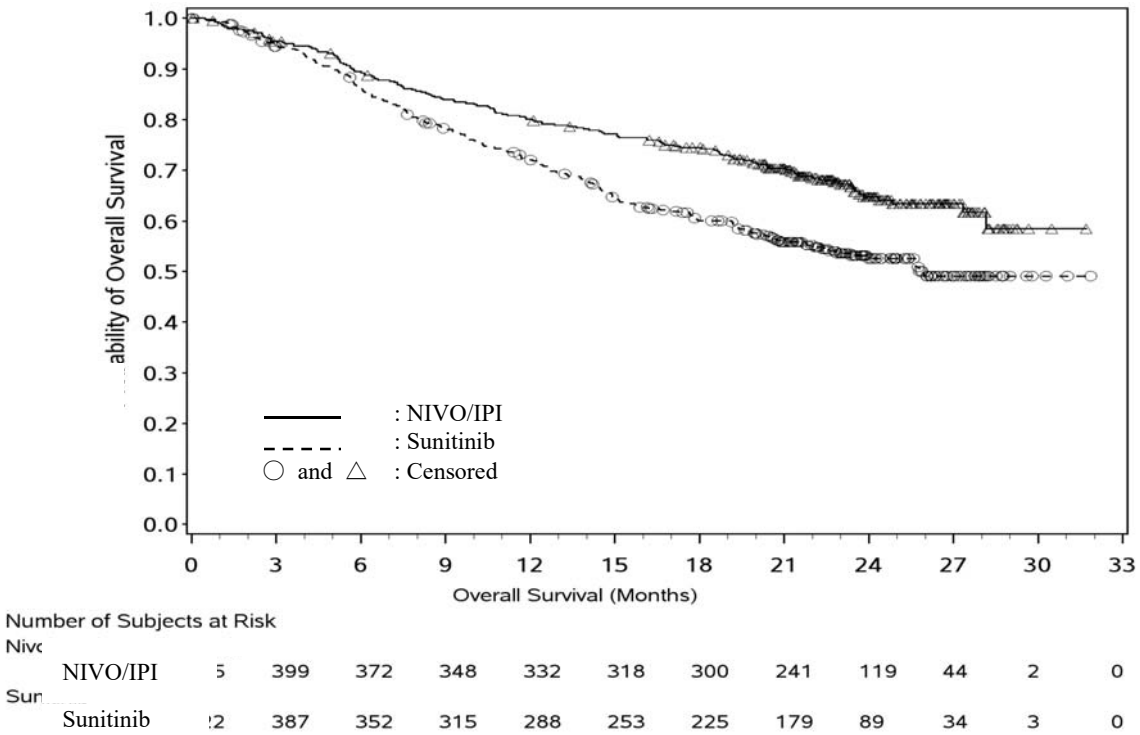


Figure 4. Kaplan-Meier curves for the interim OS analysis (intermediate- or poor-risk patients [data cutoff date, August 7, 2017])

During the treatment period or within 30 days after the last dose, 23 of 425 patients (4.2%) in the NIVO/IPI group and 25 of 422 patients (4.7%) in the sunitinib group died. Disease progression was the most common cause of death (10 patients in the NIVO/IPI group and 18 patients in the sunitinib group). Other causes of death in the NIVO/IPI group were cardiopulmonary failure, cardiac arrest, bronchitis/septic shock, sepsis, acute respiratory failure, cardio-respiratory arrest, death, suicide attempt, embolism, pneumonia, respiratory failure, pulmonary embolism, and cerebral infarction (1 patient each), and those in the sunitinib group were cardiac arrest (2 patients), and sepsis, diarrhoea, haemorrhage intracranial, sudden death, and gastrointestinal haemorrhage (1 patient each). A causal relationship to the study drug could not be ruled out for the bronchitis (1 patient) in the NIVO/IPI group, and the cardiac arrest (2 patients) and diarrhoea (1 patient) in the sunitinib group.

7.3.1.2 Foreign clinical studies

7.3.1.2.1 Foreign phase I study (CTD5.3.5.1-1, Study 016, ongoing since February 2012 [data cutoff date, March 16, 2016])

An open-label, uncontrolled study was conducted at 14 sites outside Japan, to evaluate the safety and tolerability of NIVO in combination with IPI, sunitinib, or pazopanib in patients with unresectable or metastatic RCC (target sample size, 191 subjects).

Patients received intravenous doses of NIVO 1 or 3 mg/kg and IPI 1 or 3 mg/kg[19] every 3 weeks for 4 doses each, followed by an intravenous dose of NIVO 3 mg/kg every 2 weeks (Arm I), an intravenous dose of NIVO 2 or 5 mg/kg every 3 weeks in combination with an oral dose of sunitinib 50 mg once daily[20] (Arm S), or an intravenous dose of NIVO 2 or 5 mg/kg every 3 weeks in combination with an oral dose of pazopanib 800 mg once daily (Arm P). The treatment was continued until either disease progression occurred or a withdrawal criterion was met.

Among the 194 patients enrolled in the study, 153 (47 in Arm I-1, 47 in Arm I-3, 6 in Arm IN-3, 33 in Arm S, and 20 in Arm P) received the study drugs and included in the safety analysis set.

During the treatment period or within 100 days after the last dose, 10 of 153 patients (6.5%) died (3 in Arm I-1, 4 in Arm I-3, 1 in Arm S, and 2 in Arm P). The causes of death were disease progression in 7 patients, and sudden death, pneumonia, and gastric haemorrhage in 1 patient each. A causal relationship to the study drug was ruled out in all of the patients.

7.3.2 Reference data

7.3.2.1 Foreign clinical studies

7.3.2.1.1 Foreign phase Ib study (CTD 5.3.5.4-1, Study 09, ongoing since September 2011 [data cutoff date, [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 14 sites outside Japan to evaluate the safety, tolerability, and other characteristics of NIVO therapy in patients with unresectable or metastatic clear cell RCC (target sample size, 80 subjects).

A total of 91 patients who were enrolled and treated with NIVO were included in the safety analysis set.

During the treatment period or within 100 days after the last dose, 14 of 91 patients (15.4%) died. Disease progression was the most common cause of death (10 patients), and other causes were sudden death, ischaemic stroke, respiratory failure, and cerebral haemorrhage (1 patient each). A causal relationship to NIVO was denied in all of the patients.

7.3.2.1.2 Foreign phase II study (CTD 5.3.5.4-2, Study MDX-010-11, from [redacted], 20[redacted] to [redacted], 20[redacted])

An open-label, uncontrolled study was conducted at a single site outside Japan, to evaluate the efficacy and safety of IPI in patients with unresectable or metastatic clear cell RCC (target sample size, 62 subjects).

A total of 61 patients who were enrolled and treated with IPI were included in the safety analysis set.

During the treatment period or within 70 days after the last dose, 1 of 61 patients (1.6%) died of sepsis, for which a causal relationship to IPI was denied.

7.3.R Outline of the review conducted by PMDA for the treatment of RCC

7.3.R.1 Efficacy

Among the evaluation data submitted by the applicant, PMDA considered that the global phase III study in chemotherapy-naïve patients with unresectable or metastatic clear cell RCC (Study 214) was most important, and thus decided that the efficacy of NIVO/IPI therapy would be evaluated primarily based on the results of Study 214. PMDA also decided that the efficacy of NIVO/IPI therapy in Japanese patients would be evaluated in terms of the consistency between the overall study population and the Japanese subpopulation of Study 214, according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and "Basic Principles on Global Clinical Trials (Reference Cases)" (PFSB/ELD Administrative Notice dated September 5, 2012).

As a result of its review, which is summarized below, PMDA concluded that the efficacy of NIVO/IPI therapy has been demonstrated in chemotherapy-naïve patients with unresectable or metastatic clear cell RCC who are at IMDC intermediate- or poor-risk.

7.3.R.1.1 Selection of control group

The applicant's rationale for the selection of sunitinib as the comparator in Study 214:
When Study 214 was planned, the NCCN guidelines (kidney cancer) (version 2.2014) recommended the use of sunitinib, pazopanib, and other agents for the treatment of the target patient population of Study 214. The Japanese clinical practice guideline for renal cancer (2011) recommended the use of interferon-alpha, iterleukin-2, sunitinib, and sorafenib for the treatment of IMDC favorable- or intermediate-risk patients with RCC, and the use of temsirolimus and sunitinib for the treatment of IMDC poor-risk patients with RCC.

Since sunitinib was recommended by clinical practice guidelines both in and outside Japan for the treatment of RCC across all IMDC risk categories, sunitinib was selected as the comparator in Study 214.

PMDA accepted the applicant's explanation.

7.3.R.1.2 Efficacy endpoints and evaluation results

In Study 214, OS of NIVO/IPI therapy to sunitinib in IMDC intermediate- or poor-risk patients was one of the coprimary endpoints to demonstrate the superiority of NIVO/IPI therapy to sunitinib [see Section 7.3.1.1.1].

The results of the interim OS analysis in the Japanese subpopulation of Study 214 (Table 20) and Kaplan-Meier curves for OS (Figure 5) are shown below.

Table 20. Interim OS analysis in Japanese patients (intermediate- or poor-risk patients, data cutoff date, August 7, 2017)

	NIVO/IPI	Sunitinib
N	31	29
Number of events (%)	5 (16.1)	5 (17.2)
Median [95% CI] (months)	— [—, —]	— [—, —]
Hazard ratio [95% CI]*	0.76 [0.21, 2.72]	

—, Not evaluable; *, Cox regression stratified by IMDC score (0, 1 to 2, 3 to 6)

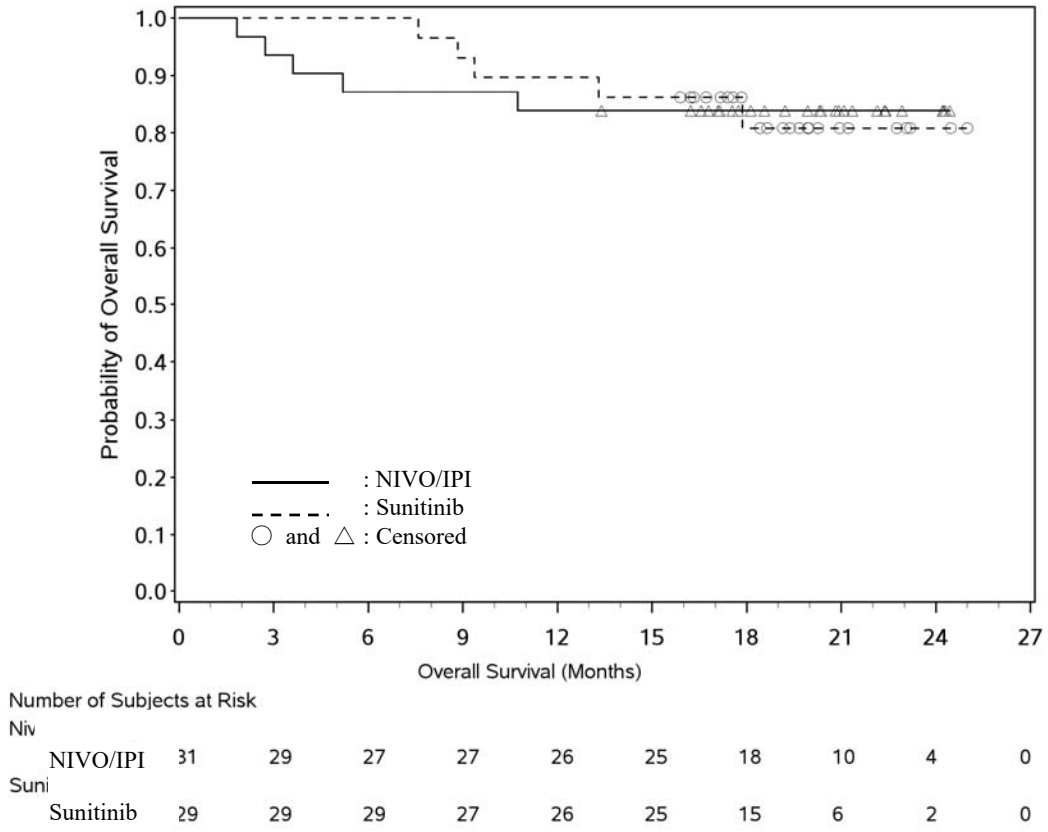


Figure 5. Kaplan-Meier curves for interim OS analysis in Japanese patients (intermediate- or poor-risk patients [data cutoff date, August 7, 2017])

PMDA's view:

Chemotherapy-naïve patients with unresectable or metastatic clear cell RCC will receive treatment, in anticipation of prolonging their survival. Therefore, OS is an appropriate primary endpoint for Study 214.

Since the numbers of patients and events in the Japanese subpopulation of Study 214 were limited, the efficacy of NIVO/IPI therapy in Japanese patients cannot be concluded, based only on the results obtained for the Japanese subpopulation. In addition, the Kaplan-Meier curves for OS in the Japanese intermediate- or poor-risk patients were not completely consistent with those in all of the intermediate- or poor-risk patients in Study 214. However, the results of Study 214 demonstrated the superiority of NIVO/IPI therapy to sunitinib in OS, in chemotherapy-naïve patients with unresectable or metastatic clear cell RCC who are at IMDC intermediate or poor risk [see Section 7.3.1.1.1]. Therefore, PMDA concluded that NIVO/IPI therapy has demonstrated efficacy in chemotherapy-naïve patients with unresectable or metastatic RCC, including Japanese patients, in view of the following findings.

- There have been no clear differences in the efficacy of NIVO or IPI for the respective approved indications between Japanese and non-Japanese patients.
- There are no clear differences in the diagnosis and treatment systems for RCC, between in and outside Japan.

