Review Report

April 13, 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) (JAN*)
Applicant	Bristol-Meyers Squibb K.K.
Date of Application	September 29, 2017
Dosage Form/Strength	Injection: One 10 mL vial contains 50 mg of ipilimumab (genetical recombination).
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 300 of 2013 [*25 yaku*]; PFSB/ELD Notification No. 0315-2 dated March 15, 2013, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety 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 malignant melanoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the 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

Unresectable malignant melanoma

(No change)

Dosage and Administration

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.

(Underline denotes addition.)

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

March 9, 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**	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg
	Non-proprietary Name	Nivolumab (Genetical Recombination)
	Applicant	Ono Pharmaceutical Co., Ltd.
	Date of Application	September 29, 2017
	Dosage Form/Strength	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).
	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 (No change)

Proposed Dosage and Administration

1. Treatment of unresectable malignant melanoma

Chemotherapy-naïve patients:

- The usual adult dosage of nivolumab (genetical recombination) is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks.
- In combination therapy with ipilimumab (genetical recombination), the usual adult dosage of nivolumab (genetical recombination) is 1 mg/kg body weight, administered as an intravenous infusion every 3 weeks for 4 doses, followed by nivolumab (genetical recombination) 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, and recurrent or distant metastatic head and neck cancer

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

(Underline denotes addition.)

(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 September 29, 2017

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

Proposed Indication(s) Unresectable malignant melanoma

(No change)

Proposed Dosage and Administration

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.

(Underline denotes addition.)

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List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed 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, BMS). 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 BMS). 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.

1.2 Development history, etc.

Outside Japan, as the clinical development program of the combination of NIVO and IPI (NIVO/IPI therapy) for the treatment of malignant melanoma, BMS initiated a phase Ib study in patients with unresectable malignant melanoma (Study 004) in December 2009, and a phase II study (Study 069) and phase III study (Study 067) in chemotherapy-naïve patients with unresectable malignant melanoma in August 2013 and [redacted], 20[redacted], respectively.

In the US, a marketing application for NIVO in combination with IPI was filed in March 2015 based primarily on the results of Study 069 for the treatment of malignant melanoma, and an accelerated approval was granted in September 2015 for the indication, "OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with *v-raf murine sarcoma viral oncogene homolog B1* (*BRAF*) V600 wild-type, unresectable or metastatic melanoma." Another application for NIVO in combination with IPI was filed in July 2015 based mostly on the results of Study 067, and an approval was granted in January 2016 for the indication, "OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma." IPI was approved in March 2011 for the indication, "YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic

melanoma," and can therefore be used in combination with NIVO for the treatment of malignant melanoma.

In the EU, a marketing application for NIVO in combination with IPI was filed in June 2015 for the treatment of malignant melanoma based primarily on the results of Study 067, and an approval was granted in May 2016 for the indication, "OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults." IPI was approved in October 2013 for the indication, "YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults," and can therefore be used in combination with NIVO for the treatment of malignant melanoma.

As of January 2018, NIVO/IPI therapy has been approved in 57 countries/regions for the treatment of malignant melanoma.

In Japan, a phase II study in chemotherapy-naïve patients with unresectable malignant melanoma (Study 17) was initiated in [redacted] 20[redacted].

The present partial change applications were filed primarily on the basis of results of Study 067 results to add dosing regimens of NIVO and IPI, used in combination for the treatment of malignant melanoma.

NIVO and IPI were designated as orphan drugs in June and March 2013, respectively, with the intended indication of "malignant melanoma" (Drug Designation Nos. 308 and 300 of 2013 [*25 yaku*]).

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

Since the present application is for a new dosage, no data relating to the quality of NIVO or IPI were submitted.

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

Although the applicants submitted new study data on non-clinical pharmacology of NIVO and IPI, PMDA concluded that the content of the data was consistent with that of the data evaluated at the initial applications.

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

Although the present application is for a new dosage, no new study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of NIVO or IPI had been evaluated at the initial applications.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for a new dosage, no toxicity data on 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 application is for a new dosage, no new data on biopharmaceutic studies or associated analytical methods were submitted because the biopharmaceutic studies and associated analytical methods for NIVO and IPI had been evaluated at the initial applications.

6.1 Clinical pharmacology

6.1.1 Population pharmacokinetics (PPK) analyses

6.1.1.1 PPK analysis for NIVO

PPK analysis for NIVO was conducted with a nonlinear mixed effect model (NONMEM, version 7.3.0), based on the pharmacokinetic (PK) data (25,555 time points in 4805 subjects) obtained from the following clinical studies: a Japanese phase I study (Study ONO-4538-01), a Japanese phase II study (Study ONO-4538-02), foreign phase I studies (Studies CA209001, CA209003, CA209009, CA209012, and CA209016), a foreign phase Ib study (Study 004), a foreign phase I/II study (Study CA209032), foreign phase II studies (Studies CA209010, CA209063, and 069), foreign phase III studies (Studies CA209017, CA209037, CA209057, CA209066, and 067), and global phase III studies (Studies ONO-4538-03/CA209025, ONO-4538-10/CA209026, ONO-4538-16/CA209214, and ONO-4538-27/CA209227). The PK of NIVO was described with a 2-compartment model.

The PK analysis used a base model developed on the basis of the PPK analysis of NIVO monotherapy.[1] The base model included (a) the effects of body weight, estimated glomerular filtration rate (eGFR), performance status (PS), sex, and ethnicity on clearance (CL); and (b) the effects of body weight and sex on central volume distribution (VC). Based on the base model, a full model was developed by incorporating the following covariates: the concomitant use of IPI and cancer type (non-small cell lung cancer [NSCLC], malignant melanoma, renal cell carcinoma [RCC], and small cell lung cancer [SCLC]) for NIVO CL. In the full model, the effects of these covariates on CL or VC of NIVO were within the inter-individual variations (35.2% for CL, 36.6% for VC), suggesting that the effects of these covariates on the PK of NIVO are limited.

6.1.1.2 PPK analysis for IPI

PPK analysis for IPI was conducted with a nonlinear mixed effect model (NONMEM, version 7.3.0), based on the PK data (9555 time points in 2356 subjects) obtained from the following clinical studies: a Japanese phase II study (Study CA184396), a foreign phase I study (Study CA209012), a foreign phase Ib study (Study 004), a foreign phase I/II study (Study CA209032), foreign phase II studies (Studies CA184004, CA184007, CA184008, CA184022, and 069), a foreign phase III study (Study 067), and global phase III studies (Studies ONO-4538-16/CA209214 and ONO-4538-27/CA209227). The PK of IPI was described with a 2-compartment model.

[1] PPK analysis (software: NONMEM, Version 7.3.0) was conducted on the PK data for NIVO (18,645 time points in 3458 subjects) obtained from a Japanese phase I study (Study ONO-4538-01), a Japanese phase II study (Study ONO-4538-02), foreign phase I studies (Studies CA209001, CA209003, CA209009, and CA209039), a foreign phase I/II study (Study CA209032), foreign phase II studies (Studies CA209010, CA209063, and CA209205), foreign phase III studies (Studies CA209017, CA209037, CA209057, CA209066, and 067), a global phase II study (Study ONO-4538-22/CA209275), and global phase III studies (Studies ONO-4538-03/CA209025, ONO-4538-10/CA209026, and ONO-4538-11/CA209141).

The PK analysis used a base model developed on the basis of the PPK analysis of IPI monotherapy.[2] The base model included (a) the effects of body weight and lactate dehydrogenase (LDH) on CL; and (b) the effect of body weight on VC. Based on the base model, a full model was developed by incorporating the following covariates: the concomitant use of NIVO and cancer type (squamous non-small cell lung cancer [SQ-NSCLC], non-squamous non-small cell lung cancer [NSQ-NSCLC], malignant melanoma, RCC, and SCLC) for IPI CL. In the full model, the effects of these covariates on CL or VC of IPI were within the inter-individual variations (33.0% for CL, 24.9% for VC), suggesting that the effects of these covariates on the PK of IPI are limited.

6.1.2 Effects of anti-IPI antibodies on the PK of IPI

The following findings regarding the expression of antibodies against IPI were observed in patients receiving NIVO 1 mg/kg and IPI 3 mg/kg intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks in a Japanese phase II study (Study 17), Cohort 8 of a foreign phase Ib study (Study 004), a foreign phase II study (Study 069), and a foreign phase III study (Study 067).

- Anti-IPI antibody[3]-positive patients
  - (a) There were no patients who were positive for anti-IPI antibodies at ≥2 consecutive measurements after the start of treatment with IPI in Studies 17, 004 (Cohort 8), 069, and 067.
  - (b) Anti-IPI antibodies were detected at the last measurement in 0 patients in Study 17, 0 patients in Study 004 (Cohort 8), 2 of 70 patients (2.9%) in Study 069, and 8 of 290 patients (2.8%) in Study 067.
  - (c) Anti-IPI antibodies were detected after the start of treatment with IPI, but were not detected at the last measurement in 2 of 30 patients (6.7%) in Study 17, 1 of 32 patients (3.1%) in Study 004 (Cohort 8), 6 of 70 patients (8.6%) in Study 069, and 16 of 290 patients (5.5%) in Study 067.
- Anti-IPI neutralizing antibodies were detected in 0 patients in Study 004 (Cohort 8), 0 patients in Study 069, and 1 of 290 patients (0.3%) in Study 067. Anti-IPI neutralizing antibodies were not assessed in Study 17.