7.3.R.2 Safety [for adverse events, see Section "7.6 Adverse events reported in clinical studies"]

PMDA's view:

As a result of the following review, PMDA concluded that special attention should be paid to the following adverse events when NIVO/IPI therapy is administered to patients with unresectable or metastatic RCC, as these events were identified as requiring attention at the regulatory reviews for the approved indications of (a) NIVO and (b) IPI:

(a) Interstitial lung disease (ILD); hepatic function disorder; abnormal thyroid function; infusion reaction; skin disorder; colitis, severe diarrhoea; myasthenia gravis, myocarditis, rhabdomyolysis, myositis; neurological disorder; renal disorder; venous thrombosis and embolism; adrenal disorder; encephalitis; type 1 diabetes mellitus; immune thrombocytopenic purpura; and cardiac disorder (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated August 22, 2017").

(b) Diarrhoea, colitis, gastrointestinal perforation; skin disorder; liver disorder; hypophysitis, hypopituitarism, hypothyroidism, adrenal insufficiency; peripheral neuropathy; renal disorder; ILD; myositis; and infusion reaction (see "Review Report for Yervoy Injection 50 mg [for intravenous use], dated May 19, 2015" and the "Package Insert for Yervoy Injection 50 mg [for intravenous use]").

PMDA's conclusion:

Although attention should be paid to the above events, NIVO/IPI therapy is also tolerable in patients with RCC, provided that physicians with sufficient knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions, including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions, and drug interruption of NIVO and IPI.

7.3.R.2.1 Safety profile

The applicant's explanation about the safety profile of NIVO/IPI therapy in patients with unresectable or metastatic RCC, based on the safety data from Study 214:

Table 21 shows a safety summary of Study 214.

Table 21. Safety summary (Study 214)

	n (%)	
	NIVO/IPI N = 547	Sunitinib N = 535
All adverse events	544 (99.5)	532 (99.4)
Grade ≥3 adverse events	374 (68.4)	425 (79.4)
Adverse events leading to death	25 (4.6)	31 (5.8)
Serious adverse events	305 (55.8)	213 (39.8)
Adverse events leading to drug discontinuation	168 (30.7)	114 (21.3)
Adverse events leading to drug interruption*	293 (53.6)	231 (43.2)

*, No dose reduction rule was specified for the NIVO/IPI group.

In Study 214, the adverse events of any grade reported with a ≥5% higher incidence in the NIVO/IPI group than in the sunitinib group were pruritus (180 patients [32.9%] in the NIVO/IPI group, 58 patients [10.8%] in the sunitinib group), rash (141 patients [25.8%], 84 patients [15.7%]), pyrexia (136 patients [24.9%], 91 patients [17.0%]), arthralgia (123 patients [22.5%], 83 patients [15.5%]), lipase increased (96 patients [17.6%], 65 patients [12.1%]), amylase increased (76 patients [13.9%], 42 patients [7.9%]), myalgia (65 patients [11.9%], 34 patients [6.4%]), hyperthyroidism (63 patients [11.5%], 16 patients [3.0%]), hyperglycaemia (57 patients [10.4%], 23 patients [4.3%]), pneumonitis (32 patients [5.9%], 4 patients [0.7%]), and adrenal insufficiency (32 patients [5.9%], 0 patients]. The Grade ≥3 adverse events with a ≥2% higher incidence in the NIVO/IPI group than in the sunitinib group were lipase increased (60 patients [11.0%], 41 patients [7.7%]), amylase increased (34 patients [6.2%], 17 patients [3.2%]), ALT increased (27 patients [4.9%], 11 patients [2.1%]), hyperglycaemia (22 patients [4.0%], 4 patients [0.7%]), pneumonia (17 patients [3.1%], 5 patients [0.9%]), hypophysitis (15 patients [2.7%], 0 patients), adrenal insufficiency (12 patients [2.2%], 0 patients), and colitis (12 patients [2.2%], 0 patients). The serious adverse events with a ≥2% higher incidence in the NIVO/IPI group than in the sunitinib group were diarrhoea (24 patients [4.4%], 3 patients [0.6%]), pneumonitis (15 patients [2.7%], 1 patient [0.2%]), and hypophysitis (14 patients [2.6%], 0 patients). The adverse event leading to drug discontinuation, with a ≥2% higher incidence in the NIVO/IPI group than in the sunitinib group was diarrhoea (15 patients [2.7%], 4 patients [0.7%]). The adverse events leading to drug interruption or dose reduction, with a ≥2% higher incidence in the NIVO/IPI group than in the sunitinib group were diarrhoea (33 patients [6.0%], 13 patients [2.4%]), lipase increased (24 patients [4.4%], 5 patients [0.9%]), blood creatinine increased (23 patients [4.2%], 4 patients [0.7%]), ALT increased (18 patients [3.3%], 3 patients [0.6%]), pyrexia (15 patients [2.7%], 2 patients [0.4%]), pneumonitis (15 patients [2.7%], 0 patients), AST increased (14 patients [2.6%], 1 patient [0.2%]), hyperthyroidism (14 patients [2.6%], 0 patients), pneumonia (13 patients [2.4%], 1 patient [0.2%]), hypophysitis (13 patients [2.4%], 0 patients), adrenal insufficiency (12 patients [2.2%], 0 patients), and dyspnoea (12 patients [2.2%], 0 patients]. There were no adverse events leading to death, with a ≥2% higher incidence in the NIVO/IPI group than in the sunitinib group.

The applicant's explanation about the differences in the safety profile of NIVO/IPI therapy between Study 214, and a foreign phase III study (Study 067) and a Japanese phase II study (Study 17), which evaluated the efficacy and safety of NIVO/IPI therapy in patients with unresectable malignant melanoma:

Table 22 shows the results of comparisons of the incidences of the adverse events observed in the NIVO/IPI group of Study 214 with those in the combined NIVO/IPI groups of Studies 067 and 17.

Table 22. Safety summary in patients with RCC and patients with malignant melanoma (NIVO/IPI groups of Studies 214, 067 and 17)

	n (%)	
	RCC N = 547	Malignant melanoma N = 343
All adverse events	544 (99.5)	342 (99.7)
Grade ≥3 adverse events	374 (68.4)	264 (77.0)
Adverse events leading to death	25 (4.6)	25 (7.3)
Serious adverse events	305 (55.8)	243 (70.8)
Adverse events leading to drug discontinuation	168 (30.7)	157 (45.8)
Adverse events leading to drug interruption	293 (53.6)	197 (57.4)

No adverse events of any grade were reported with a ≥10% higher incidence in patients with RCC than in patients with malignant melanoma. No Grade ≥3 adverse events, adverse events leading to death, serious adverse events, or adverse events leading to drug discontinuation or drug interruption were reported with a ≥5% higher incidence in patients with RCC than in patients with malignant melanoma.

The adverse events of any grade, which were not reported in the NIVO/IPI group of Study 067 or Study 17 but were reported with a ≥1% incidence in the NIVO/IPI group of Study 214 were palmar-plantar erythrodysaesthesia syndrome (9 of 547 patients [1.6%]) and white blood cell count decreased (6 of 547 patients [1.1%]). There were no such adverse events of Grade ≥3 in severity.

Thus, some adverse events occurred frequently or were newly identified in patients with RCC who received NIVO/IPI therapy in Study 214, as compared with those in patients receiving NIVO/IPI therapy for the approved indication of malignant melanoma. However, no clinically relevant Grade ≥3 adverse events were reported in Study 214. Therefore, the safety of NIVO/IPI therapy in the treatment of RCC is comparable with the safety found with the approved indication.

PMDA's view:

NIVO/IPI therapy is also tolerable in patients with RCC, provided that physicians with sufficient knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions, including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions, and drug interruption of NIVO and IPI, in view of the following findings.

- No Grade ≥3 adverse events, adverse events leading to death, serious adverse events, or adverse events leading to drug discontinuation or drug interruption were reported with a ≥5% higher incidence in the NIVO/IPI group of Study 214 than in the NIVO/IPI group of Study 067 or Study 17. Adverse events were manageable with the interruption of NIVO or IPI, or other measures.

- All newly identified adverse events in Study 214 were classified as Grade ≤2 and no new safety concerns were discovered regarding the use of NIVO/IPI therapy in patients with RCC.

7.3.R.2.2 Differences in the safety between Japanese and non-Japanese patients

The applicant's explanation about the differences in the safety of NIVO/IPI therapy between Japanese and non-Japanese patients, based on the results of Study 214:

Table 23 shows a safety summary in Japanese and non-Japanese patients receiving NIVO/IPI therapy in Study 214.

Table 23. Safety summary (NIVO/IPI group of Study 214)

	n (%)	
	Japanese N = 38	Non-Japanese N = 509
All adverse events	38 (100)	506 (99.4)
Grade ≥3 adverse events	28 (73.7)	346 (68.0)
Adverse events leading to death	2 (5.3)	23 (4.5)
Serious adverse events	24 (63.2)	281 (55.2)
Adverse events leading to drug discontinuation	15 (39.5)	153 (30.1)
Adverse events leading to drug interruption	16 (42.1)	277 (54.4)

The adverse events of any grade reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients in the NIVO/IPI group of Study 214 were constipation (Japanese, 11 patients [28.9%]; non-Japanese, 82 patients [16.1%]), viral upper respiratory tract infection (11 patients [28.9%], 35 patients [6.9%]), upper respiratory tract infection (7 patients [18.4%], 27 patients [5.3%]), malignant neoplasm progression (6 patients [15.8%], 20 patients [3.9%]), and lymphocyte count decreased (6 patients [15.8%], 2 patients [0.4%]). The Grade ≥3 adverse events reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were lipase increased (6 patients [15.8%], 54 patients [10.6%]), malignant neoplasm progression (5 patients [13.2%], 17 patients [3.3%]), hypertension (3 patients [7.9%], 15 patients [2.9%]), hyperkalaemia (3 patients [7.9%], 7 patients [1.4%]), lymphocyte count decreased (2 patients [5.3%], 1 patient [0.2%]), secondary adrenocortical insufficiency (2 patients [5.3%], 0 patients), and hepatic function abnormal (2 patients [5.3%], 0 patients). The serious adverse events with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were malignant neoplasm progression (5 patients [13.2%], 17 patients [3.3%]) and secondary adrenocortical insufficiency (2 patients [5.3%], 0 patients). The adverse events leading to drug interruption, with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were pneumonitis (3 patients [7.9%], 12 patients [2.4%]) and hepatic function abnormal (2 patients [5.3%], 0 patients). No adverse events leading to death or adverse events leading to drug discontinuation were reported with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:

Due to the small number of Japanese patients treated with NIVO/IPI therapy for unresectable or metastatic RCC receiving NIVO/IPI therapy, there are limitations in comparing the safety of NIVO/IPI therapy between Japanese patients and non-Japanese patients. Nevertheless, PMDA concluded that

NIVO/IPI therapy is also tolerable in Japanese patients with unresectable or metastatic RCC, in view of the following finding.

- Most of the adverse events reported with a higher incidence in Japanese patients than in non-Japanese patients in Study 214 were assessed as Grade ≤2, and these were all known adverse events of NIVO or IPI, administered alone, and were manageable with the interruption of NIVO or IPI, or other measures.

7.3.R.3 Clinical positioning and indications

The proposed indication of NIVO for RCC had no change from the approved indication. The proposed indication of IPI was "treatment of unresectable or metastatic renal cell carcinoma," which was identical to the approved indication of NIVO. The following precautionary statements were proposed for the "Precautions for Indications" sections of the package inserts for NIVO and IPI.

NIVO

- 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.
- The efficacy and safety of NIVO in adjuvant chemotherapy have not been established.
- Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, particularly regarding the characteristics, such as IMDC risk classification, of patients enrolled in clinical studies, and a thorough understanding of the efficacy and safety of NIVO.

IPI

- Eligibility of patients for treatment with IPI should be determined based on a good understanding of the "Clinical Studies" section of the package insert and the efficacy and safety of IPI, particularly regarding the characteristics, such as IMDC risk classification, of patients enrolled in clinical studies.
- The efficacy and safety of IPI in adjuvant chemotherapy have not been established.

As a result of its review, described in Sections "7.3.R.1 Efficacy" and "7.3.R.2 Safety," and the following subsections, PMDA concluded that the proposed indication, "treatment of unresectable or metastatic RCC" is appropriate, provided that detailed information on the target patient population of Study 214 (e.g., histology, IMDC risk categories that responded to NIVO/IPI therapy) is included in the "Clinical Studies" sections of the package inserts for NIVO and IPI, and that the following precautionary statements should be included in the "Precautions for Indications" sections.

NIVO

- The efficacy and safety of NIVO in adjuvant therapy have not been established.
- Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, and a thorough understanding of the efficacy and safety of NIVO.
- The use of NIVO for the treatment of chemotherapy-naïve patients with unresectable or metastatic RCC should be limited to IMDC intermediate- or poor-risk patients.

IPI

- The efficacy and safety of IPI in adjuvant therapy have not been established.
- Eligibility of patients for treatment with IPI should be determined based on a good understanding of the "Clinical Studies" section of the package insert and the efficacy and safety of IPI.
- The use of IPI should be limited to IMDC intermediate- or poor-risk patients.

7.3.R.3.1 Intended population of NIVO/IPI therapy

Among major foreign and Japanese clinical practice guidelines and standard textbooks on oncology, the following guidelines include a statement about NIVO/IPI therapy for RCC.

- EAU guidelines (*Eur Urol.* 2018;73:311-15)
  NIVO/IPI therapy is strongly recommended as the standard of care in IMDC intermediate- or poor-risk patients with untreated clear cell RCC.

PMDA asked the applicant to explain the clinical positioning and indication of NIVO/IPI therapy for unresectable or metastatic RCC.

The applicant's explanation:

Based on the results of Study 214, NIVO/IPI therapy can be positioned as a therapeutic option for chemotherapy-naïve patients with unresectable or metastatic clear cell RCC who have IMDC intermediate or poor risk.