The applicant's explanation:

The assessment of the serum IPI concentrations in patients receiving IPI 3 mg/kg intravenously every 3 weeks, who were included in the PPK analysis [see Section 6.1.1.2], showed no clear differences between anti-IPI antibody[3]-positive and -negative patients (Table 1). The results suggest that anti-IPI antibodies have no clear effects on the PK of IPI.

[2] PPK analysis (software: NONMEM, Version 6.1.1) was conducted on the PK data for IPI (2095 time points in 499 subjects) obtained from foreign phase II studies (Studies CA184004, CA184007, CA184008, and CA184022).

[3] Anti-IPI antibodies were assessed by the [redacted] method, in which the IPI in samples was unlikely to affect the measurement of anti-IPI antibodies (see the Review Report for Yervoy Injection 50 mg [for intravenous use], dated May 19, 2015).

Table 1. Serum IPI concentrations in anti-IPI antibody-positive and -negative patients (μg/mL)

Time points	n	Anti-IPI antibody-positive	n	Anti-IPI antibody-negative
Day 22 predose	7	11.0 ± 2.59	132	11.6 ± 4.87
Day 43 predose	13	16.3 ± 6.57	135	16.9 ± 6.77
Day 64 predose	7	13.7 ± 6.89	80	17.0 ± 7.34
Day 85 predose	1	32.3	29	18.3 ± 8.20
Day 169 predose	1	3.51	23	2.29 ± 1.75

Arithmetic mean ± SD (individual data for n = 1)

6.1.3 Pharmacokinetic interactions between NIVO and IPI

The applicant explained that NIVO/IPI therapy is unlikely to cause pharmacokinetic interactions between NIVO and IPI, based on the following finding:

- There were no clear differences in serum NIVO concentration[4] between patients receiving NIVO 0.3 to 10 mg/kg every 3 weeks and those receiving NIVO 0.3 to 10 mg/kg in combination with IPI 3 mg/kg every 3 weeks, who were included in the PPK analysis [see Section 6.1.1.1] (Table 2).

Table 2. Serum NIVO concentrations (μg/mL/[mg/kg]) in patients receiving NIVO monotherapy and those receiving NIVO/IPI therapy

Time points		n	NIVO	n	NIVO/IPI
Day 1	Postdose	286	20.0 ± 10.2	458	20.7 ± 15.6
Day 22	Predose	283	5.09 ± 2.05	410	4.48 ± 5.64
	Postdose	33	16.2 ± 3.45	13	22.4 ± 7.51
Day 43	Predose	103	7.87 ± 3.36	344	5.64 ± 3.33
	Postdose	30	18.2 ± 3.77	228	22.7 ± 7.81
Day 64	Predose	96	9.79 ± 4.55	68	6.57 ± 3.54
	Postdose	27	19.2 ± 3.98	34	20.7 ± 6.83

Arithmetic mean ± SD

- There were no clear differences in serum IPI concentrations between patients receiving IPI 3 mg/kg every 3 weeks and those receiving NIVO 1 mg/kg in combination with IPI 3 mg/kg every 3 weeks, who were included in the PPK analysis [see Section 6.1.1.2] (Table 3).

Table 3. Serum IPI concentrations (μg/mL) in patients receiving IPI monotherapy and those receiving NIVO/IPI therapy

Time points		n	IPI	n	NIVO/IPI
Day 1	Postdose	105	61.0 ± 17.3	105	69.2 ± 17.0
Day 22	Predose	17	13.4 ± 3.56	148	11.6 ± 4.77
Day 43	Predose	89	17.3 ± 7.45	106	16.3 ± 8.84
	Postdose	43	74.9 ± 18.8	13	80.7 ± 25.4
Day 64	Predose	45	16.7 ± 8.14	82	16.6 ± 7.33

Arithmetic mean ± SD

6.R Outline of the review conducted by PMDA

PMDA accepted the applicant's explanation about the PK of NIVO and IPI, based on the data submitted.

[4] The serum NIVO concentration data were adjusted for dose (mg/kg), because the data were generated from several dose levels (0.3 to 10 mg/kg).

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

The applicant submitted efficacy and safety evaluation data, in the form of results from the 4 clinical studies presented in Table 4, including a Japanese phase II study, a foreign phase Ib study, a foreign phase II study, and a foreign phase III study.

Table 4. Clinical studies 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	17	II	Chemotherapy-naïve patients with unresectable malignant melanoma	30	NIVO 1 mg/kg and IPI 3 mg/kg administered intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks	Efficacy Safety
	Foreign	004	Ib	Patients with unresectable malignant melanoma	Dose escalation phase 53 (a) 14 (b) 17 (c) 16 (d) 6 Extension phase 41	Dose escalation phase NIVO and IPI administered intravenously every 3 weeks for 4 doses, followed by NIVO every 3 weeks for 4 doses, and then NIVO and IPI every 12 weeks for 8 doses, at the following doses (a) Cohort 1: NIVO 0.3 mg/kg, IPI 3 mg/kg (b) Cohort 2: NIVO 1 mg/kg, IPI 3 mg/kg (c) Cohort 2a: NIVO 3 mg/kg, IPI 1 mg/kg (d) Cohort 3: NIVO 3 mg/kg, IPI 3 mg/kg Extension phase Cohort 8: NIVO 1 mg/kg and IPI 3 mg/kg administered intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks for 48 doses	Safety Tolerability PK
		069	II	Chemotherapy-naïve patients with unresectable malignant melanoma	142 (a) 95 (b) 47	(a) NIVO 1 mg/kg and IPI 3 mg/kg administered intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks (b) Placebo and IPI 3 mg/kg administered intravenously every 3 weeks for 4 doses, followed by placebo every 2 weeks	Efficacy Safety
		067*	III	Chemotherapy-naïve patients with unresectable malignant melanoma	945 (a) 314 (b) 316 (c) 315	(a) NIVO/IPI group NIVO 1 mg/kg and IPI 3 mg/kg administered intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks (b) NIVO group NIVO 3 mg/kg administered intravenously every 2 weeks (c) IPI group IPI 3 mg/kg administered intravenously every 3 weeks for 4 doses	Efficacy Safety

* In Study 067, which was a double-blind study, the placebo for NIVO and the placebo for IPI were administered according to the dosing schedule for the active drugs, to maintain the blind.

A summary of the clinical studies is presented below.

Common adverse events other than deaths reported in these studies are presented in Section "7.2 Adverse events reported in clinical studies," and PK data are presented in Section "6.1 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase II study (CTD 5.3.5.2.1: Study 17, ongoing since [redacted] 20[redacted] [data cutoff date, [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at [redacted] sites in Japan, to evaluate the efficacy and safety of NIVO/IPI therapy in chemotherapy-naïve patients with unresectable malignant melanoma (target sample size, 30 patients).

Patients received NIVO 1 mg/kg and IPI 3 mg/kg intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks. The treatment was continued until disease progression occurred or until a withdrawal criterion was met.

All 30 enrolled patients were treated with the study drugs and included in efficacy analyses. The same patients were included in the safety analysis set.

The primary endpoint was the response rate, as assessed centrally using the Response Evaluation Criteria in Solid Tumors (RECSIT, ver. 1.1). At the start of the study, the threshold response rate was set at 10.0% and expected response rate was 45.0%, based on the results of Study 069.[5] However, these values were changed to 23.8% for threshold response rate and 52.0% for expected response rate in the protocol amendment based on the results of Study 067.[6] The target sample size was also changed from 14 patients to 30 patients, as a result of the protocol amendment (Protocol version 4.0, dated [redacted], 20[redacted]).

Table 5 shows an efficacy summary of the best overall response and response rate. The lower limit of 95% confidence interval (CI) for the response rate did not exceed the predetermined threshold response rate (23.8%).

Table 5. Best overall responses and response rate (RECIST ver. 1.1; efficacy analysis set; central assessment; data cutoff date, [redacted], 20[redacted][7])

Best overall responses	n (%)
	N = 30
CR	1 (3.3)
PR	9 (30.0)
SD	12 (40.0)
PD	7 (23.3)
NE	1 (3.3)
Response (CR + PR) (Response rate [95% CI*])	10 (33.3 [17.3, 52.8])

*, Clopper-Pearson method

No deaths occurred during the study treatment period or within 28 days after the last dose.

[5] The response rates [95% CI] were 55.8 [45.2, 66.0] in the NIVO/IPI group and 8.5 [2.4, 20.4] in the IPI group.
[6] The response rates [95% CI] were 57.6 [52.0, 63.2] in the NIVO/IPI group and 19.0 [14.9, 23.8] in the IPI group.
[7] The primary analysis was [redacted] but was performed when the result of the imaging assessment was obtained from the last enrolled patient at 6 months after the first dose of study drug administration.

7.1.2 Foreign clinical studies

7.1.2.1 Foreign phase Ib study (CTD 5.3.3.2.1: Study 004, December 2009 to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted at 4 sites in a foreign country to evaluate the tolerability, safety, and other aspects of NIVO/IPI therapy in patients with unresectable malignant melanoma (target sample size, 94 patients).

Patients in Cohorts 1 to 5[8] received NIVO and IPI intravenously every 3 weeks for 4 doses, followed by NIVO every 3 weeks for 4 doses, and then NIVO and IPI every 12 weeks for 8 doses. Patients in Cohort 8 received NIVO 1 mg/kg and IPI 3 mg/kg intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks for 48 doses. The dose in Cohort 3 was determined to exceed the maximal tolerated dose (MTD); and enrollment in Cohorts 4 and 5 was discontinued. The protocol was amended to add Cohort 2a[9] (Protocol version 4, dated [redacted], 20[redacted]).

All 94 patients enrolled in the dose escalation phase (Cohorts 1 to 3 and 2a) and the extension phase (Cohort 8) were treated with the study drug and included in the safety analysis set.

In the dose escalation phase (Cohorts 1 to 3 and 2a) of the study, tolerability was evaluated during the dose limiting toxicity (DLT) assessment period until 63 days after the first dose of NIVO or IPI, or until 21 days after the third doses of both study drugs, whichever occurs later.

All 37 patients enrolled in Cohorts 1 to 3 (14 in Cohort 1, 17 in Cohort 2, and 6 in Cohort 3) received the study drug. DLTs occurred in 1 of 14 patients in Cohort 1 (Grade 3 AST increased/ALT increased), 2 of 17 patients in Cohort 2 (Grade 2 uveitis, and Grade 2 and 3 AST increased/ALT increased in 1 patient each), and 3 of 6 patients in Cohort 3 (Grade 3 lipase increased in 1 patient, and Grade 4 lipase increased in 2 patients). All 16 patients enrolled in Cohort 2a received the study drug, and no patients experienced DLTs as a result of tolerability assessment. Based on these results, the MTD of NIVO/IPI therapy was determined to be the doses for Cohorts 2 and 2a.

During the study treatment period or within 100 days after the last dose, 10 patients (4 in Cohort 1 and 6 in Cohort 8) died. Of the 10 patients, 9 (4 in Cohort 1 and 5 in Cohort 8) died of disease progression. Other causes of death were multi-organ failure/enterococcal sepsis in the remaining 1 patient for which a causal relationship to the study drug could not be ruled out.

[8] The planned doses of NIVO and IPI for each cohort were as follows: Cohort 1, NIVO 0.3 mg/kg, IPI 3 mg/kg; Cohort 2, NIVO 1 mg/kg, IPI 3 mg/kg; Cohort 3, NIVO 3 mg/kg, IPI 3 mg/kg; Cohort 4, NIVO 10 mg/kg, IPI 3 mg/kg; Cohort 5, NIVO 10 mg/kg, IPI 10 mg/kg

[9] The dosing regimen for Cohort 2a was NIVO 3 mg/kg and IPI 1 mg/kg administered intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 3 weeks for 4 doses, and then NIVO 3 mg/kg and IPI 1 mg/kg every 12 weeks for 8 doses.

7.1.2.2 Foreign phase II study (CTD 5.3.5.1.1: Study 069, ongoing since August 2013 [efficacy data cutoff date, July 24, 2014; safety data cutoff date, [redacted], 20[redacted]])

A double-blind, randomized study was conducted at 21 sites in 2 countries outside Japan, to compare the efficacy and safety of NIVO/IPI therapy with those of IPI monotherapy in chemotherapy-naïve patients with unresectable malignant melanoma (target sample size, approximately 100 patients).

Patients received (a) NIVO/IPI therapy or (b) IPI monotherapy, according to the following dosing regimens. The treatment was continued until disease progression or until a withdrawal criterion was met.

(a) NIVO 1 mg/kg and IPI 3 mg/kg were administered intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks.
(b) Placebo and IPI 3 mg/kg were administered intravenously every 3 weeks for 4 doses, followed by placebo every 2 weeks.

All 142 enrolled and randomized patients (95 in the NIVO/IPI group and 47 in the IPI group) were included in the efficacy analysis set, and 140 of these 142 patients (94 in the NIVO/IPI group and 46 in the IPI group) were treated with the study drug and included in the safety analysis set.

The primary endpoint was the response rate, as assessed by the investigators using RECIST ver. 1.1 in chemotherapy-naïve patients with *BRAF* wild-type unresectable malignant melanoma (72 in the NIVO/IPI group and 37 in the IPI group). The primary analysis was conducted after the last randomized patient with *BRAF* wild-type malignant melanoma had been followed-up for at least 24 weeks after study drug administration.

Table 6 shows response rate, which is the primary efficacy endpoint, in patients with *BRAF* wild-type malignant melanoma. The superiority of NIVO/IPI therapy to IPI therapy was demonstrated.

Table 6. Best overall responses and response rates
(RECIST ver. 1.1; efficacy analysis set; investigator assessment; data cutoff date, July 24, 2014)

Best overall responses	n (%)	
	NIVO/IPI N = 72	IPI N = 37
CR	12 (16.7)	0
PR	31 (43.1)	4 (10.8)
SD	10 (13.9)	12 (32.4)
PD	10 (13.9)	16 (43.2)
NE	9 (12.5)	5 (13.5)
Response (CR + PR) (Response rate [95% CI*[1]])	43 (59.7 [47.5, 71.1])	4 (10.8 [3.0, 25.4])
Odds ratio [95% CI]	12.23 [3.69, 51.40]	
P-value (2-sided)*[2]	<0.0001	

*1, Exact method; *2, Fisher's exact test with a significance level of 0.05 (2-sided)

During the study treatment period or within 30 days after the last dose, 5 patients in the NIVO/IPI group and 2 patients in the IPI group died. Of the 7 patients, 3 (1 in the NIVO/IPI group and 2 in the IPI group) died of disease progression. Other causes of deaths were septic shock, pulmonary embolism, embolic stroke, and ventricular arrhythmia in 1 patient each in the NIVO/IPI group. For ventricular arrhythmia in 1 patient, a causal relationship to the study drug could not be ruled out.

7.1.2.3 Foreign phase III study (CTD 5.3.5.1.2: Study 067, ongoing since [redacted] 20[redacted] [efficacy data cutoff date, August 1, 2016 (overall survival [OS]), [redacted], 20[redacted] (progression free survival [PFS]); safety data cutoff date, August 1, 2016])

A double-blind, randomized study was conducted at 137 sites in 21 countries outside Japan, to compare the efficacy and safety of NIVO/IPI therapy or NIVO monotherapy with those of IPI monotherapy in chemotherapy-naïve patients with unresectable malignant melanoma (target sample size, approximately 915 patients).

Patients received (a) NIVO/IPI therapy, (b) NIVO monotherapy, or (c) IPI monotherapy according to the following dosing regimens. The treatment was continued until disease progression or until a withdrawal criterion was met.

(a) NIVO 1 mg/kg and IPI 3 mg/kg were administered intravenously every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks.
(b) NIVO 3 mg/kg was administered intravenously every 2 weeks.
(c) IPI 3 mg/kg was administered intravenously every 3 weeks for 4 doses.[10]

All 945 enrolled and randomized patients (314 in the NIVO/IPI group, 316 in the NIVO group, and 315 in the IPI group) were included in the intent-to-treat (ITT) population and used for the efficacy analyses. Of the ITT population, 937 patients (313 in the NIVO/IPI group, 313 in the NIVO group, and 311 in the IPI group) were treated with the study drug and included in the safety analysis set.

OS was the single primary endpoint at the start of the study. However, the protocol was amended to add PFS, as assessed by the investigators using RECIST ver. 1.1 as a co-primary endpoint, to evaluate the possible impacts of post-treatments in the context of increased treatment options for unresectable malignant melanoma (Protocol version 2, dated [redacted], 20[redacted]).

Primary analyses for OS and PFS were planned to be conducted when all of the patients had been followed up for 28 months and 9 months, respectively, after study drug administration. Multiplicity resulting from the setting of 2 primary endpoints was adjusted by splitting the significance level as 0.04 for OS and 0.01 for PFS. Multiplicity resulting from the implementation of 2 statistical tests comparing the NIVO/IPI group or the NIVO group with the IPI group was adjusted by using the Hochberg method for OS and the Bonferroni method for PFS.

Table 7 shows the results of the primary analyses for OS (data cutoff date, August 1, 2016) and PFS (data cutoff date, [redacted], 20[redacted]), and Figures 1 and 2 show the Kaplan-Meier curves for OS and PFS, respectively. These results demonstrated the superiority of NIVO/IPI therapy or NIVO monotherapy to IPI monotherapy, in both OS and PFS.

[10] IPI 3 mg/kg was administered intravenously every 3 weeks for 4 doses, followed by placebo every 2 weeks.