The use of NIVO/IPI therapy is inappropriate for (a) the treatment of favorable-risk patients with RCC, but acceptable for (b) the treatment of patients with RCC of histological types other than clear cell, for the following reasons.

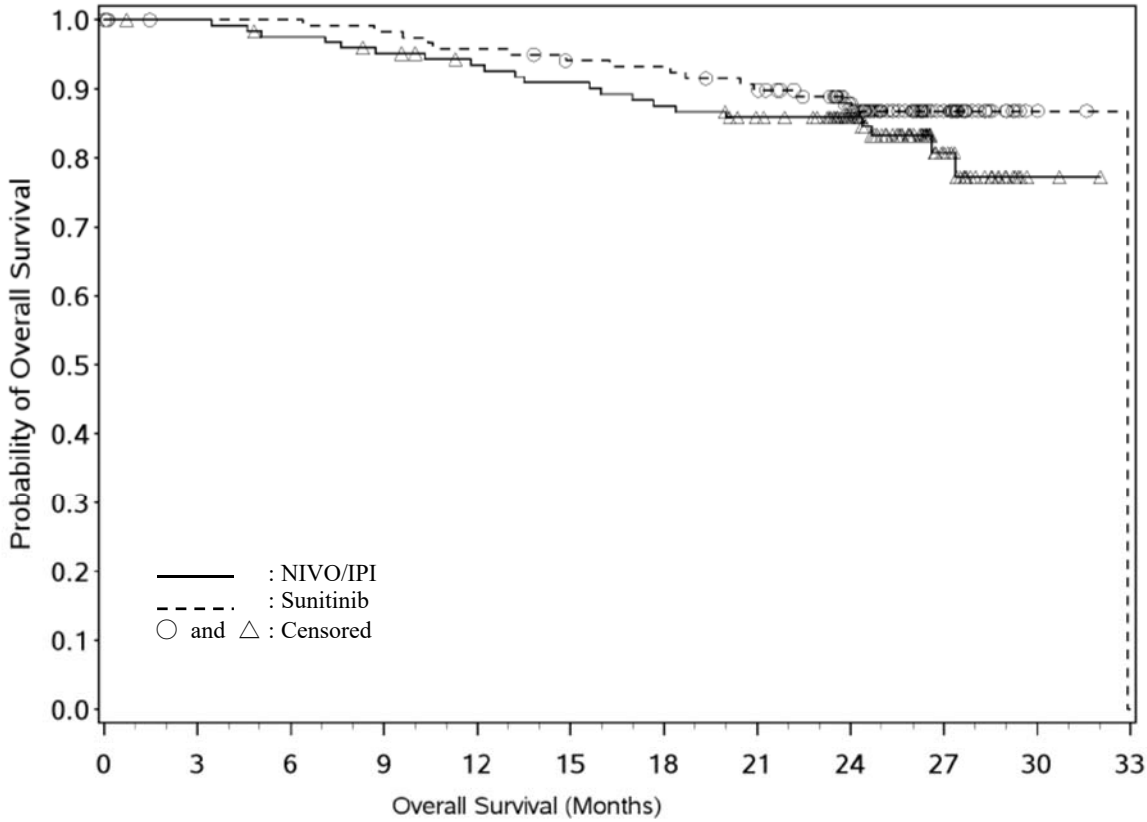
(a) The interim OS analysis (Table 24) and Kaplan-Meier curves (Figure 6) for OS in favorable-risk patients in Study 214 showed better results in the sunitinib group than in the NIVO/IPI group. Therefore, NIVO/IPI therapy cannot be recommended in IMDC favorable-risk patients with RCC.

(b) Although no clinical data are available for the efficacy or safety of NIVO/IPI therapy in patients with RCC of any histological type other than clear cell, the Japanese clinical practice guidelines (kidney cancer) do not recommend therapeutic options separately by histological type, and the treatments recommended for clear cell RCC have also been used for non-clear cell RCC in clinical practice. Therefore, NIVO/IPI therapy can also be a therapeutic option for patients with non-clear cell RCC. A foreign phase IIIb/IV study is ongoing to evaluate the efficacy and safety of NIVO/IPI therapy in chemotherapy-naïve patients with unresectable or metastatic non-clear cell RCC (Study CA209920).

Table 24. Interim OS analysis (Favorable-risk patients, data cutoff date, August 7, 2017)

	NIVO/IPI	Sunitinib
N	125	124
Number of events (%)	21 (16.8)	16 (12.9)
Median [95%CI] (months)	— [—, —]	32.92 [—, —]
Hazard ratio [99.8%CI][*1]	1.45 [0.51, 4.12]	
P-value (2-sided)[*2]	0.2715	

—, Not evaluable; *1, Cox regression stratified by IMDC score (0, 1 to 2, 3 to 6) and region (US, Canada/Western Europe/Northern Europe, others); *2, Log-rank test stratified by IMDC score (0, 1 to 2, 3 to 6) and region (US, Canada/Western Europe/Northern Europe, others) with a 2-sided significance level of 0.002



NIVO/IPI	125	124	120	116	111	108	104	98	78	27	2	0
Sunitinib	124	119	119	117	114	110	109	104	84	32	3	0

Figure 6. Kaplan-Meier curves for interim OS analysis (Favorable-risk patients, data cutoff date on August 7, 2017)

Based on the above, the indication of NIVO/IPI therapy was proposed as "treatment of unresectable or metastatic RCC," provided that details regarding the characteristics of the patients enrolled in Study 214 are provided in the "Clinical Studies" sections of the package inserts for NIVO and IPI, and that the following statements are included in the "Precautions for Indications" sections.

NIVO

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

- Eligible patients must be selected based on a careful review of the content of the “Clinical Studies” section, particularly regarding the characteristics, such as IMDC risk classification, of patients enrolled in clinical studies, and a thorough understanding of the efficacy and safety of NIVO.

IPI

- Eligibility of patients for treatment with IPI should be determined based on a good understanding of the “Clinical Studies” section of the package insert and the efficacy and safety of IPI, particularly regarding the characteristics, such as IMDC risk classification, of patients enrolled in clinical studies.
- The efficacy and safety of IPI in adjuvant chemotherapy have not been established.

PMDA’s view:

PMDA accepted the applicant’s explanation in general. However, since the results of Study 214 demonstrated the clinical benefit of NIVO/IPI therapy in IMDC intermediate- or poor-risk patients, the intended population of NIVO/IPI therapy should be specified as intermediate- or poor-risk patients in the “Precautions for Indications” sections of the package inserts. The following precautionary statement proposed by the applicant for the “Precautions for Indications” section of the package insert for NIVO should be included in the “Precautions for Dosage and Administration” section: “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.” [see Section 7.4.R.1].

PMDA’s conclusion:

Based on the above review, the indication of NIVO/IPI therapy should be “treatment of unresectable or metastatic renal cell carcinoma,” and the “Clinical Studies" sections of the package inserts for NIVO and IPI should provide the fact that the target patient population of Study 214 was patients with clear cell RCC, as well as the fact that the clinical benefit of NIVO/IPI therapy was demonstrated in IMDC intermediate- or poor-risk patients. In addition, the following statements should be included in the “Precautions for Indication” sections.

NIVO

- The efficacy and safety of NIVO in adjuvant therapy have not been established.
- Eligible patients must be selected based on a careful review of the content of the “Clinical Studies” section, and a thorough understanding of the efficacy and safety of NIVO.
- The use of NIVO for the treatment of chemotherapy-naïve patients with unresectable or metastatic RCC should be limited to IMDC intermediate- or poor-risk patients.

IPI

- The efficacy and safety of IPI in adjuvant therapy have not been established.
- Eligibility of patients for treatment with IPI should be determined based on a good understanding of the “Clinical Studies” section of the package insert and the efficacy and safety of IPI.
- The use of IPI should be limited to IMDC intermediate- or poor-risk patients.

7.3.R.3.2 Efficacy and safety of NIVO/IPI therapy by PD-L1 expression status, and the intended population

NIVO is an antibody against human PD-1. PMDA therefore asked the applicant to explain the efficacy and safety of NIVO/IPI therapy by the expression status of PD-L1,[17] a ligand of PD-1, and to identify the intended population of NIVO/IPI therapy.

The applicant's explanation:

In Study 214, PD-L1 expression levels were assessed using the PD-L1 IHC assay, which was jointly developed by Bristol-Myers Squib and Dako North America. The (a) efficacy and (b) safety of NIVO/IPI therapy by PD-L1 expression status (cutoff values: 1%, 5%, and 10%) in the treatment of unresectable or metastatic RCC are as follows.[23]

(a) Efficacy:

Table 25 and Figure 7 show the OS in patients with intermediate- or poor-risk patients with RCC by PD-L1 expression status in Study 214 (cutoff values; 1%, 5%, and 10%) (data cutoff date, August 7, 2017).

Patients treated with NIVO/IPI therapy showed prolonged OS, compared with those treated with sunitinib in both the PD-L1-positive and -negative populations at all of the cutoff values. Therefore, the efficacy of NIVO/IPI therapy can be expected, regardless of PD-L1 expression status.

Table 25. Efficacy of NIVO/IPI therapy by PD-L1 expression status (NIVO/IPI group vs. sunitinib group in Study 214, intermediate- or poor-risk patients with RCC)

Percentage of cells with PD-L1	Treatment	N	OS		
			Median [95%CI] (months)	Hazard ratio*1 [95% CI]	P-value for the interaction*2
<1%	NIVO/IPI	284	— [28.16, —]	0.73 [0.56, 0.96]	0.0657
	Sunitinib	278	— [23.98, —]		
≥1%	NIVO/IPI	100	— [—, —]	0.45 [0.29, 0.71]	
	Sunitinib	114	19.61 [14.78, —]		
<5%	NIVO/IPI	321	— [28.16, —]	0.68 [0.52, 0.88]	0.3169
	Sunitinib	312	— [23.98, —]		
≥5%	NIVO/IPI	63	— [—, —]	0.53 [0.31, 0.89]	
	Sunitinib	80	16.20 [11.04, —]		
<10%	NIVO/IPI	329	— [28.16, —]	0.68 [0.52, 0.88]	0.2874
	Sunitinib	322	— [23.98, —]		
≥10%	NIVO/IPI	55	— [22.97, —]	0.50 [0.28, 0.88]	
	Sunitinib	70	15.80 [10.02, —]		

—, Not evaluable; *1, Cox regression; *2, Cox regression with (a) treatment group, (b) PD-L1 expression status, and (c) interaction between treatment group and PD-L1 expression status as covariates

[23] PD-L1 expression was assessed in 546 patients in the NIVO/IPI group and 541 patients in the sunitinib group; among these patients, 499 in the NIVO/IPI group and 503 in the sunitinib group had quantifiable results.

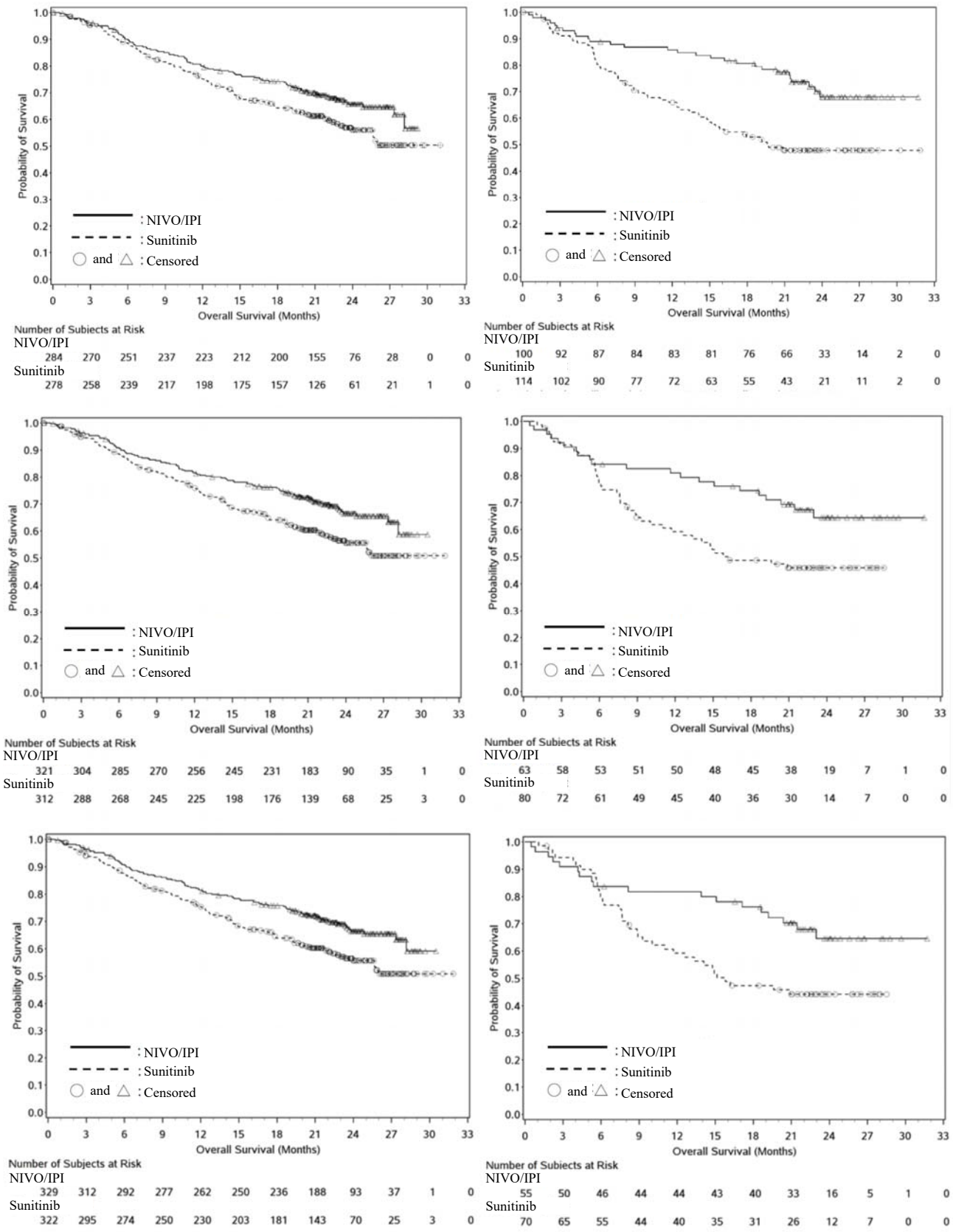


Figure 7. Kaplan-Meier curves for OS by PD-L1 expression status
(Intermediate- or poor-risk patients, data cutoff date on August 7, 2017)
(Upper left, PD-L1 expression <1%; upper right, ≥1%; middle left, <5%; middle right, ≥5%; lower left, <10%; lower right, ≥10%)

(b) Safety:

Table 26 shows the safety data by PD-L1 expression status in Study 214.