Table 7. Results of OS and PFS analyses
(ITT population, OS [data cutoff date, August 1, 2016], PFS [data cutoff date, [redacted], 20[redacted]])

		NIVO/IPI	NIVO	IPI
	N	314	316	315
OS	Number of events (%)	128 (40.8)	142 (44.9)	197 (62.5)
	Median [95% CI] (months)	—	— [29.08, —]	19.98 [17.08, 24.61]
	Hazard ratio [98% CI][*1]	0.55 [0.42, 0.72]	0.63 [0.48, 0.81]	NA
	P-value (2-sided)[*2, *3]	<0.0001	<0.0001	NA
PFS	Number of events (%)	151 (48.1)	174 (55.1)	234 (74.3)
	Median [95% CI] (months)	11.50 [8.90, 16.72]	6.87 [4.34, 9.46]	2.89 [2.79, 3.42]
	Hazard ratio [99.5% CI][*1]	0.42 [0.31, 0.57]	0.57 [0.43, 0.76]	NA
	P-value (2-sided)[*2, *4]	<0.0001	<0.0001	NA

—, Not evaluable; *1, Cox regression comparing the NIVO/IPI group or the NIVO group versus the IPI group, stratified by PD-L1 expression status (≥5%, <5%),[11] *BRAF* gene (mutation positive, wild-type), and metastasis stage (M0, M1a, M1b, M1c); *2, Log-rank test stratified by PD-L1 expression status (≥5%, <5 %),[11] *BRAF* gene (mutation positive, wild-type), and metastasis stage (M0, M1a, M1b, M1c); *3, 2-sided significance level, 0.02; *4, 2-sided significance level, 0.005

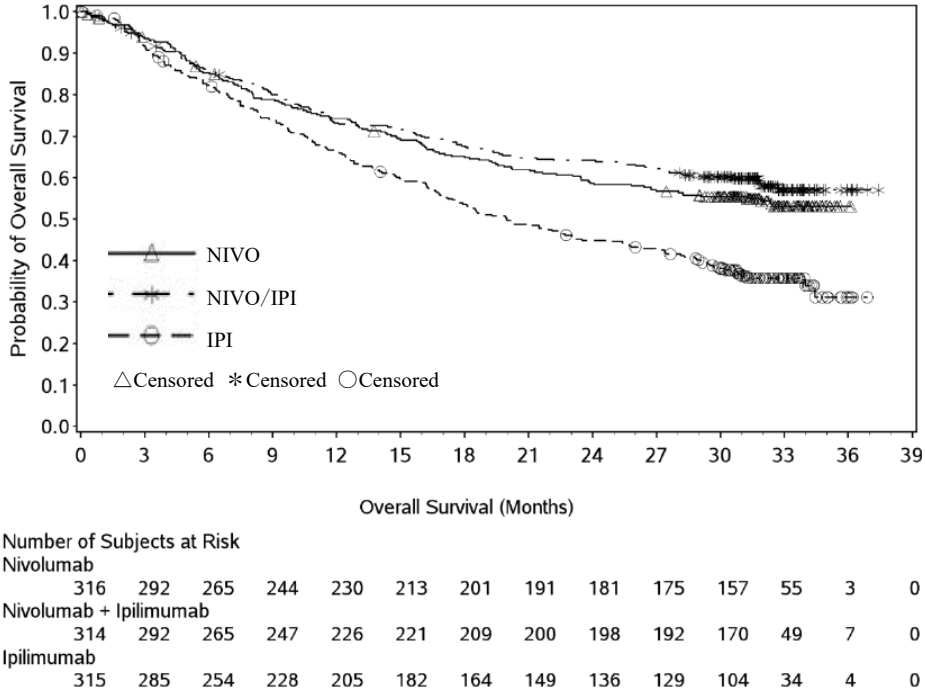


Figure 1. Kaplan-Meier curves for OS
(ITT population; data cutoff date, August 1, 2016)

[11] PD-L1 expression status was assessed as the percentage of tissue cells with PD-L1 in the tumor tissue, and was measured by a preliminary IHC testing (verified version), as no validated IHC assay was available at the start of Study 067 [see Section 7.R.4.2].

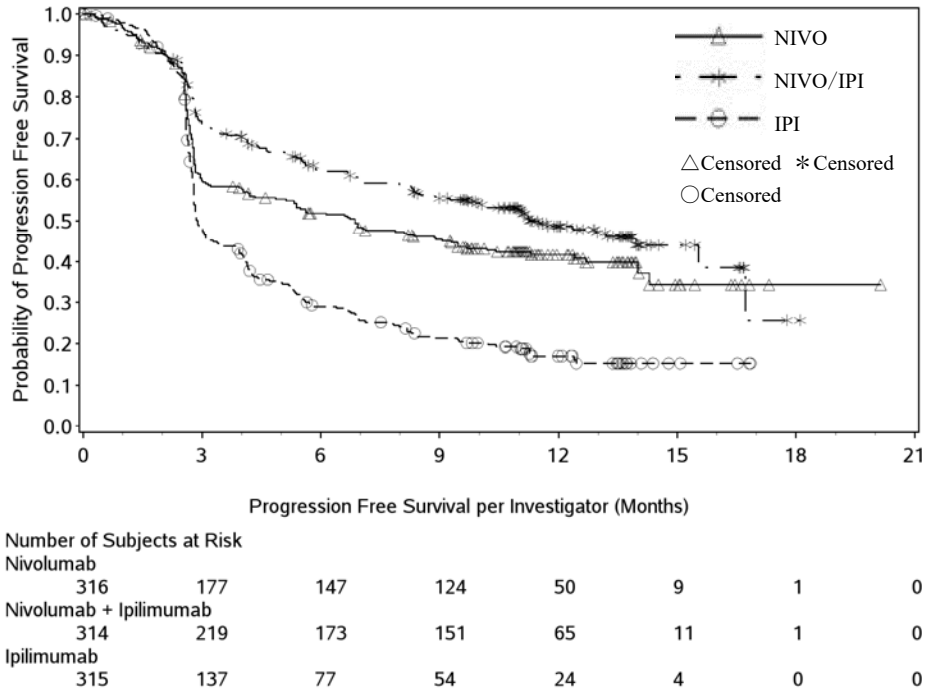


Figure 2. Kaplan-Meier curves for PFS
(ITT population; data cutoff date, [redacted], 20[redacted])

During the treatment period or within 30 days after the last dose, 21 patients in the NIVO/IPI group, 14 patients in the NIVO group, and 20 patients in the IPI group died. Of these patients, 37 (11 in the NIVO/IPI group, 9 in the NIVO group, and 17 in the IPI group) died of disease progression. The causes of deaths in the remaining patients were sudden death, respiratory failure, and pulmonary embolism in 2 patients each, and sudden cardiac death, pneumonia/pleural effusion, dyspnoea, and pneumonia in 1 patient each in the NIVO/IPI group; diverticular perforation, upper gastrointestinal haemorrhage, death, gastric haemorrhage, and gastrointestinal disorder in 1 patient each in the NIVO group; and pulmonary embolism, cardiac arrest, and haemorrhage intracranial in 1 patient each in the IPI group. For cardiac arrest in 1 patient of the IPI group, a causal relationship to the study drug could not be ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

Among the evaluation data submitted by the applicant, PMDA determined that the foreign phase III study in chemotherapy-naïve patients with unresectable malignant melanoma (Study 067) was important for evaluating the efficacy and safety of NIVO/IPI therapy in patients with malignant melanoma, and therefore focused its review on the study.

PMDA also determined that the efficacy and safety of NIVO/IPI therapy in Japanese patients with malignant melanoma would be reviewed based primarily on the results of the Japanese phase II study in chemotherapy-naïve patients with unresectable malignant melanoma (Study 17).

7.R.2 Efficacy

As a result of the review described below, PMDA concluded that the efficacy of NIVO/IPI therapy had been demonstrated in chemotherapy-naïve patients with unresectable malignant melanoma.

7.R.2.1 Selection of control group

The applicant's explanation about the rationale for selecting the IPI group as the control group in Study 067:

When Study 067 was planned, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Melanoma (NCCN guidelines) (ver. 2.2013) and other guidelines recommended IPI for the treatment of patients with malignant melanoma, the target patient population of Study 067, based on the report that IPI demonstrated efficacy when compared with gp100, an antigen peptide derived from malignant melanoma (*N Eng J Med.* 2010;363:711-23). The IPI group was therefore selected as the control group in Study 067.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints and evaluation results

In Study 067, OS was a co-primary endpoint to demonstrate the superiority of NIVO/IPI therapy to IPI monotherapy [see Section 7.1.2.3].

The applicant's explanation about the efficacy of NIVO/IPI therapy in Japanese patients with unresectable malignant melanoma:

In Study 17, the response rate [95% CI], the primary endpoint as assessed centrally using RECIST ver. 1.1, was 33.3 [17.3, 52.8], and the lower limit of the 95% CI did not exceed the predetermined threshold response rate (23.8%). Although an additional analysis was not planned at the start of the study, such analysis (data cutoff date, [redacted], 20[redacted])[12] was conducted and revealed a response rate [95% CI] of 43.3 [25.5, 62.6] as assessed centrally using RECIST ver. 1.1. In consideration of such results, NIVO/IPI therapy is expected to be effective also in Japanese patients with unresectable malignant melanoma.

PMDA's view:

Patients with unresectable malignant melanoma receive treatments to prolong their survival; OS is thus an appropriate primary endpoint in Study 067.

Based on the results of Study 067, which show the superiority of NIVO/IPI therapy to IPI monotherapy in OS prolongation [see Section 7.1.2.3], and the results of the additional analysis, which show a certain level of response rate in the NIVO/IPI group of Study 17, as well as the following findings, PMDA concluded that the efficacy of NIVO/IPI therapy was demonstrated in the target patient population of Study 067, including Japanese patients with malignant melanoma.

[12] Since a response rate analysis was performed with a median follow-up of approximately 12 months in Study 067, the additional analysis was performed 12 months after the first dose for the last enrolled patient in Study 17.

- 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 have been no clear differences in the diagnosis and therapeutic systems for malignant melanoma, between in and outside of Japan.

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

PMDA's view:

As a result of the following review, PMDA concluded that attention should be paid to the following adverse events when administering NIVO/IPI therapy to patients with unresectable malignant melanoma; these events were identified as requiring special 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 tolerable in patients with unresectable 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 excessive immune-mediated adverse reactions, and drug interruption of NIVO or IPI.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of NIVO/IPI therapy based on the safety data from Study 067:

Table 8 shows the safety summary of Study 067.

Table 8. Safety summary (Study 067)

	n (%)		
	NIVO/IPI N = 313	NIVO N = 313	IPI N = 311
All adverse events	312 (99.7)	312 (99.7)	308 (99.0)
Grade ≥3 adverse events	241 (77.0)	164 (52.4)	192 (61.7)
Adverse events leading to death	25 (8.0)	21 (6.7)	25 (8.0)
Serious adverse events	223 (71.2)	133 (42.5)	171 (55.0)
Adverse events leading to drug discontinuation	147 (47.0)	57 (18.2)	78 (25.1)
Adverse events leading to drug interruption	182 (58.1)	112 (35.8)	127 (40.8)

The adverse events of any grade reported with a ≥10% higher incidence in the NIVO/IPI group than in both the NIVO and IPI groups were nausea (137 patients [43.8%] in the NIVO/IPI group, 95 patients [30.4%] in the NIVO group, 95 patients [30.5%] in the IPI group), pyrexia (125 patients [39.9%], 50 patients [16.0%], 56 patients [18.0%]), vomiting (98 patients [31.3%], 63 patients [20.1%], 52 patients [16.7%]), ALT increased (65 patients [20.8%], 24 patients [7.7%], 16 patients [5.1%]), and AST increased (57 patients [18.2%], 23 patients [7.3%], 17 patients [5.5%]). The grade ≥3 adverse events reported with a ≥5% higher incidence in the NIVO/IPI group than in both the NIVO and IPI groups were ALT increased (29 patients [9.3%], 4 patients [1.3%], 7 patients [2.3%]) and AST increased (21 patients [6.7%], 5 patients [1.6%], 4 patients [1.3%]). The serious adverse events with a ≥2% higher incidence in the NIVO/IPI group than in both the NIVO and IPI groups were diarrhoea (33 patients [10.5%], 6 patients [1.9%], 25 patients [8.0%]), pyrexia (26 patients [8.3%], 2 patients [0.6%], 10 patients [3.2%]), vomiting (10 patients [3.2%], 3 patients [1.0%], 3 patients [1.0%]), nausea (9 patients [2.9%], 2 patients [0.6%], 1 patient [0.3%]), pulmonary embolism (8 patients [2.6%], 2 patients [0.6%], 2 patients [0.6%]), and transaminases increased (8 patients [2.6%], 1 patient [0.3%], 0 patient). The adverse events leading to drug discontinuation with a ≥2% higher incidence in the NIVO/IPI group than in both the NIVO and IPI groups were colitis (30 patients [9.6%], 2 patients [0.6%], 22 patients [7.1%]), diarrhoea (25 patients [8.0%], 7 patients [2.2%], 15 patients [4.8%]), ALT increased (15 patients [4.8%], 3 patients [1.0%], 3 patients [1.0%]), AST increased (14 patients [4.5%], 2 patients [0.6%], 2 patients [0.6%]), and transaminases increased (7 patients [2.2%], 0 patients, 0 patients). The adverse events leading to drug interruption with a ≥2% higher incidence in the NIVO/IPI group than in both the NIVO and IPI groups were ALT increased (21 patients [6.7%], 4 patients [1.3%], 3 patients [1.0%]), lipase increased (17 patients [5.4%], 10 patients [3.2%], 9 patients [2.9%]), AST increased (16 patients [5.1%], 4 patients [1.3%], 3 patients [1.0%]), fatigue (14 patients [4.5%], 0 patients, 3 patients [1.0%]), hyperthyroidism [14 patients [4.5%], 4 patients [1.3%], 0 patients), hypophysitis (13 patients [4.2%], 1 patient [0.3%], 6 patients [1.9%]), nausea (12 patients [3.8%], 1 patient [0.3%], 3 patients [1.0%]), pneumonitis (12 patients [3.8%], 3 patients [1.0%], 2 patients [0.6%]), and hypothyroidism (8 patients [2.6%], 1 patient [0.3%], 2 patients [0.6%]).

The applicant's explanation:
The incidence rate of adverse events tended to be higher in the NIVO/IPI group than in both the NIVO and IPI groups. Nonetheless, in view of the following findings, NIVO/IPI therapy is tolerable, provided that appropriate actions such as the interruption of treatment with NIVO or IPI are taken.

- A total of 472 serious adverse events that require special attention occurred in 223 patients (71.2%) in the NIVO/IPI group, but most of them resolved (resolved, 424 events [89.8%]; improved, 3 events [0.6%]; fatal, 28 events [5.9%]; not resolved, 13 events [2.8%]; unknown, 4 events [0.8%]).
- For all of the adverse events leading to deaths, a causal relationship to the study drug was ruled out.

PMDA's view:

Some adverse events developed more frequently in the NIVO/IPI group than in the NIVO or IPI group in Study 067. Nonetheless, considering that most of these were known adverse events of NIVO or IPI monotherapy, and based on the applicant's above explanation, NIVO/IPI therapy is tolerable in patients with unresectable 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 excessive immune-mediated adverse reactions, and drug interruption of NIVO or IPI. However, special attention should be paid to the adverse events that were reported more frequently in the NIVO/IPI group than in the NIVO or IPI group in Study 067, when administering NIVO/IPI therapy to patients with malignant melanoma, and information on the occurrence of these adverse events should be provided to healthcare professionals through the package insert or other materials.

7.R.3.2 Differences in the safety of NIVO/IPI therapy 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 Studies 17 and 067:

Table 9 shows the safety summary in Japanese and non-Japanese patients receiving NIVO/IPI therapy in Studies 17 and 067.

Table 9. Safety summary (NIVO/IPI groups in Studies 17 and 067)

	n (%)	
	Japanese (Study 17) N = 30	Non-Japanese (Study 067) N = 313
All adverse events	30 (100)	312 (99.7)
Grade ≥3 adverse events	23 (76.7)	241 (77.0)
Adverse events leading to death	0	25 (8.0)
Serious adverse events	20 (66.7)	223 (71.2)
Adverse events leading to drug discontinuation	10 (33.3)	147 (47.0)
Adverse events leading to drug interruption	15 (50.0)	182 (58.1)

The adverse events of any grade with a ≥20% higher incidence in Study 17 than in the NIVO/IPI group of Study 067 were rash (18 patients [60.0%] in Study 17, 103 patients [32.9%] in the NIVO/IPI group of Study 067), lipase increased (12 patients [40.0%], 49 patients [15.7%]), and hepatic function abnormal (7 patients [23.3%], 0 patients). The Grade ≥3 adverse events with a ≥10% higher incidence in Study 17 than in the NIVO/IPI group of Study 067 were lipase increased (7 patients [23.3%], 39 patients [12.5%]), hyponatraemia (5 patients [16.7%], 10 patients [3.2%]), and hepatic function

abnormal (4 patients [13.3%], 0 patients). The serious adverse events with a ≥5% higher incidence in Study 17 than in the NIVO/IPI group of Study 067 were hepatic function abnormal (4 patients [13.3%], 0 patients), liver disorder (2 patients [6.7%], 0 patients), hyponatraemia (2 patients [6.7%], 2 patients [0.6%]), decreased appetite (2 patients [6.7%], 2 patients [0.6%]), and ILD (2 patients [6.7%], 2 patients [0.6%]). The adverse events leading to drug discontinuation with a ≥5% higher incidence in Study 17 than in the NIVO/IPI group of Study 067 were hepatic function abnormal (2 patients [6.7%], 0 patients), hyponatraemia (2 patients [6.7%], 0 patients), and ILD (2 patients [6.7%], 0 patients). The adverse event leading to drug interruption with a ≥5% higher incidence in Study 17 than in the NIVO/IPI group of Study 067 was hepatic function abnormal (2 patients [6.7%], 0 patients).

PMDA's conclusion:
Although attention needs be paid to the adverse events with a higher incidence in Japanese patients than in non-Japanese patients when administering NIVO/IPI therapy to Japanese patients, most of these events were known adverse events of NIVO or IPI monotherapy. In addition, there were no clear trends towards higher incidences of adverse events leading to death, serious adverse events, or adverse events leading to drug discontinuation in Japanese patients than in non-Japanese patients. Based on these results, PMDA concluded that NIVO/IPI therapy is tolerable in Japanese patients as in non-Japanese patients.

7.R.4 Clinical positioning and indications

The proposed indications of both NIVO and IPI were "unresectable malignant melanoma," with no change from the approved indications. The following precautionary statements were included in the "Precautions for Indications" sections of the package inserts for NIVO and IPI, which were identical to those for the proposed indications.