Although the results should be interpreted carefully due to the small number of patients, the safety of NIVO/IPI therapy by PD-L1 expression status did not differ significantly between PD-L1-positive and -negative populations at any of the cutoff values. Therefore, NIVO/IPI therapy is tolerable, regardless of PD-L1 expression status, in intermediate- or poor-risk patients with unresectable or metastatic RCC.

Table 26. Safety summary by PD-L1 expression status (Study 214)

	n/N (%)			
	NIVO/IPI	Sunitinib	NIVO/IPI	Sunitinib
PD-L1 expression rate	<1%		≥1%	
All adverse events	382/385 (99.2)	368/369 (99.7)	113/113 (100)	123/125 (98.4)
Grade ≥3 adverse events	267/385 (69.4)	301/369 (81.6)	77/113 (68.1)	96/125 (76.8)
Serious adverse events	218/385 (56.6)	143/369 (38.8)	59/113 (52.2)	56/125 (44.8)
PD-L1 expression rate	<5%		≥5%	
All adverse events	424/427 (99.3)	405/407 (99.5)	71/71 (100)	86/87 (98.9)
Grade ≥3 adverse events	298/427 (69.8)	331/407 (81.3)	46/71 (64.8)	66/87 (75.9)
Serious adverse events	241/427 (56.4)	155/407 (38.1)	36/71 (50.7)	44/87 (50.6)
PD-L1 expression rate	<10%		≥10%	
All adverse events	437/440 (99.3)	418/420 (99.5)	58/58 (100)	73/74 (98.6)
Grade ≥3 adverse events	306/440 (69.5)	341/420 (81.2)	38/58 (65.5)	56/74 (75.7)
Serious adverse events	248/440 (56.4)	161/420 (38.3)	29/58 (50.0)	38/74 (51.4)

The investigations in (a) and (b) above suggest that NIVO/IPI therapy can be recommended, regardless of PD-L1 expression status, in chemotherapy-naïve patients with unresectable or metastatic clear cell RCC who are at IMDC intermediate or poor risk.

PMDA's conclusion:

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

7.4.R Dosage and administration

As shown in the table below, the proposed "Dosage and Administration" and "Precautions for Dosage and Administration" sections of the package inserts for NIVO and IP were changed from the approved sections, based on the data from clinical pharmacology studies, and data relating to malignant pleural mesothelioma, adjuvant therapy of malignant melanoma, and RCC submitted for the present applications.

	Dosage and Administration	Precautions for Dosage and Administration
NIVO	• Malignant melanoma, unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, recurrent or distant metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, or unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks. • Unresectable or metastatic RCC The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks. In combination therapy with IPI, the usual adult dosage of NIVO is 3 mg/kg body weight, administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg as an intravenous infusion every 2 weeks.	• The efficacy and safety of NIVO administered beyond 1 year as an adjuvant chemotherapy of malignant melanoma have not been established. • In the treatment of malignant melanoma, NSCLC, cHL, head and neck cancer, gastric cancer, or malignant pleural mesothelioma, the efficacy and safety of NIVO in combination with other antineoplastic drugs have not been established. • In the treatment of RCC, the efficacy and safety of NIVO in combination with antineoplastic drugs (including cytokines) other than IPI have not been established. • NIVO should be administered as an intravenous infusion over at least 30 minutes. • An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion.
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 times. • Unresectable or metastatic RCC 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 times.	• IPI should not be used in combination with antineoplastic agents other than NIVO. • The criteria for suspension or discontinuation of treatment in the event of adverse reactions (omitted, since they are identical to those at the initial approval) • IPI should be administered intravenously over a period of 90 minutes in patients with malignant melanoma, or 30 minutes in patients with RCC. When necessary, IPI should be diluted with normal saline or 5% glucose solution for injection.

As a result of its review, described in the following sections, PMDA concluded that the "Dosage and Administration" and "Precautions for Dosage and Administration" sections of the package inserts for NIVO and IPI should be modified as shown in the table below.

- "Efficacy" Sections [7.1.R.1, 7.2.R.1, and 7.3.R.1]
- "Safety" Sections [7.1.R.2, 7.2.R.2, and 7.3.R.2]
- "Intended population of NIVO/IPI therapy" Section [7.3.R.3.1]
- Subsections of 7.4.R [7.4.R.1 and 7.4.R.2]
- "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" (Descriptions added or modified at the review of NIVO/IPI therapy for unresectable malignant melanoma)

	Dosage and Administration	Precautions for Dosage and Administration
NIVO	• Malignant melanoma The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. When administered in combination with IPI to chemotherapy-naïve patients with 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. • Unresectable or metastatic RCC The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 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. • Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, recurrent or distant metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, or unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks.	• In the treatment of unresectable malignant melanoma, 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. • In the treatment of 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. • In the treatment of NSCLC, cHL, head and neck cancer, gastric cancer, or malignant pleural mesothelioma, the efficacy and safety of NIVO in combination with other antineoplastic drugs have not been established. • NIVO should be administered as an intravenous infusion over at least 30 minutes. • An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion.
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 times. For the treatment of chemotherapy-naïve patients with unresectable malignant melanoma, IPI should not be used in combination with antineoplastic agents other than NIVO. • Unresectable or metastatic RCC 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 times.	• The criteria for suspension or discontinuation of treatment in the event of adverse reactions (omitted, since they are identical to those at the initial approval) • In the treatment of unresectable malignant melanoma, 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 should be administered intravenously over a period of 90 minutes in patients with unresectable malignant melanoma, or 30 minutes in patients with unresectable or metastatic RCC. When necessary, IPI should be diluted with normal saline or 5% glucose solution for injection.

7.4.R.1 Dosage and administration for NIVO and IPI

The applicant's explanation about the rationale for the dosage and administration of NIVO monotherapy:

In view of the below investigations, the dosage regimen of NIVO monotherapy will be changed from the approved body weight-based dosage to the following fixed dosage for the proposed indications and the approved indications: "The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks."

- In Study 41 involving patients with chemotherapy-treated, unresectable, advanced or recurrent malignant pleural mesothelioma, NIVO was administered at a fixed dosage of 240 mg every 2 weeks, rather than the approved body weight-based dosage, based on the results of a PPK analysis [see Section 6.1.2.1] and other findings. The results of Study 41 demonstrated that NIVO administered at the fixed dose provided a clinically significant response rate [see Section 7.1.R.1] and showed good tolerability [see Section 7.1.R.2].

- As the exposure to NIVO administered at 240 mg every 2 weeks is expected to be higher than the exposure with NIVO 3 mg/kg every 2 weeks in Japanese patients [see Section 6.1.2.1], the therapeutic effects of NIVO are unlikely to be reduced by the change in the dosage regimen of NIVO from 3 mg/kg every 2 weeks to 240 mg every 2 weeks.
- As the incidence of adverse events did not clearly differ among patients treated with NIVO 3 mg/kg every 2 weeks for various cancer types [see Sections 7.1.R.2 and 7.2.R.2], it is also likely that no clear differences in the incidence of adverse events will occur among cancer types when NIVO is administered at a fixed dosage of 240 mg every 2 weeks.
- A fixed dosage is clinically advantageous compared with a body weight-based dosage, for instance, in terms of a reduced risk of human errors in the preparation of dosing solutions.
- In the case in which the dosage regimen differs according to cancer type, confusion may occur in clinical practice.

At the time the present applications were submitted, the dosage regimens of NIVO in the combination therapy with IPI for malignant melanoma and RCC were proposed on a body weight basis (1 mg/kg for malignant melanoma and 3 mg/kg for RCC), based on the dosages used in Study 067 (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated April 13, 2018") and Study 214. However, the dosage regimens can be changed from body weight-based dosages (1 and 3 mg/kg) to fixed dosages (80 and 240 mg) in view of the following investigations. In addition, the changes in dosage regimens are also appropriate from medical safety and other perspectives.

- The exposure to NIVO administered at 80 mg in combination with IPI 3 mg every 3 weeks is expected to be higher than the exposure with NIVO 1 mg/kg in combination with IPI 3 mg/kg every 3 weeks in Japanese patients. Similarly, the exposure to NIVO administered at 240 mg in combination with IPI 1 mg every 3 weeks is expected to be higher than the exposure with NIVO 3 mg/kg in combination with IPI 1 mg/kg every 3 week in Japanese patients [see Section 6.1.2.1]. Therefore, the change in the dosage of NIVO in the combination therapy with IPI from body weight-based dosages (1 and 3 mg/kg) to fixed dosages (80 and 240 mg) is unlikely to attenuate the therapeutic effects of NIVO.
- The incidences of adverse events leading to drug discontinuation or leading to death, and Grade ≥2 immune-mediated adverse events are not expected to clearly differ between patients receiving NIVO 240 mg in combination with IPI 1 mg/kg every 3 weeks and those receiving NIVO 3 mg/kg in combination with 1 mg/kg every 3 weeks [see Section 6.1.3.2]. In addition, the incidences of adverse events leading to drug discontinuation or leading to death are not expected to clearly differ between patients receiving NIVO 80 mg in combination with IPI 3 mg every 3 weeks and those receiving NIVO 1 mg/kg in combination with IPI 3 mg/kg every 3 weeks [see Section 6.1.3.2].

The applicant's rationale for dosage and administration of "NIVO 3 mg/kg in combination with IPI 1 mg/kg every 3 weeks for 4 doses" proposed for the treatment of unresectable or metastatic RCC:
Based on the following findings, dosage and administration for Study 214 involving patients with unresectable or metastatic RCC was determined to be "NIVO 3 mg/kg in combination with IPI 1 mg/kg every 3 weeks for 4 doses" and the results of Study 214 demonstrated the clinical benefit of NIVO/IPI

therapy. Therefore, the dosage regimen used in Study 214 was proposed for dosage and administration of NIVO in the treatment of unresectable or metastatic RCC.

- The results of Study 016, Study 09, and Study MDX-010-11 showed that NIVO/IPI therapy reduced tumor growth, compared with NIVO or IPI administered alone in patients with unresectable or metastatic RCC.
- The results of Study 016 showed that NIVO 3 mg/kg in combination with IPI 1 mg/kg resulted in an inhibition of tumor growth similar to that observed with NIVO 1 mg/kg in combination with IPI 3 mg/kg in patients with unresectable or metastatic RCC.
- The results of Study 016 showed that NIVO 1 mg/kg in combination with IPI 3 mg/kg resulted in a lower incidence of adverse events leading to drug discontinuation or other adverse events and better tolerability, compared with NIVO 1 mg/kg in combination with IPI 3 mg/kg [see Section 7.6.4].

PMDA's conclusion:

PMDA accepted the applicant's explanation in general. However, the maximum duration of adjuvant therapy with NIVO for malignant melanoma should be specified in the "Dosage and Administration" section, for the following reasons. The statements as to combination therapies with antineoplastic agents other than NIVO or IPI proposed for the "Precautions for Dosage and Administration" sections are unnecessary, because such matters are clearly stated in the "Dosage and Administration" sections, and there is no need to repeat similar cautionary statements in the "Precautions for Dosage and Administration" sections.

- In Study 238, which involved patients with resected malignant melanoma, the duration of treatment with NIVO was 12 months. Therefore, no clinical data are available as to the clinical benefit of NIVO when administered beyond 12 months.
- The patients enrolled in Study 238 underwent surgery for a complete cure. The administration of NIVO without careful consideration should be avoided in patients who have completed a 12-month adjuvant therapy with NIVO.

Based on the above, PMDA concluded that the following precautionary statements should be included in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections for the package inserts for NIVO and IPI, for the present partial change applications.

NIVO

- Dosage and Administration
  - Malignant melanoma:

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

    When administered in combination with IPI to chemotherapy-naïve patients with 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.

- Unresectable or metastatic RCC:

  The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 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.
- Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, recurrent or distant metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, or unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy:

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

- Precautions for dosage and administration
  - In the treatment of 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.
  - In the treatment of NSCLC, cHL, head and neck cancer, gastric cancer, or malignant pleural mesothelioma, the efficacy and safety of NIVO in combination with other antineoplastic drugs have not been established.

IPI

- Dosage and administration
  - Unresectable or metastatic RCC

    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 times.
- Precautions for dosage and administration:
  - The criteria for suspension or discontinuation of treatment in the event of adverse reactions (omitted, since they are identical to those at the initial approval)

7.4.R.2 Infusion times of NIVO and IPI

The applicant's explanation about the infusion times of (a) NIVO and (b) IPI:

(a) In the pivotal clinical studies submitted for the approved indications (malignant melanoma, NSCLC, RCC, cHL, head and neck cancer, and gastric cancer) and Study 238, NIVO was administered as an intravenous infusion over at least 60 minutes. However, a shortened infusion time is acceptable in view of the findings presented below. Therefore, the following statement is included in the "Precautions for Dosage and Administration" section: "NIVO should be administered as an intravenous infusion over at least 30 minutes."
   - The results of a PPK analysis were expected to reveal no clear difference in exposure to NIVO between patients receiving NIVO 3 mg/kg or 240 mg as an intravenous infusion over 30 minutes

every 2 weeks and patients receiving NIVO as a 60-minute infusion every 2 weeks [see Section 6.1.2.2].

- In Study 41, in which NIVO was administered as a 30-minute infusion, the incidence of hypersensitivity/infusion-related reactions was 1 of 34 patients (2.9%), while the incidence of such adverse events was 40 of 1159 patients (3.5%) in the clinical studies in which NIVO was administered as a 60-minute infusion for the approved indications. Thus, there was no clear difference in the incidence of hypersensitivity/infusion-related reactions between 30-minute and 60-minute infusions.
- In Study 41, the response rate was clinically significant. Therefore, there is no particular concern about the efficacy of NIVO in association with shortened infusion time to 30 minutes [see Section 7.1.1.1.1].

(b) The results of Study 214, in which IPI was administered as an intravenous infusion over 30 minutes showed the clinical benefit of NIVO/IPI therapy. Therefore, IPI should be administered as "an intravenous infusion over 30 minutes" in the combination therapy with NIVO for unresectable or metastatic RCC.

PMDA accepted the applicant's explanation.

7.5.R Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plans for (a) the treatment of malignant pleural mesothelioma, (b) the adjuvant therapy of malignant melanoma and the change in the dosage regimens of NIVO from body weight-based dosages to fixed dosages, and (c) the treatment of RCC:

(a) The applicant plans to conduct a post-marketing surveillance covering patients treated with NIVO for unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy. The purpose of the surveillance is to evaluate the safety and other aspects of NIVO therapy in clinical practice.

- The safety profile of NIVO found in Study 41 was comparable with the safety profile observed with the previously approved indications [see Section 7.1 R.2.1]. In addition, a certain amount of post-marketing safety information has been collected from patients treated with NIVO for the previously approved indications. In view of these facts, the post-marketing surveillance in patients with unresectable, advanced or recurrent malignant pleural mesothelioma was designed to collect information about all adverse events occurring in clinical practice, without selecting any particular safety specifications.
- The target sample size is 100 patients, considering the comparability of the safety profile of NIVO between the post-marketing surveillance and Study 41. Most of the adverse events observed in Study 41 are collectable with this sample size.
- The observation period is 6 months, because in Study 41, most of the adverse events occurred within 6 months after the start of NIVO therapy.

(b) In view of the following facts, it is unnecessary to initiate the post-marketing surveillance covering patients treated with NIVO for the adjuvant therapy of malignant melanoma soon after the approval.
- There is a certain amount of clinical experience with NIVO in patients with malignant melanoma in clinical practice, including an ongoing post-marketing surveillance covering patients with unresectable malignant melanoma.
- The safety profile of NIVO in Study 238 was comparable to the safety profile observed with the approved indications [see Section 7.2.R.2.1].
- No particular safety concerns specific to Japanese patients arose in Study 238 [see Section 7.2.R.2.2].
- In view of the results of a PPK analysis and a review based on the data from Study 41 [see Sections 6.1.3.2 and 7.1.R.2.1], the change in the dosage regimens of NIVO from body weight-based dosages to fixed dosages is unlikely to cause any particular safety concerns. Safety information will be collected from patients receiving NIVO at the fixed dosages for the approved indications in the ongoing and planned post-marketing surveillance.

(c) The applicant plans to conduct a post-marketing surveillance covering patients treated with NIVO/IPI therapy for unresectable or metastatic RCC. The purpose of the surveillance is to evaluate the safety and other aspects of NIVO/IPI therapy in clinical practice.
- The safety specifications for the surveillance include colitis, diarrhoea, gastrointestinal perforation; and hepatic function disorder, cholangitis sclerosing, based on the Grade ≥3 adverse events that led to drug discontinuation in the NIVO/IPI group of Study 214 and other findings.
- The target sample size is 120 patients, based on the incidence of the events selected as the safety specifications for the surveillance in the NIVO/IPI group of Study 214 and for other reasons.
- The observation period is 13 weeks, because in the NIVO/IPI group of Study 214, most of the events selected as the safety specifications for the surveillance occurred within 3 months after the start of NIVO/IPI therapy.

PMDA's conclusion:

PMDA's conclusions on the post-marketing surveillance plans for (a) the treatment of malignant pleural mesothelioma, (b) the adjuvant therapy of malignant melanoma (including the change in the dosage regimens of NIVO from body weight-based dosages to fixed dosages), and (c) the treatment of RCC:

(a) Although a certain amount of post-marketing safety data have been collected from patients treated with NIVO for the approved indications, only a limited amount of safety data is available in Japanese patients treated with NIVO for malignant pleural mesothelioma. Therefore, a post-marketing surveillance should be conducted to collect safety information from Japanese patients treated with NIVO for malignant pleural mesothelioma, and the surveillance results, including safety information, should be promptly provided to healthcare professionals. The post-marketing surveillance plan proposed by the applicant is acceptable.

(b) As a result of its review described in Sections "7.2.R.2 Safety" and "7.4.R.1 Dosage and administration," there is little need to initiate a new post-marketing surveillance soon after the

approval, and the necessary safety information may be collected through routine pharmacovigilance activities. For the changes in the dosage regimens of NIVO from body weight-based dosages to fixed dosages, safety data should be collected from patients treated with fixed dosages of NIVO in combination with IPI, through the currently planned post-marketing surveillance in patients treated with NIVO/IPI therapy for unresectable 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").

(c) Only a limited amount of safety data is available in Japanese patients treated with NIVO/IPI therapy for RCC. Therefore, the applicant should conduct a post-marketing surveillance to collect such safety data and information on treatments administered for adverse events. The post-marketing surveillance plan proposed by the applicant is acceptable.

7.6 Adverse events reported in clinical studies

Among the clinical study data submitted for the safety evaluation, data on deaths are presented in the sections of "Evaluation data" [Sections 7.1.1, 7.2.1, and 7.3.1] and "Reference data" [Section 7.3.2]. Other major adverse events are presented below.

7.6.1 Japanese phase II study (Study 41)

Adverse events were reported in 32 of 34 patients (94.1%). Adverse events for which a causal relationship to NIVO could not be ruled out were reported in 23 of 34 patients (67.6%). Table 27 shows the adverse events reported with a ≥10% incidence.

Table 27. Adverse events with a ≥10% incidence

SOC PT (MedDRA ver.20.0)	n (%) N = 34	
	All grades	Grade ≥3
All adverse events	32 (94.1)	13 (38.2)
Gastrointestinal disorders		
Diarrhoea	5 (14.7)	2 (5.9)
Nausea	4 (11.8)	0
Stomatitis	5 (14.7)	1 (2.9)
General disorders and administration site conditions		
Pyrexia	6 (17.6)	0
Infections and infestations		
Viral upper respiratory tract infection	8 (23.5)	0
Investigations		
Lipase increased	4 (11.8)	2 (5.9)
Weight decreased	4 (11.8)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (11.8)	0
Skin and subcutaneous tissue disorders		
Rash	4 (11.8)	0

Serious adverse events were reported in 11 of 34 patients (32.4%). The serious adverse events were anaemia, hypothyroidism, diarrhoea, pyrexia, hypersensitivity, bronchitis, biliary tract infection,

decreased appetite, type 1 diabetes mellitus, cancer pain, ILD, and pneumonitis (1 patient [2.9%] each). A causal relationship to NIVO could not be ruled out for the hypothyroidism, diarrhoea, pyrexia, decreased appetite, type 1 diabetes mellitus, ILD, and pneumonitis occurring in 1 patient each.

Adverse events leading to drug discontinuation were reported in 2 of 34 patients [5.9%]. The adverse events leading to drug discontinuation were ILD and pneumonitis (1 patient [2.9%] each). For both of these adverse events, a causal relationship to NIVO could not be ruled out.

7.6.2 Global phase III study (Study 238)

Adverse events were reported in 438 of 452 patients (96.9%) in the NIVO group and 446 of 453 patients (98.5%) in the IPI group. Adverse events for which a causal relationship to NIVO could not be ruled out were reported in 385 of 452 patients (85.2%) in the NIVO group and 434 of 453 patients (95.8%) in the IPI group. Table 28 shows the adverse events reported with a ≥15% incidence in either treatment group.

Table 28. Adverse events reported with a ≥15% incidence in either treatment group

System Organ Class Preferred Term (MedDRA ver. 20.0)	n (%)			
	NIVO N = 452		IPI N = 453	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
Gastrointestinal disorders				
Diarrhoea	167 (36.9)	11 (2.4)	247 (54.5)	48 (10.6)
Nausea	104 (23.0)	1 (0.2)	127 (28.0)	0
Abdominal pain	53 (11.7)	0	73 (16.1)	4 (0.9)
General disorders and administration site conditions				
Asthenia	72 (15.9)	1 (0.2)	70 (15.5)	7 (1.5)
Fatigue	193 (42.7)	3 (0.7)	185 (40.8)	4 (0.9)
Pyrexia	32 (7.1)	0	96 (21.2)	5 (1.1)
Musculoskeletal and connective tissue disorders				
Arthralgia	87 (19.2)	2 (0.4)	59 (13.0)	2 (0.4)
Nervous system disorders				
Headache	106 (23.5)	2 (0.4)	142 (31.3)	9 (2.0)
Respiratory, thoracic, and mediastinal disorders				
Cough	82 (18.1)	0	78 (17.2)	0
Skin and subcutaneous tissue disorders				
Pruritus	127 (28.1)	0	167 (36.9)	5 (1.1)
Rash	115 (25.4)	5 (1.1)	150 (33.1)	16 (3.5)
Investigations				
ALT increased	33 (7.3)	5 (1.1)	81 (17.9)	28 (6.2)
AST increased	28 (6.2)	2 (0.4)	71 (15.7)	20 (4.4)

Serious adverse events were reported in 79 of 452 patients (17.5%) in the NIVO group and 183 of 453 patients (40.4%) in the IPI group. The serious adverse events reported in ≥5 patients in the NIVO group were melanoma recurrent in 8 patients (1.8%) and cellulitis in 7 patients (1.5%). The serious adverse events reported in ≥5 patients in the IPI group were diarrhoea in 35 patients (7.7%), colitis in 32 patients (7.1%), hypophysitis in 14 patients (3.1%), pyrexia in 9 patients (2.0%), and autoimmune colitis, pneumonitis, and hepatitis in 5 patients (1.1%) each. A causal relationship to IPI could not be ruled out

for the diarrhoea and colitis in 32 patients each, hypophysitis in 14 patients, pyrexia in 6 patients, and autoimmune colitis, pneumonitis, and hepatitis in 5 patients each.

Adverse events leading to drug discontinuation were reported in 44 of 452 patients (9.7%) in the NIVO group and 193 of 453 patients (42.6%) in the IPI group. The adverse events that led to drug discontinuation in ≥5 patients in the NIVO group were diarrhoea in 7 patients (1.5%) and colitis in 5 patients (1.1%). The adverse events that led to drug discontinuation in ≥5 patients in the IPI group were diarrhoea in 46 patients (10.2%), colitis in 37 patients (8.2%), hypophysitis in 19 patients (4.2%), ALT increased in 16 patients (3.5%), AST increased in 13 patients (2.9%), and hepatitis and pneumonitis in 7 patients (1.5%) each. A causal relationship to the study drug could not be ruled out for the diarrhoea in 7 patients and colitis in 5 patients in the NIVO group, and for the diarrhoea in 45 patients, colitis in 37 patients, hypophysitis in 19 patients, ALT increased in 15 patients, AST increased in 12 patients, and hepatitis and pneumonitis in 7 patients each in the IPI group.

7.6.3 Global phase III study (Study 214)

Adverse events were reported in 544 of 547 patients (99.5%) in the NIVO/IPI group and 532 of 535 patients (99.4%) in the sunitinib group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 509 of 547 patients (93.1%) in the NIVO/IPI group and 521 of 535 patients (97.4%) in the sunitinib group. Table 29 shows adverse events reported with a ≥25% incidence in either treatment group.

Table 29. Adverse events reported with a ≥25% incidence in either treatment group

System Organ Class Preferred Term (MedDRA ver. 20.0)	n (%)			
	NIVO/IPI N = 547		Sunitinib N = 535	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	544 (99.5)	374 (68.4)	532 (99.4)	425 (79.4)
Endocrine disorders				
Hypothyroidism	96 (17.6)	2 (0.4)	145 (27.1)	1 (0.2)
Gastrointestinal disorders				
Diarrhoea	205 (37.5)	25 (4.6)	310 (57.9)	33 (6.2)
Nausea	163 (29.8)	11 (2.0)	230 (43.0)	8 (1.5)
Stomatitis	29 (5.3)	0	153 (28.6)	14 (2.6)
Vomiting	109 (19.9)	5 (0.9)	149 (27.9)	11 (2.1)
General disorders and administration site conditions				
Fatigue	246 (45.0)	34 (6.2)	291 (54.4)	54 (10.1)
Pyrexia	136 (24.9)	4 (0.7)	91 (17.0)	3 (0.6)
Mucosal inflammation	18 (3.3)	0	157 (29.3)	14 (2.6)
Metabolism and nutrition disorders				
Decreased appetite	114 (20.8)	10 (1.8)	156 (29.2)	5 (0.9)
Nervous system disorders				
Dysgeusia	40 (7.3)	0	185 (34.6)	1 (0.2)
Respiratory, thoracic and mediastinal disorders				
Cough	145 (26.5)	1 (0.2)	125 (23.4)	2 (0.4)
Skin and subcutaneous tissue disorders				
Pruritus	180 (32.9)	3 (0.5)	58 (10.8)	0
Rash	141 (25.8)	8 (1.5)	84 (15.7)	0
Palmar-plantar erythrodysaesthesia syndrome	9 (1.6)	0	237 (44.3)	50 (9.3)
Vascular disorders				
Hypertension	52 (9.5)	18 (3.3)	231 (43.2)	94 (17.6)

Serious adverse events were reported in 305 of 547 patients (55.8%) in the NIVO/IPI group and 213 of 535 patients (39.8%) in the sunitinib group. The serious adverse events reported in ≥15 patients in the NIVO/IPI group were diarrhoea in 24 patients (4.4%), malignant neoplasm progression in 22 patients (4.0%), pyrexia in 18 patients (3.3%), pneumonia in 17 patients (3.1%), and pneumonitis in 15 patients (2.7%). The serious adverse event reported in ≥15 patients in the sunitinib group was malignant neoplasm progression in 31 patients (5.8%). A causal relationship to the study drug could not be ruled out for the diarrhoea in 21 patients, pneumonitis in 15 patients, pyrexia in 9 patients, and malignant neoplasm progression and pneumonia in 1 patient each in the NIVO/IPI group.