NIVO

- 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.

IPI

- The efficacy and safety of IPI in postoperative adjuvant chemotherapy 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. In particular, when administrating IPI as monotherapy to previously untreated patients, therapeutic options other than IPI should also be carefully considered.

As a result of its review in Sections "7.R.2 Efficacy", "7.R.3 Safety," and the following sections, PMDA concluded that no changes or modifications to the indications of NIVO or IPI are necessary, and that the proposed precautionary statements in the "Precautions for Indications" sections are acceptable for NIVO, while those for IPI should be modified as follows:

IPI

- The efficacy and safety of IPI in postoperative adjuvant chemotherapy 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. In particular, when administrating IPI as monotherapy to chemotherapy-naïve patients, other therapeutic options should also be carefully considered.

7.R.4.1 Clinical positioning of NIVO/IPI therapy

The descriptions of NIVO/IPI therapy for unresectable malignant melanoma in the Japanese and foreign clinical practice guidelines, and in a standard textbook of clinical oncology in and outside of Japan are summarized below.

Clinical practice guidelines

- NCCN guidelines (ver. 1. 2018)
  Based on the results for PFS and the response rate in Study 067, NIVO/IPI therapy is recommended as the first-line or second-line treatment of unresectable malignant melanoma. The OS data from Study 067 have not been published.

PMDA asked the applicant to explain the clinical positioning of NIVO/IPI therapy in the treatment of unresectable malignant melanoma in chemotherapy-naïve patients and the necessity to change or modify the approved indications of NIVO or IPI for the present partial change application.

The applicant's explanation:
Based on the results of Study 067, NIVO/IPI therapy can be positioned as a therapeutic option for unresectable malignant melanoma in chemotherapy-naïve patients. Study 067 enrolled patients with unresectable malignant melanoma, regardless of *BRAF* mutation status, and the hazard ratios [95% CIs] of OS in the NIVO/IPI group relative to those in the IPI group (data cutoff date, August 1, 2016) were 0.43 [0.28, 0.66] in patients with *BRAF* mutation and 0.62 [0.48, 0.80] in patients without *BRAF* mutation. Thus, NIVO/IPI therapy can be expected to be effective in patients with unresectable malignant melanoma, regardless of *BRAF* mutation status.

The applicant proposed the following choice between NIVO/IPI therapy and conventional therapies for the treatment of unresectable malignant melanoma in chemotherapy-naïve patients, with or without the *BRAF* mutation.

- *BRAF* mutation-positive patients (conventional therapies; dabrafenib/trametinib, vemurafenib):
  Since there have been no results regarding clinical studies comparing the efficacy and safety of NIVO/IPI therapy with those of dabrafenib/trametinib or vemurafenib, which therapy should be preferentially chosen is not yet known. However, the NCCN guidelines (ver. 1.2018) recommend that dabrafenib/trametinib or vemurafenib should be chosen in preference to NIVO/IPI therapy in patients for whom the achievement of an early response is clinically important. Therefore, the appropriate selection of treatment (e.g., the preferential choice of dabrafenib/trametinib or vemurafenib) should be made according to the conditions of individual patients, in patients with *BRAF* mutation-positive malignant melanoma.

- *BRAF* mutation-negative (conventional treatments: NIVO, IPI, pembrolizumab):
  - Differentiation between NIVO/IPI therapy and NIVO monotherapy: Although Study 067 was not designed to compare NIVO/IPI therapy and NIVO monotherapy, NIVO/IPI therapy tended to prolong OS, but to cause more adverse events, as compared with NIVO monotherapy. Therefore, an appropriate treatment should be chosen according to the conditions of individual patients, after fully understanding the efficacy and safety of NIVO/IPI therapy and NIVO monotherapy.
  - Differentiation between NIVO/IPI therapy and IPI monotherapy: Since NIVO/IPI therapy significantly prolonged OS, as compared with IPI in Study 067, NIVO/IPI therapy is chosen in preference to IPI monotherapy. However, as the Japanese clinical practice guidelines also recommend IPI monotherapy as a therapeutic option for *BRAF* mutation-negative malignant melanoma, IPI may continue to be used in clinical practice.
  - Differentiation between NIVO/IPI therapy and pembrolizumab: Since there have been no results regarding clinical studies comparing the efficacy and safety of NIVO/IPI therapy with those of pembrolizumab, which therapy should be preferentially chosen is not yet known. An appropriate treatment should be chosen according to the conditions of individual patients, after fully considering whether the adverse reactions associated with NIVO/IPI therapy would be manageable.

Based on these findings, no changes from the approved indications of NIVO or IPI are needed for the present partial change application, provided that the following precautionary statements are included in the "Precautions for Indications" section.

NIVO

- 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.

IPI

- The efficacy and safety of IPI in postoperative adjuvant chemotherapy 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. In particular, when administrating IPI as monotherapy to previously untreated patients, therapeutic options other than IPI should also be carefully considered.

PMDA's conclusion:

PMDA largely accepted the applicant's explanation. However, PMDA concluded that the proposed precautionary statement regarding chemotherapy-naïve patients for IPI should be modified as follows and included in the "Precautions for Indications" section.

- 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. In particular,

when administrating IPI as monotherapy to chemotherapy-naïve patients, other therapeutic options should also be carefully considered.

7.R.4.2 Efficacy and safety of NIVO/IPI therapy by programmed cell death-ligand 1 (PD-L1) expression status, and the intended patient population

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

The applicant's response:

In Study 067, the percentage of tumor cells with PD-L1 in the tumor tissue was determined by the verified version of an immunohistochemical (IHC) testing method, the Dako 28-8 assay, to stratify patients by PD-L1 expression status at randomization [see Section 7.1.2.3]. Later, the validated version of the Dako 28-8 assay became available and was used to evaluate the efficacy and safety of NIVO/IPI therapy in PD-L1-positive and -negative patients. PD-L1 positivity was defined with cutoff values of 1%, 5%, and 10%. The efficacy and safety of NIVO/IPI therapy by PD-L1 expression status are summarized below.[13]

(a) Efficacy:

Tables 10 and 11 show the OS data by PD-L1 expression status (cutoff values; 1%, 5%, and 10%) and Figure 3 shows the Kaplan-Meier curves for OS in these populations (Study 067 data, cutoff date, August 1, 2016). The implementation of further investigation of the interaction between PD-L1 expression and OS was predetermined, if the *P* value for the interaction was <0.2.

Comparisons between the NIVO/IPI group and the IPI group demonstrated the superiority of NIVO/IPI therapy to IPI monotherapy in OS prolongation in both PD-L1-positive and -negative patients at all of the cutoff values. On the other hand, in comparisons between the NIVO/IPI group and the NIVO group, the add-on effect of IPI tended to be lower in PD-L1-positive patients than in PD-L1-negative patients at all of the cutoff values. Nonetheless, in view of the following findings, the results provide insufficient evidence to show that PD-L1 expression status is a predictor of response to NIVO/IPI therapy. Based on the results from the entire patient population of Study 067, the efficacy of NIVO/IPI therapy can be expected in PD-L1-positive patients, as well as in PD-L1-negative patients.

- Interaction tests between PD-L1 expression status and OS yielded a *P*-value of ≥0.2 at all of the cutoff values; thus, the predetermined criterion for further investigation (*P* value <0.2) was not met.
- Study 067 was not designed sufficiently well to detect the significant differences between the NIVO/IPI group and the NIVO group.
- The results of the OS analyses by PD-L1 expression status performed in Study 067 were the results of an explanatory subgroup analysis.

[13] The validated IHC assay was used in the assessment of PD-L1 expression in 304 patients in the NIVO/IPI group, 308 in the NIVO group, and 303 in the IPI group. Of these patients, PD-L1 data were available in 278 in the NIVO/IPI group, 288 in the NIVO group, and 277 in the IPI group.

Table 10. Efficacy of NIVO/IPI therapy by PD-L1 expression status (NIVO/IPI versus IPI in Study 067; data cutoff date, August 1, 2016)

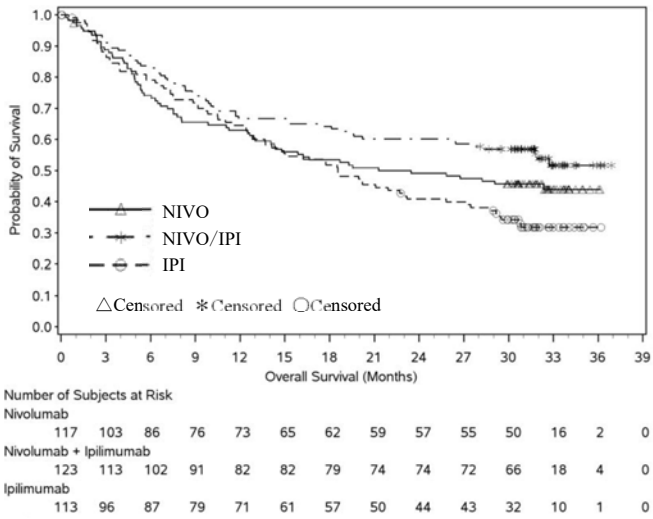
Percentage of cells with PD-L1	Treatment	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for the interaction
<1%	NIVO/IPI	123	— [26.45, —]	0.59 [0.42, 0.83]	0.7061
	IPI	113	18.56 [13.67, 23.20]		
≥1%	NIVO/IPI	155	— [—, —]	0.54 [0.39, 0.74]	
	IPI	164	22.11 [17.08, 29.67]		
<5%	NIVO/IPI	210	— [31.84, —]	0.54 [0.41, 0.71]	0.7186
	IPI	202	18.50 [13.70, 22.51]		
≥5%	NIVO/IPI	68	— [—, —]	0.60 [0.36, 1.01]	
	IPI	75	28.88 [18.10, —]		
<10%	NIVO/IPI	232	— [32.72, —]	0.56 [0.43, 0.73]	0.9145
	IPI	223	18.56 [14.98, 23.03]		
≥10%	NIVO/IPI	46	— [—, —]	0.54 [0.29, 1.01]	
	IPI	54	29.08 [17.91, —]		