Adverse events leading to drug discontinuation were reported in 168 of 547 patients (30.7%) in the NIVO/IPI group and 114 of 535 patients (21.3%) in the sunitinib group. The adverse events that led to drug discontinuation in ≥10 patients in the NIVO/IPI group were ALT increased and diarrhoea in 15 patients (2.7%) each, malignant neoplasm progression in 14 patients (2.6%), AST increased in 12 patients (2.2%), and pneumonitis in 11 patients (2.0%). The adverse event that led to drug discontinuation in ≥10 patients in the sunitinib group was malignant neoplasm progression in 12 patients (2.2%). A causal relationship to the study drug could not be ruled out for the ALT increased in 15 patients, diarrhoea in 14 patients, AST increased in 12 patients, and pneumonitis in 11 patients in the NIVO/IPI group.

7.6.4 Foreign phase I study (Study 016)

Adverse events were reported in 47 of 47 patients (100%) in Arm I-1, 47 of 47 patients (100%) in Arm I-3, 6 of 6 patients (100%) in Arm IN-3, 33 of 33 patients (100%) in Arm S, and 20 of 20 patients (100%) in Arm P. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 43 of 47 patients (91.5%) in Arm I-1, 45 of 47 patients (95.7%) in Arm I-3, 6 of 6 patients (100%) in Arm IN-3, 33 of 33 patients (100%) in Arm S, and 20 of 20 patients (100%) in Arm P. The adverse events reported with a ≥75% incidence in each group were fatigue and pyrexia in 6 patients (100%), hypothyroidism, diarrhoea, decreased appetite, arthralgia, and cough in 5 patients (83.3%) in Arm IN-3, fatigue in 29 patients (87.9%) in Arm S, and nausea in 16 patients (80.0%) and fatigue in 15 patients (75.0%) in Arm P.

Serious adverse events were reported in 29 of 47 patients (61.7%) in Arm I-1, 30 of 47 patients (63.8%) in Arm I-3, 4 of 6 patients (66.7%) in Arm IN-3, 19 of 33 patients (57.6%) in Arm S, and 13 of 20 patients (65.0%) in Arm P. The serious adverse events reported in ≥6 patients in each treatment group were malignant neoplasm progression in 6 patients (12.8%) in Arm I-1, and diarrhoea and colitis in 6 patients (12.8%) each in Arm I-3. For the colitis in 6 patients and diarrhoea in 5 patients in Arm I-3, a causal relationship to the study drug could not be ruled out in any of the patients.

Adverse events leading to drug discontinuation were reported in 5 of 47 patients (10.6%) in Arm I-1, 15 of 47 patients (31.9%) in Arm I-3, 2 of 6 patients (33.3%) in Arm IN-3, 13 of 33 patients (39.4%) in Arm S, and 5 of 20 patients (25.0%) in Arm P. The adverse event that led to drug discontinuation in ≥5 patients in each treatment group was ALT increased in 5 patients (10.6%) in Arm I-3; a causal relationship to the study drug was ruled out in any of these patients.

7.6.5 Foreign phase Ib study (Study 09)

Adverse events were reported in all of 91 patients (100%), and adverse events for which a causal relationship to NIVO could not be ruled out were reported in 81 of 91 patients (89.0%). The adverse event reported with a ≥50% incidence was fatigue in 53 patients (58.2%).

Serious adverse events were reported in 47 of 91 patients (51.6%). The serious adverse event that was reported in ≥5 patients was malignant neoplasm progression in 9 patients (9.9%); a causal relationship to NIVO was denied in all of these patients.

Adverse events leading to discontinuation of NIVO were reported in 22 of 91 patients (24.2%). The adverse event that led to discontinuation of NIVO in ≥5 patients was malignant neoplasm progression in 7 patients (7.7%); a causal relationship to NIVO was denied in all of these patients.

7.6.6 Foreign phase II study (Study MDX010-11)

Adverse events were reported in 59 of 61 patients (96.7%). Adverse events for which a causal relationship to IPI could not be ruled out were reported in 54 of 61 patients (88.5%). The adverse event reported with a ≥40% incidence was diarrhoea in 25 patients (41.0%).

Serious adverse events were reported in 32 of 61 patients (52.5%). The serious adverse events reported in ≥10 patients were diarrhoea and colitis in 16 patients (26.2%) each; a causal relationship to IPI could not be ruled out in any of these patients.

Adverse events leading to discontinuation of IPI were reported in 17 of 61 patients (27.9%). The adverse event that led to drug discontinuation in ≥10 patients was colitis in 12 patients (19.7%); a causal relationship to IPI could not be ruled out in all of these 12 patients.

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 inspections and assessment are currently ongoing. The results of the inspections and assessment, and PMDA's conclusion are reported in the Review Report (2).

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

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

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

On the basis of the data submitted, PMDA has concluded that NIVO administered alone or in combination with IPI has efficacy in the treatment of the following disease conditions, and that NIVO administered alone or in combination with IPI has acceptable safety in view of its benefits. NIVO administered alone or in combination with IPI is clinically meaningful because it offers new treatment options for patients with these disease conditions. PMDA has also concluded that changes in the dosage regimens of NIVO from body weight-based dosages to fixed dosages are acceptable.

- NIVO monotherapy for unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy
- NIVO monotherapy for the adjuvant therapy of malignant melanoma
- NIVO/IPI therapy for unresectable or metastatic RCC

The indications, dosage and administration, etc. of NIVO and IPI should be further investigated.

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

Review Report (2)

July 25, 2018

Product Submitted for Approval

(a)	**Brand Name**	(a) Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg (b) Opdivo Intravenous Infusion 240 mg
	Non-proprietary Name	Nivolumab (Genetical Recombination)
	Applicant	Ono Pharmaceutical Co., Ltd.
	Date of Application	(a) December 22, 2017; January 15, 2018[24] (b) July 25, 2018[24]

(b)	**Brand Name**	Yervoy Injection 50 mg (for intravenous use)
	Non-proprietary Name	Ipilimumab (Genetical Recombination)
	Applicant	Bristol-Meyers Squibb K.K.
	Date of Application	January 15, 2018

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 Sections "7.1.R.1 Efficacy," "7.2.R.1 Efficacy," and "7.3.R.1 Efficacy" of the Review Report (1), PMDA made the following conclusions on (a) nivolumab (genetical recombination) ("NIVO") for malignant pleural mesothelioma, (b) NIVO for the adjuvant therapy of malignant melanoma, and (c) NIVO in combination with ipilimumab (genetical recombination) ("IPI") for RCC.

[24] For (a) Opdivo Intravenous Infusion 20 mg and Opdivo Intravenous Infusion 100 mg, and for (b) Opdivo Intravenous Infusion 240 mg, partial change applications to add a new dosage and administration for combination therapy with nivolumab (genetical recombination) and ipilimumab (genetical recombination) for the treatment of renal cell carcinoma were filed on (a) January 15, 2018 and (b) March 27, 2018, respectively. For Opdivo Intravenous infusion 240 mg, an approval application was filed on January 31, 2018 (for additional dosage form, etc.) and March 27, 2018; however, another approval application was filed on July 25, 2018 based on the same data that had been submitted at the above-mentioned applications, since the addition of a new dosage and administration of Opdivo Intravenous Infusion 20 mg and Opdivo Intravenous Infusion 100 mg in combination therapy with nivolumab (genetical recombination) and ipilimumab (genetical recombination) for malignant melanoma was approved on May 25, 2018 (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").

(a) Based on the results of the primary endpoint (response rate) and other endpoints in a Japanese phase II study in chemotherapy-treated[25] patients with unresectable, advanced or recurrent malignant pleural mesothelioma (Study 41), a certain level of efficacy of NIVO has been demonstrated in the target patient population of Study 41.
(b) The results of a global phase III study in patients with resected stage[26] IIIb/c or IV malignant melanoma[27] (Study 238) showed the superiority of NIVO to IPI in the primary endpoint of investigator-assessed RFS.[28] Based on this result and other findings, the efficacy of NIVO has been demonstrated in the target patient population of Study 238.
(c) A global phase III study in chemotherapy-naïve patients with unresectable or metastatic[29] clear cell RCC (Study 214) showed the superiority of NIVO/IPI therapy to sunitinib in the primary endpoint of OS, in patients categorized as being at intermediate or poor risk disease as per the IMDC criteria.[30] Based on this result and other findings, the efficacy of NIVO/IPI therapy has been demonstrated in intermediate- or poor-risk patients among the target patient population of Study 214.

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

1.2 Safety

As a result of its review, described in Sections "7.1.R.2 Safety," "7.2.R.2 Safety," and "7.3.R.2 Safety" of the Review Report (1), PMDA concluded that the following adverse events should be closely monitored when NIVO is administered to chemotherapy-treated patients with unresectable, advanced or recurrent malignant pleural mesothelioma, when NIVO is administered to patients with resected stage IIIb/c or IV malignant melanoma in an adjuvant setting, or when NIVO is administered in combination with IPI to patients with unresectable or metastatic RCC. These events were identified as requiring attention at the regulatory reviews for the approved indications of (a) NIVO or (b) IPI.

(a) Interstitial lung disease (ILD); hepatic function disorder; abnormal thyroid function; infusion reaction; skin disorder; colitis, severe diarrhoea; myasthenia gravis, myocarditis, rhabdomyolysis, myositis; neurological disorder; renal disorder; venous thrombosis and embolism; adrenal disorder; encephalitis; type 1 diabetes mellitus; immune thrombocytopenic purpura; and cardiac disorder

[25] Patients were eligible, if they were resistant or intolerant to platinum-based antineoplastic therapy in combination with PEM, and had received ≤2 prior therapies.
[26] Disease stage was assessed according to the staging system of the American Joint Committee on Cancer (AJCC), seventh edition.
[27] Patients who have undergone complete resection
[28] Defined as the time between the date of randomization and the date of (a) first recurrence (local recurrence, regional lymph node metastasis, or distant metastasis), (b) new primary malignant melanoma, or (c) death from any cause, whichever occurs first
[29] Disease stage IV per the AJCC staging system
[30] Patients who met none of the factors (a) to (f) below were categorized as being at "favorable risk," patients who met 1 or 2 factors at "intermediate risk," and patients who met 3 or more factors at "poor risk."
(a) < 1 year from the time of the initial diagnosis of RCC to randomization for Study 214
(b) Karnofsky performance status <80%
(c) Hemoglobin level < lower limit of normal
(d) Corrected calcium level >10 mg/dL
(e) Neutrophil count > upper limit of normal
(f) Platelet count > upper limit of normal

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

PMDA concluded that NIVO administered alone to patients with malignant pleural mesothelioma or patients with resected malignant melanoma, or in combination with IPI to patients with RCC is tolerable, provided that physicians with sufficient knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions, including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions, and drug interruption.

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

1.3 Clinical positioning and indications

As a result of its review described in Sections "7.1.R.3 Clinical positioning and indication," "7.2.R.3 Clinical positioning and indication," and "7.3.R.3 Clinical positioning and indication" of the Review Report (1), PMDA concluded that the statements presented in the table below should be included in the "Indications" and "Precautions for Indications" sections of the package inserts for NIVO and IPI, for (a) "NIVO monotherapy for malignant pleural mesothelioma," (b) "NIVO monotherapy for the adjuvant therapy of malignant melanoma," and (c) "NIVO/IPI therapy for RCC."

		Indications	Precautions for Indications
(a)	NIVO	Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy	• The efficacy and safety of NIVO as a first-line treatment have not been established.
(b)		Malignant melanoma (Changed from the approved indication of "unresectable malignant melanoma")	• Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, and a thorough understanding of the efficacy and safety of NIVO.
(c)		Unresectable or metastatic RCC (No change from the approved indication)	• The efficacy and safety of NIVO in adjuvant therapy have not been established. • Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, and a thorough understanding of the efficacy and safety of NIVO. • The use of NIVO for the treatment of chemotherapy-naïve patients with unresectable or metastatic RCC should be limited to IMDC intermediate- or poor-risk patients.
	IPI	Unresectable or metastatic RCC	• The efficacy and safety of IPI in adjuvant therapy have not been established. • Eligibility of patients for treatment with IPI should be determined based on a good understanding of the "Clinical Studies" section of the package insert and the efficacy and safety of IPI. • The use of IPI should be limited to IMDC intermediate- or poor-risk patients.

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

Based on the above, PMDA instructed the applicant to include the above precautionary statements in the "Indications" and "Precautions for Indications" sections of the package inserts for NIVO and IPI. The applicant agreed.

1.4 Dosage and administration

As a result of its review, described in Section "7.4.R Dosage and administration" of the Review Report (1), PMDA concluded that the statements presented in the table below should be included in the "Dosage and administration" and "Precautions for Dosage and Administration" sections of the package inserts for NIVO and IPI.

	Dosage and Administration	Precautions for Dosage and Administration
NIVO	• Malignant melanoma The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. When administered in combination with IPI to chemotherapy-naïve patients with 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. • Unresectable or metastatic RCC The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 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. • Unresectable, advanced or recurrent NSCLC, relapsed or refractory cHL, recurrent or distant metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, or unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy The usual adult dosage of NIVO is 240 mg administered as an intravenous infusion every 2 weeks.	• In the treatment of unresectable malignant melanoma, 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. • In the treatment of 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. • In the treatment of NSCLC, cHL, head and neck cancer, gastric cancer, or malignant pleural mesothelioma, the efficacy and safety of NIVO in combination with other antineoplastic drugs have not been established. • NIVO should be administered as an intravenous infusion over at least 30 minutes. • An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion.
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 times. For the treatment of chemotherapy-naïve patients with unresectable malignant melanoma, IPI should not be used in combination with antineoplastic agents other than NIVO. • Unresectable or metastatic RCC 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 times.	• The criteria for suspension or discontinuation of treatment in the event of adverse reactions (omitted, since they are identical to those at the initial approval) • In the treatment of unresectable malignant melanoma, 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 should be administered intravenously over a period of 90 minutes in patients with unresectable malignant melanoma, or 30 minutes in patients with unresectable or metastatic RCC. When necessary, IPI should be diluted with normal saline or 5% glucose solution for injection.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion and made the following comments.

- The dosage regimen proposed by PMDA restricts the intended patient population of NIVO/IPI therapy for unresectable malignant melanoma to chemotherapy-naïve patients. Considering that the study patient population of the foreign phase III study that has demonstrated the efficacy of NIVO/IPI therapy in the treatment of unresectable malignant melanoma (Study 067) (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") was chemotherapy-naïve patients, the intended population of NIVO/IPI therapy should be chemotherapy-naïve patients. Thus, PMDA's conclusion is understandable. On the other hand, there are only limited therapeutic options for the second-line and subsequent treatment of patients with malignant melanoma with *BRAF* mutations who have received *BRAF* inhibitor therapies (a combination therapy of dabrafenib mesilate and trametinib dimethyl sulfoxide, or vemurafenib monotherapy). Therefore, it is preferable to also allow chemotherapy-treated patients to choose NIVO/IPI therapy.

Taking account of the above comment raised in the Expert Discussion, PMDA asked the applicant to explain the efficacy and safety of NIVO/IPI therapy in chemotherapy-treated patients with unresectable malignant melanoma.

The applicant's explanation:
In patients who received NIVO/IPI therapy (Cohort 8) in a foreign phase I study in patients with unresectable malignant melanoma (Study CA209004), the response rate (95% CI) determined by the modified WHO criteria was 46.4% (13 of 28 patients) [27.5%, 66.1%] in chemotherapy-naïve patients and 38.5% (5 of 13 patients) [13.9%, 68.4%] in chemotherapy-treated patients.

Table 30 shows a safety summary of Cohort 8 of Study CA209004.

Table 30. Safety summary (Cohort 8 of Study CA209004)

	n (%)	
	Chemotherapy-naïve N = 28	Chemotherapy-treated N = 13
All adverse events	28 (100)	13 (100)
Grade ≥3 adverse events	22 (78.6)	8 (61.5)
Adverse events leading to death	1 (3.6)	0
Serious adverse events	19 (67.9)	7 (53.8)
Adverse events leading to drug discontinuation	8 (28.6)	3 (23.1)

PMDA's view:
Since the results of Study CA209004 (Cohort 8) showed no clear differences in the efficacy or safety of NIVO/IPI therapy between chemotherapy-naïve patients and chemotherapy-treated patients, and based on other considerations, there seems to be no need to restrict the intended population of NIVO/IPI therapy for unresectable malignant melanoma to chemotherapy-naïve patients.

PMDA's conclusion:
The dosage and administration of NIVO and IPI in the combination therapy for unresectable malignant melanoma should be modified as follows, provided that a statement to the effect that the necessity of NIVO/IPI therapy should be carefully considered is included in the "Precautions for Dosage and Administration" section.

NIVO

- Dosage and administration
  - Malignant melanoma

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

    When administered in combination with IPI to patients with 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.
- Precautions for Dosage and Administration
  - 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 content of the "Clinical Studies" section, particularly regarding the characteristics, such as prior treatments, of patients enrolled in clinical studies, and a thorough understanding of the efficacy and safety of 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

- Dosage and administration
  - 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 times. IPI should not be used in combination with antineoplastic agents other than NIVO.
- Precautions for Dosage and Administration
  - When administered in combination with NIVO to patients with unresectable malignant melanoma, the necessity of the combination therapy should be carefully determined based on a careful review of the content of the "Clinical Studies" section, particularly regarding the characteristics, such as prior treatments, of patients enrolled in 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 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.

Based on the above, PMDA instructed the applicant to include the above statements in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections of the package inserts for NIVO and IPI. The applicant agreed.

1.5 Risk management plan (draft)

The applicant's explanation about their post-marketing surveillance plans for (a) the treatment of malignant pleural mesothelioma, (b) the adjuvant therapy of malignant melanoma and the changes in the dosage regimens of NIVO from body weight-based dosages to fixed dosages, and (c) the treatment of RCC:

(a) A post-marketing surveillance covering patients treated with NIVO for unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy is planned, as described below. The purpose of the surveillance is to evaluate the safety and other aspects of NIVO in clinical practice.
- Safety specification: all adverse events
- Planned sample size: 100 patients
- Observation period: 6 months

(b) There is a certain amount of clinical experience with NIVO in patients with malignant melanoma in routine clinical practice. In view of the results of PPK analyses and Study 41 [see the Review Report (1) Sections 6.1.3.2 and 7.1.R.2.1], there should be no particular safety concern associated with the change in the dosage regimens of NIVO from body weight-based dosages to fixed dosages. For these and other reasons, it is not necessary to initiate the post marketing surveillance for the adjuvant therapy of malignant melanoma and the change of the dosage regimen of NIVO from body weight-based dosages to fixed dosages soon after the approval.

(c) The post-marketing surveillance covering patients treated with NIVO/IPI therapy for unresectable or metastatic RCC is planned, as described below. The purpose of the surveillance is to evaluate the safety and other aspects of NIVO/IPI therapy in clinical practice.
- Safety specifications: colitis, diarrhoea, gastrointestinal perforation; and liver disorder, cholangitis sclerosing
- Planned sample size: 120 patients
- Observation period: 13 weeks

In view of the discussions presented in Section "7.5.R Post-marketing investigations" in the Review Report (1), PMDA formed the following conclusions as to the post-marketing surveillance plans for (a) the treatment of malignant pleural mesothelioma, (b) the adjuvant therapy of malignant melanoma and the change in the dosage regimens of NIVO from body weight-based dosages to fixed dosages, and (c) the treatment of RCC.

(a) Only a limited amount of safety data is available in Japanese patients treated with NIVO for malignant pleural mesothelioma. Therefore, the applicant should conduct a post-marketing surveillance to collect such safety data. The surveillance plan proposed by the applicant is acceptable.

(b) For the adjuvant therapy of malignant melanoma, there is little need to initiate new post-marketing surveillance soon after the approval, and the necessary safety data may be collected through routine pharmacovigilance activities. For the changes in the dosage regimens of NIVO from body weight-based dosages to fixed dosages, safety data should be collected from patients treated with fixed dosages of NIVO in combination with IPI, through the currently planned post-marketing surveillance in patients treated with NIVO/IPI therapy for unresectable 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").

(c) Only a limited amount of safety data are available in Japanese patients treated with NIVO/IPI therapy for RCC. Therefore, the applicant should conduct a post-marketing surveillance to collect such safety data and information on treatments administered for adverse events. The post-marketing surveillance plan proposed by the applicant is acceptable.

PMDA's conclusion was supported by the expert advisors at the Expert Discussion.

In view of the discussion above, PMDA has concluded that the risk management plans (draft) for NIVO and IPI should include the safety and efficacy specifications presented in Tables 31 and 33, and that the applicants should conduct additional pharmacovigilance activities, efficacy investigations/studies, and additional risk minimization activities presented in Tables 32, 34, 35, and 36.

Table 31. Safety and efficacy specifications in the risk management plan for NIVO (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• ILD • Myasthenia gravis, myocarditis, myositis, rhabdomyolysis • Colitis, severe diarrhoea • Type 1 diabetes mellitus • Hepatic function disorder, cholangitis sclerosing • Abnormal thyroid function • Neurological disorder • Renal disorder (including renal failure and tubulointerstitial nephritis) • Adrenal disorder • Encephalitis • Severe skin disorder • Venous thrombosis and embolism • Infusion reaction • Immune thrombocytopenic purpura • Use in patients with a history of organ transplantation (including hematopoietic stem cell transplantation)	• Excessive immune response • Embryonic/fetal toxicity • Cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles) • Haemolytic anaemia • Increased risk of severe comorbidities associated with allogenic hematopoietic stem cell transplantation after NIVO therapy (Haematological malignancy)	None
Efficacy specification		
• Efficacy in the treatment of patients with unresectable malignant melanoma in clinical practice • Efficacy in the treatment of patients with unresectable, advanced or recurrent NSCLC in clinical practice • Efficacy in the treatment of patients with unresectable or metastatic RCC in clinical practice • Efficacy in the treatment of patients with recurrent or refractory cHL in clinical practice • Efficacy in the treatment of patients with recurrent or distant metastatic head and neck cancer in clinical practice • Efficacy in the treatment of patients with unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy in clinical practice		

No changes are made in the present partial change applications

Table 32. Summary of additional pharmacovigilance activities, efficacy investigations/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
• Early post-marketing phase vigilance in patients with unresectable malignant melanoma (NIVO/IPI therapy) • Early post-marketing phase vigilance in patients with unresectable or metastatic RCC (NIVO/IPI therapy)	• 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)	• Disseminate data gathered during the early post-marketing phase vigilance in patients with unresectable malignant melanoma (NIVO/IPI therapy)

• 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 distant 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) • Use-results survey in patients with unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy • Specified use-results survey in patients with unresectable or metastatic RCC (NIVO/IPI therapy) • Post-marketing clinical study in patients with unresectable malignant melanoma (extension study of Study 02) • Post-marketing clinical study in patients with unresectable, advanced or recurrent SQ-NSCLC (extension study of Study 05) • Post-marketing clinical study in patients with unresectable, advanced or recurrent NSQ-NSCLC (extension study of Study 06) • Post-marketing clinical study in chemotherapy-naïve patients with unresectable malignant melanoma (extension study of Study 08) • Post-marketing clinical study involving 2 dosing regimens in patients with unresectable malignant melanoma (extension study of Study ONO-4538-31) • Post-marketing clinical study in chemotherapy-treated patients with advanced or metastatic clear cell RCC (extension study of Study 025) • Post-marketing clinical study in patients with relapsed or refractory cHL (extension study of Study 15) • Post-marketing clinical study in patients with unresectable, advanced or recurrent gastric cancer who have received ≥2 chemotherapy regimens (extension study of Study 12) • Post-marketing clinical study in chemotherapy-naïve patients with advanced or metastatic RCC (extension study of Study 214, NIVO/IPI therapy) • Post-marketing clinical study in patients with unresectable, advanced or metastatic malignant pleural mesothelioma (extension study of Study 41)	• 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 distant 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 study in patients with unresectable malignant melanoma (extension study of Study 02) • Post-marketing clinical study in patients with unresectable, advanced or recurrent SQ-NSCLC (extension study of Study 05) • Post-marketing clinical study in patients with unresectable, advanced or recurrent NSQ-NSCLC (extension study of Study 06) • Post-marketing clinical study in chemotherapy-naïve patients with unresectable malignant melanoma (extension study of Study ONO-4538-08) • Post-marketing clinical study involving 2 dosing regimens in patients with unresectable malignant melanoma (extension study of Study ONO-4538-31) • Post-marketing clinical study in chemotherapy-treated patients with advanced or metastatic clear cell RCC (extension study of Study 025) • Post-marketing clinical study in patients with relapsed or refractory cHL (extension study of Study 15) • Post-marketing clinical study in patients with unresectable, advanced or recurrent gastric cancer who have received ≥2 chemotherapy regimens (extension study of Study 12)	• Disseminate data gathered during the early post-marketing phase vigilance in patients with unresectable or metastatic RCC (NIVO/IPI therapy) • Organize and disseminate information for healthcare professionals • Organize and disseminate information for patients

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

Table 33. Safety and efficacy specifications in the risk management plan for IPI (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Diarrhoea, colitis, gastrointestinal perforation • Liver disorder • Skin disorder • Hypophysitis, hypopituitarism, hypothyroidism, adrenal insufficiency • Peripheral neuropathy • Renal disorder • ILD • Infusion reaction • Myositis	• Excessive immune response • Reproductive and developmental toxicity • Sepsis	None
Efficacy specification		
• Efficacy in the treatment of patients with unresectable malignant melanoma in clinical practice		

No changes are made in the present partial change applications

Table 34. Summary of additional pharmacovigilance activities, efficacy investigations/studies, and additional risk minimization activities included under the risk management plan for IPI (draft)

Additional pharmacovigilance activities	Efficacy investigations/studies	Additional risk minimization activities
• Early post-marketing phase vigilance in patients with unresectable malignant melanoma (NIVO/IPI therapy) • Early post-marketing phase vigilance in patients with unresectable or metastatic RCC (NIVO/IPI therapy) • 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) • Post-marketing clinical study in chemotherapy-naïve patients with advanced or metastatic RCC (extension study of Study 214, NIVO/IPI therapy)	• Specified use-results survey in patients with unresectable malignant melanoma (all-case surveillance)	• Disseminate data gathered during the early post-marketing phase vigilance in patients with unresectable malignant melanoma (NIVO/IPI therapy) • Disseminate data gathered during the early post-marketing phase vigilance in patients with unresectable or metastatic RCC (NIVO/IPI therapy) • Organize and disseminate information for healthcare professionals • Organize and disseminate information for patients