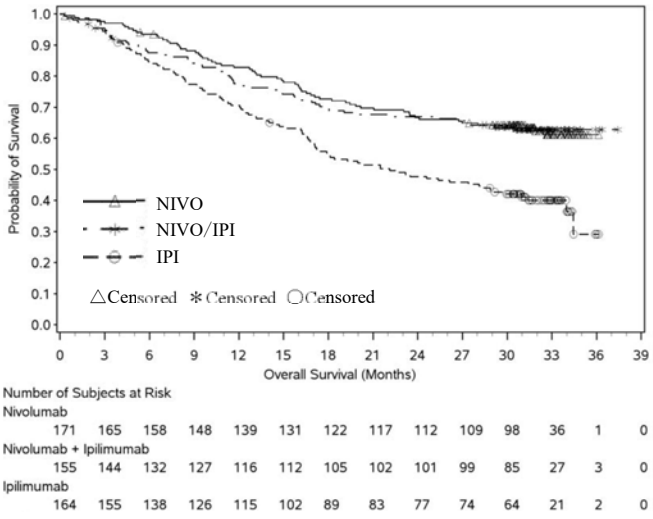
—, Not evaluable; *, Cox regression, with treatment group, PD-L1 expression status, and the interaction between treatment group and PD-L1 expression status as covariates

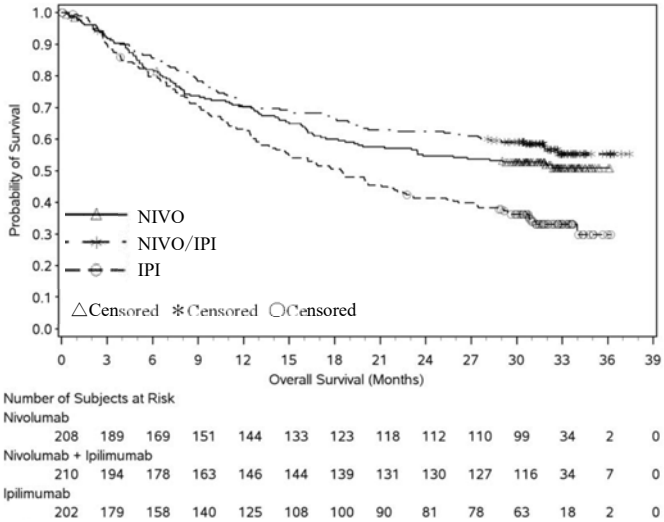
Table 11. Efficacy of NIVO/IPI therapy by PD-L1 expression status (NIVO/IPI versus NIVO in Study 067; data cutoff date, August 1, 2016)

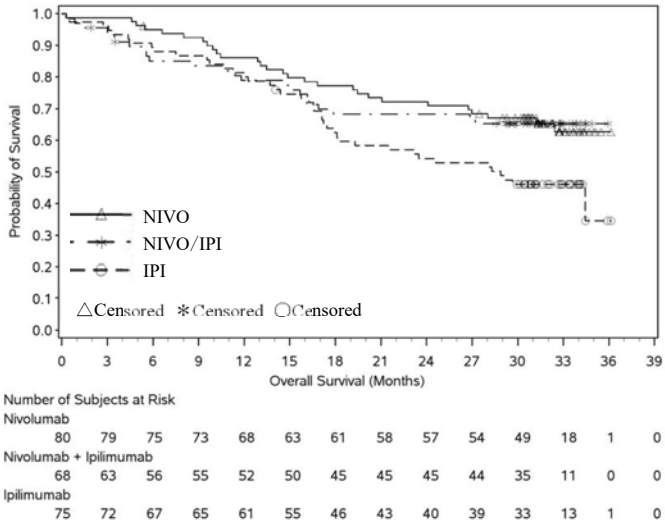
Percentage of cells with PD-L1	Treatment	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for the interaction
<1%	NIVO/IPI	123	— [26.45, —]	0.74 [0.52, 1.06]	0.2049
	NIVO	117	23.46 [13.01, —]		
≥1%	NIVO/IPI	155	— [—, —]	1.03 [0.72, 1.48]	
	NIVO	171	— [—, —]		
<5%	NIVO/IPI	210	— [31.84, —]	0.85 [0.64, 1.13]	0.4900
	NIVO	208	— [23.06, —]		
≥5%	NIVO/IPI	68	— [—, —]	1.05 [0.61, 1.83]	
	NIVO	80	— [—, —]		
<10%	NIVO/IPI	232	— [32.72, —]	0.89 [0.68, 1.18]	0.9835
	NIVO	229	— [23.46, —]		
≥10%	NIVO/IPI	46	— [—, —]	0.89 [0.46, 1.71]	
	NIVO	59	— [31.24, —]		

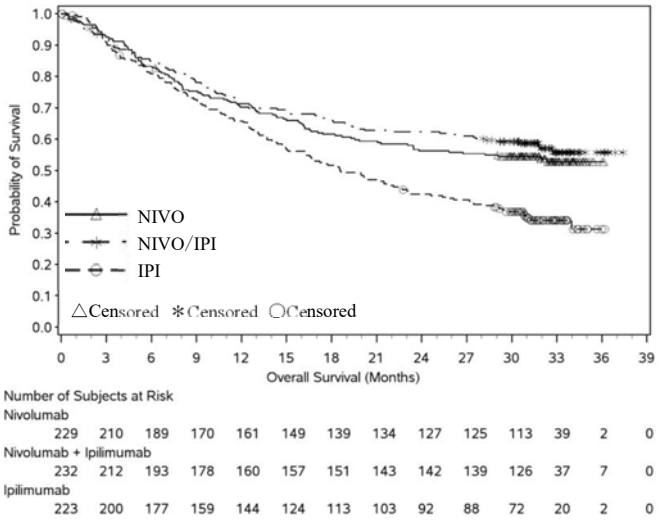
—, Not evaluable; *, Cox regression, with treatment group, PD-L1 expression status, and the interaction between treatment group and PD-L1 expression status as covariates











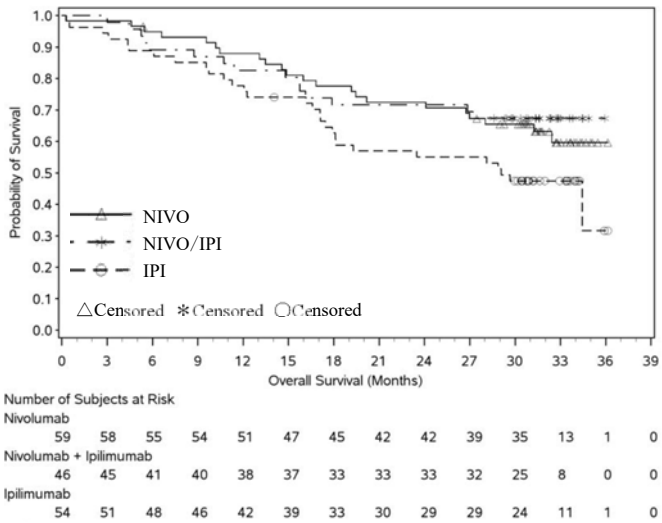


Figure 3. Kaplan-Meier curves for OS by PD-L1 expression status (data cutoff date, August 1, 2016)

(Upper left, PD-L1 expression <1%; upper right, PD-L1 expression ≥1%; middle left, PD-L1 expression <5%; middle right, PD-L1 expression ≥5%; lower left, PD-L1 expression <10%; lower right, PD-L1 expression ≥10%)

(b) Safety:

Table 12 shows the results for safety by PD-L1 expression status in Study 067.

Although the results should be interpreted carefully due to the small number of patients, no clear differences in the safety of NIVO/IPI therapy were noted between PD-L1-positive and -negative patients at any of the cutoff values. The incidence of adverse events tended to be higher in the NIVO/IPI group than in the NIVO or IPI group, regardless of PD-L1 expression status; however, the adverse events are manageable by taking appropriate actions including drug interruption of NIVO or IPI [see Section 7.R.3.1]. Based on the above, NIVO/IPI therapy is tolerable, regardless of PD-L1 expression status.