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

Table 35. Outline of post-marketing surveillance in patients with malignant pleural mesothelioma (draft)

Objective	To evaluate the safety, etc. of NIVO in clinical practice
Survey method	Central registration system
Population	Patients treated with NIVO for unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy
Observation period	6 months
Planned sample size	100 patients
Main survey items	Safety specification: all adverse events Other key survey items: patient characteristics (e.g., age, sex, prior treatments, stage classification), exposure to NIVO, concomitant drugs/therapies, adverse events (including actions taken and outcome), and other relevant items

Table 36. Outline of post-marketing surveillance in patients with RCC (draft)

Objective	To evaluate the incidences of and measures taken for colitis, diarrhoea, gastrointestinal perforation; and hepatic function disorder, cholangitis sclerosing in patients who receive NIVO/IPI therapy in clinical practice
Survey method	Central registration system
Population	Patients treated with NIVO/IPI therapy for unresectable or metastatic RCC
Observation period	13 weeks
Planned sample size	120 patients
Main survey items	Safety specifications: colitis, diarrhoea, gastrointestinal perforation; and hepatic function disorder, cholangitis sclerosing Other key survey items: patient characteristics (e.g., age, sex, prior treatments, stage classification), exposure to NIVO and IPI, concomitant drugs/therapies, adverse events (including actions taken and outcome), and other relevant items

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

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

The new drug application data were subjected to 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its regulatory review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.2-1, CTD 5.3.5.1-1.1, and CTD 5.3.5.1-2.1) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The clinical studies were generally performed in accordance with GCP. PMDA thus concluded that there were no obstacles to conducting its regulatory review based on the application documents submitted. However, the inspection revealed the following finding at some of the study sites used by the applicant for CTD 5.3.5.1-2.1, despite its minor impact on the overall assessment of the studies. The heads of the sites were notified of the issue.

Issue that should be corrected

Study sites

- Protocol deviations (noncompliance with procedures for SAE reporting)

3. Overall Evaluation

As a result of the above review, PMDA has concluded that NIVO and IPI may be approved after modifying the proposed indications and dosage and administration as follows, with the condition of approval 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 period for the present applications are as follows.

NIVO

- Treatment of malignant melanoma (The re-examination period is the reminder of the ongoing re-examination period [until July 3, 2024].)
- Treatment of unresectable, advanced or recurrent NSCLC (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)
- Treatment of unresectable or metastatic RCC (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)
- Treatment of recurrent or refractory cHL (The re-examination period is the remainder of the ongoing re-examination period [until December 1, 2026].)
- Treatment of recurrent or distant metastatic head and neck cancer (The re-examination period is the remainder of the ongoing re-examination period [until October 16, 2021].)
- Treatment of 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].)
- Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy (The re-examination period is 10 years.)

IPI

- Unresectable or metastatic RCC (The re-examination period is 5 years and 10 months.)

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

Indications (Single underline denotes additions. Strikethrough denotes deletions.)

1. Treatment of ~~unresectable~~ malignant melanoma
2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer
3. Treatment of unresectable or metastatic renal cell carcinoma
4. Treatment of relapsed or refractory classical Hodgkin lymphoma
5. Treatment of recurrent or distant metastatic head and neck cancer
6. Treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy
7. <u>Treatment of unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy</u>

Dosage and Administration (Single underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of May 25, 2018.)

1. Treatment of ~~unresectable~~ malignant melanoma

~~Chemotherapy-naïve patients:~~

The usual adult dosage of nivolumab (genetical recombination) is 240 mg~~3 mg/kg body weight~~, administered as an intravenous infusion every 2 weeks. For the adjuvant therapy of malignant melanoma, the maximum duration of treatment is 12 months. In combination therapy with ipilimumab (genetical recombination) for unresectable malignant melanoma, the usual adult dosage of nivolumab (genetical recombination) is 80 mg~~1 mg/kg body weight~~ administered as an intravenous infusion every 3 weeks for 4 doses, followed by 240 mg~~3 mg/kg body weight~~ as an intravenous infusion every 2 weeks.

~~Chemotherapy-treated patients:~~

~~The usual adult dosage of nivolumab (genetical recombination) is 3 mg/kg body weight administered as an intravenous infusion every 2 weeks, or 2 mg/kg body weight as an intravenous infusion every 3 weeks.~~

2. Treatment of ~~unresectable, advanced or recurrent non-small cell lung cancer,~~ unresectable or metastatic renal cell carcinoma~~, relapsed or refractory classical Hodgkin lymphoma, recurrent or distant metastatic head and neck cancer, or unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy~~

The usual adult dosage of nivolumab (genetical recombination) is 240 mg~~3 mg/kg body weight~~, administered as an intravenous infusion every 2 weeks.

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

3. Treatment of unresectable, advanced or recurrent non-small cell lung cancer, relapsed or refractory classical Hodgkin lymphoma, recurrent or distant metastatic head and neck cancer, unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy, or unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy

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

Condition of Approval

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

Warnings (No change)

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

Contraindication (No change)

Patients with a history of hypersensitivity to the ingredients of Opdivo

Precautions for Indications (Single underline denotes additions. Strikethrough denotes deletions.)

(1) The efficacy and safety of Opdivo have not been established in chemotherapy-naïve patients with unresectable, advanced or recurrent non-small cell lung cancer.

(2) The use of Opdivo for the treatment of chemotherapy-naïve patients with unresectable or metastatic renal cell carcinoma should be limited to IMDC[Note)] intermediate- or poor-risk patients. ~~The efficacy and safety of Opdivo have not been established in chemotherapy-naïve patients with unresectable or metastatic renal cell carcinoma or patients with unresectable or metastatic renal cell carcinoma who have received cytokine therapy as the only prior treatment.~~

(3) The efficacy and safety of Opdivo have not been established in platinum-based chemotherapy-naïve patients with recurrent or distant metastatic head and neck cancer.

(4) The efficacy and safety of Opdivo have not been established in first- or second-line treatment of unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy.

(5) The efficacy and safety of Opdivo as a first-line treatment have not been established in patients with unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy.

(6~~5~~) The efficacy and safety of Opdivo in adjuvant ~~chemo~~therapy have not been established in patients with non-small cell lung cancer, renal cell carcinoma, head and neck cancer, or gastric cancer.

(7~~6~~) When Opdivo is used in the treatment of malignant melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, or head and neck cancer, eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section and a thorough understanding of the efficacy and safety of Opdivo.

Note) International Metastatic RCC Database Consortium

Precautions for Dosage and Administration (Single underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of May 25, 2018.)

~~(1) The dosing regimen of Opdivo for patients with unresectable malignant melanoma must be selected based on a careful review of the content of the "Clinical Studies" section.~~

(1~~2~~) ~~Precautions for Dosage and Administration~~

~~1) Prior to treatment, the required volume of the solution should be withdrawn from a vial(s) to achieve a single dose of 3, 2, or 1 mg/kg for the treatment of malignant melanoma and a single dose of 3 mg/kg for the treatment of non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, head and neck cancer, or gastric cancer.~~

~~2)~~ Opdivo should be intravenously infused over at least 30 minutes~~1 hour~~.

(2~~3~~) An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion.

(3) The efficacy and safety of Opdivo monotherapy have not been established in chemotherapy-naïve patients with unresectable or metastatic renal cell carcinoma or patients with unresectable

or metastatic renal cell carcinoma who have received cytokine therapy as the only prior treatment.

(4) The efficacy and safety of Opdivo in combination with other antineoplastic drugs ~~(including cytokines)~~ have not been established in patients with non-small cell lung cancer, ~~renal cell carcinoma~~, classical Hodgkin lymphoma, head and neck cancer, ~~or~~ gastric cancer, or malignant pleural mesothelioma.

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

Yervoy Injection 50 mg (for intravenous use)

Indications (Underline denotes additions.)

1. Unresectable malignant melanoma
2. Unresectable or metastatic renal cell carcinoma

Dosage and Administration (Single underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of May 25, 2018.)

1. Unresectable malignant melanoma

~~Chemotherapy-naïve patients:~~

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

~~Chemotherapy-treated patients:~~

~~The usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 times.~~

2. Unresectable or metastatic renal cell carcinoma

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 times.

Condition of Approval

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 a physician with expertise and experience in cancer chemotherapy and at medical institutions capable of emergency response. Before the start of treatment, consent should be obtained from the patient or their family members who have been fully informed of the risks and benefits of Yervoy.
2. Yervoy may cause serious diarrhoea, colitis, or gastrointestinal perforation. Some patients experienced these events a few months after the completion of treatment, leading to death. Patients must be adequately monitored after the completion of treatment as well as during treatment with Yervoy. Should any abnormalities arise, appropriate measures, including corticosteroid therapy, should be taken.

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

Precautions for Indications (Single underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of May 25, 2018.)

(1) Eligibility of patients for treatment with Yervoy should be determined based on a good understanding of the "Clinical Studies" section of the package insert and the efficacy and safety of Yervoy. In particular when administering Yervoy as monotherapy to chemotherapy-naïve patients with unresectable malignant melanoma, other therapeutic options should also be carefully considered.

(2) The use of Yervoy for the treatment of unresectable or metastatic renal cell carcinoma should be limited to IMDC[Note)] intermediate- or poor-risk patients.
Note) International Metastatic RCC Database Consortium

(32) The efficacy and safety of Yervoy in adjuvant ~~chemo~~therapy have not been established.

Precautions for Dosage and Administration (Single underline denotes additions. Strikethrough denotes deletions. Double-underline denotes additions made as of May 25, 2018.)

(1) In the event of adverse reactions, treatment should be suspended or discontinued according to the following criteria:

Criteria for suspension or discontinuation of treatment

Adverse reactions	Actions
• Grade 2 adverse reactions (excluding endocrine or skin disorder) • Grade 3 skin disorder • Symptomatic endocrine disorder	• Suspend treatment until the event resolves to Grade ≤1 or baseline. For endocrine disorder, suspend 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.~~3~~4.0.

(2) When administered in combination with nivolumab (genetical recombination) to patients with unresectable malignant melanoma, the necessity of the combination therapy should be carefully determined based on a careful review of the content of the "Clinical Studies" section, particularly regarding the characteristics, such as prior treatments, of patients enrolled in clinical studies, and a thorough understanding of the efficacy and safety of Yervoy. The add-on effect of Yervoy to nivolumab (genetical recombination) on survival prolongation tends to differ according to the percentage of tumor cells with 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 a period of 90 minutes in patients with unresectable malignant melanoma, or 30 minutes in patients with unresectable or metastatic renal cell carcinoma. When necessary, Yervoy should be diluted with normal saline or 5% glucose solution for injection.

List of Abbreviations

AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
C_{avg}	average serum concentration
C_{avgd14}	average serum concentration over the first 14 days of treatment
C_{avgd28}	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_{min}	minimum serum concentration
C_{mind14}	minimum serum concentration at day14
$C_{min,ss}$	minimum serum concentration at steady state
CR	complete response
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
EAU	European Association of Urology
FAS	full analysis set
FDA	Food and Drug Administration
gastric cancer	gastric cancer and gastroesophageal junction cancer
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IMDC	International Metastatic RCC Database Consortium
intermediate- or poor-risk	intermediate risk and poor risk, as per the IMDC criteria
IPI	ipilimumab (genetical recombination)
IRRC	Independent Radiology Review Committee
ITT	intent-to-treat
Japanese clinical practice guideline for renal cancer	"Evidence-based Clinical Practice Guideline for Renal Cell Carcinoma" compiled by the Japanese Urological Association
NCCN guidelines (Kidney Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Kidney Cancer
NCCN guidelines (Malignant Pleural Mesothelioma)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Malignant Pleural Mesothelioma
NCCN guidelines (Malignant Melanoma)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Melanoma
NCI PDQ	National Cancer Institute Physician Data Query
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 non-small cell lung cancer
OS	overall survival
partial change application	application for partial change approval
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PEM	pemetrexed sodium hydrate

PFS	progression free survival
PK	pharmacokinetics
platinum-based antineoplastic therapy/PEM	a combination of platinum-based antineoplastic therapy and PEM
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	recurrence free survival
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
sorafenib	sorafenib tosylate
SQ-NSCLC	squamous non-small cell lung cancer
Study 001	Study CA209001
Study 01	Study ONO-4538-01
Study 010	Study CA209010
Study 016	Study CA209016
Study 017	Study CA209017
Study 02	Study ONO-4538-02
Study 025	Study ONO-4538-03/CA209025
Study 026	Study ONO-4538-10/CA209026
Study 03	Study CA209003
Study 032	Study CA209032
Study 037	Study CA209037
Study 039	Study CA209039
Study 04	Study CA209004
Study 05	Study ONO-4538-05
Study 057	Study CA209057
Study 06	Study ONO-4538-06
Study 063	Study CA209063
Study 066	Study CA209066
Study 067	Study CA209067
Study 069	Study CA209069
Study 08	Study ONO-4538-08
Study 09	Study CA209009
Study 12	Study ONO-4538-12
Study 141	Study ONO-4538-11/CA209141
Study 15	Study ONO-4538-15
Study 17	Study ONO-4538-17
Study 205	Study CA209205
Study 214	Study ONO-4538-16/CA209214
Study 238	Study ONO-4538-21/CA209238
Study 275	Study ONO-4538-22/CA209275
Study 41	Study ONO-4538-41
sunitinib	sunitinib malate
WHO	World Health Organization