Table 12. Safety summary by PD-L1 expression status (Study 067)

	n/N (%)					
	NIVO/IPI	NIVO	IPI	NIVO/IPI	NIVO	IPI
PD-L1 expression rate		<1%			≥1%	
All adverse events	121/122 (99.2)	116/117 (99.1)	109/110 (99.1)	155/155 (100)	169/169 (100)	161/163 (98.8)
Grade ≥3 adverse events	103/122 (84.4)	71/117 (60.7)	72/110 (65.5)	115/155 (74.2)	81/169 (47.9)	101/163 (62.0)
Serious adverse events	88/122 (72.1)	53/117 (45.3)	61/110 (55.5)	112/155 (72.3)	72/169 (42.6)	93/163 (57.1)
PD-L1 expression rate		<5%			≥5%	
All adverse events	208/209 (99.5)	205/206 (99.5)	197/199 (99.0)	68/68 (100)	80/80 (100)	73/74 (98.6)
Grade ≥3 adverse events	164/209 (78.5)	109/206 (52.9)	130/199 (65.3)	54/68 (79.4)	43/80 (53.8)	43/74 (58.1)
Serious adverse events	145/209 (69.4)	89/206 (43.2)	115/199 (57.8)	55/68 (80.9)	36/80 (45.0)	39/74 (52.7)
PD-L1 expression rate		<10%			≥10%	
All adverse events	230/231 (99.6)	226/227 (99.6)	218/220 (99.1)	46/46 (100)	59/59 (100)	52/53 (98.1)
Grade ≥3 adverse events	179/231 (77.5)	119/227 (52.4)	140/220 (63.6)	39/46 (84.8)	33/59 (55.9)	33/53 (62.3)
Serious adverse events	162/231 (70.1)	96/227 (42.3)	124/220 (56.4)	38/46 (82.6)	29/59 (49.2)	30/53 (56.6)

Based on the above findings (a) and (b), NIVO/IPI therapy can be expected to be a therapeutic option for chemotherapy-naïve patients with unresectable malignant melanoma, regardless of PD-L1 expression status.

PMDA's conclusion:

PMDA largely accepted the applicant's explanation. However, since the add-on effect of IPI to NIVO tended to be lower in PD-L1-positive patients than in PD-L1-negative patients at all of the cutoff values, and the incidence of adverse events tended to be higher in NIVO/IPI group than in NIVO group, NIVO monotherapy should also be carefully considered in patients with a high percentage of tumor cells with PD-L1 in the tumor tissue. Therefore, the efficacy of NIVO/IPI therapy by PD-L1 expression status observed in Study 067 should be included in the "Clinical Studies" sections of the package inserts for NIVO and IPI, and a precautionary statement to the effect that NIVO monotherapy should also be carefully considered in patients with a high percentage of tumor cells with PD-L1 should be included in the "Precautions for Dosage and Administration" section [see Section 7.R.5].

7.R.5 Dosage and administration

In the present partial change application, the applicant integrated the proposed dosage and administration with the approved dosage and administration for malignant melanoma. The following table shows the proposed precautionary statements in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections for NIVO and IPI.

	Dosage and Administration		Precautions for Dosage and Administration
	Chemotherapy-naïve patients	Chemotherapy-treated patients	
NIVO	• The usual adult dosage of NIVO is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks. • In combination therapy with IPI, the usual adult dosage of NIVO is 1 mg/kg body weight, administered as an intravenous infusion every 3 weeks for 4 doses, followed by NIVO 3 mg/kg body weight as an intravenous infusion every 2 weeks.	The usual adult dosage of NIVO 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.	• The dosing regimen of NIVO must be selected based on a careful review of the content of the "Clinical Studies" section. • Preparation method for injection solution and the duration of infusion ➢ 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. ➢ NIVO should be intravenously infused over at least 1 hour. • An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion. • The efficacy or safety of NIVO in combination with antineoplastic drugs other than IPI has not been established.
IPI	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.	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. • The criteria for interruption or discontinuation of treatment in the event of adverse reactions (omitted, because they are identical to those at the initial approval) • IPI should be administered intravenously over a period of 90 minutes. When necessary, IPI should be diluted with normal saline or 5% glucose solution for injection.

PMDA's conclusion:

Based on the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety," as well as Section 7.R.5.1, PMDA concluded that the proposed dosage and administration is acceptable for both NIVO and IPI. The proposed statements to be included in the "Precautions for Dosage and Administration" section should be modified as follows, in view of the review described in Section "7.R.4.2 Efficacy and safety of NIVO/IPI therapy by PD-L1 expression status, and the intended patient population."

NIVO

- The dosing regimen of NIVO must be selected based on a careful review of the content of the "Clinical Studies" section.
- The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy.
- Preparation method for injection solution and the duration of infusion
  - ➢ 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.
  - ➢ NIVO should be intravenously infused over at least 1 hour.

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

IPI

- The criteria for interruption or discontinuation of treatment in the event of adverse reactions (omitted, because they are identical to those at the initial approval)
- The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy.
- IPI should be administered intravenously over a period of 90 minutes. When necessary, IPI should be diluted with normal saline or 5% glucose solution for injection.

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

The applicant's explanation about the rationale for the dosage and administration of NIVO/IPI therapy for patients with unresectable malignant melanoma:

In Studies 067 and 17, a dosing regimen of "intravenous infusion of NIVO 1 mg/kg and IPI 3 mg/kg every 3 weeks for 4 doses, followed by NIVO 3 mg/kg every 2 weeks" was selected based on data including the following findings, and the studies demonstrated the clinical usefulness of NIVO/IPI therapy in patients with unresectable malignant melanoma. Thus the proposed "dosage and administration" for NIVO/IPI therapy was based on the dosing regimen employed in Studies 067 and 17.

- Based on the following findings, a combination of NIVO 1 mg/kg and IPI 3 mg/kg was expected to be clinically more useful in patients with malignant melanoma.
  - In the dose escalation phase of Study 004, a combination of NIVO 1 mg/kg and IPI 3 mg/kg, and a combination of NIVO 3 mg/kg and IPI 1 mg/kg were tolerable [see Section 7.1.2.1].
  - In a foreign phase I study (Study CA209003), NIVO showed a similar inhibitory effect on tumor growth over a dose range of 0.1 to 10 mg/kg in patients with malignant melanoma (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated June 18, 2014").
  - In a foreign phase II study (Study CA184022), IPI resulted in a dose-dependent increase in tumor growth inhibition, when administered to patients with malignant melanoma at doses of 0.3, 3, and 10 mg/kg (see "Review Report for Yervoy Injection 50 mg [for intravenous use], dated May 19, 2015").
- Based on the following findings, a dosing schedule of a 12-week co-administration of NIVO and IPI (4 doses, in total), followed by NIVO 3 mg/kg every 2 weeks was expected to be clinically useful in patients with malignant melanoma.
  - In Study 004, NIVO/IPI therapy demonstrated its tumor growth inhibitory effect within 12 weeks after the start of the therapy in most patients.
  - In Study CA209003, the continuation of treatment with NIVO 3 mg/kg every 2 weeks resulted in a persistent inhibition of tumor growth.

In addition, precautionary statements will be included in the "Precautions for Dosage and Administration" section of the package insert to inform that no clinical study data are available on the duration of infusion and the preparation method for injection solution employed in Study 067, and the combination of antineoplastic agents other than NIVO and IPI have not been evaluated in clinical studies. The criteria for interruption or discontinuation of treatment in the event of adverse reactions for IPI would be the same as those included in the initial approval application because the same criteria as those described in the current package insert were used in Study 067.

PMDA's view:
PMDA largely accepted the applicant's explanation. However, PMDA concluded that the proposed precautionary statement regarding combination with antineoplastic agents other than NIVO or IPI in the "Precautions for Dosage and Administration" sections is unnecessary, as it is clearly specified in the "Dosage and Administration" sections.

Based on the above review, PMDA concluded that the proposed precautionary statements in the "Precautions for Dosage and Administration" sections for NIVO and IPI should be modified as follows:
NIVO

- The dosing regimen of NIVO must be selected based on a careful review of the content of the "Clinical Studies" section.
- The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy.
- Preparation method for injection solution and the duration of infusion
  - 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.
  - NIVO should be intravenously infused over at least 1 hour.
- An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion.

IPI

- The criteria for interruption or discontinuation of treatment in the event of adverse reactions (omitted, because they are identical to those at the initial approval)
- The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy.
- IPI should be administered intravenously over a period of 90 minutes. When necessary, IPI should be diluted with normal saline or 5% glucose solution for injection.

7.R.6 Post-marketing investigations

The applicant's explanation about the proposed post-marketing surveillance plan:

From the safety specifications for the previous approvals of NIVO and IPI, the applicant selected the Grade ≥3 adverse events that occurred at a higher incidence in the NIVO/IPI group than in the NIVO or IPI group in Study 067 (i.e., colitis, diarrhoea, gastrointestinal perforation; and hepatic function disorder, cholangitis sclerosing) and plans to conduct post-marketing surveillance primarily to evaluate the incidence of and actions taken for these adverse events.

The proposed target sample size of the post-marketing surveillance is 100 patients and the proposed observation period is 13 weeks, considering the incidences of the events selected as the safety specifications in the NIVO/IPI group of Study 067.

PMDA's conclusion:
A certain amount of post-marketing safety data on NIVO or IPI monotherapy are being accumulated from patients with unresectable malignant melanoma. However, available information on NIVO/IPI therapy in Japanese patients with malignant melanoma is considered to be limited. Thus PMDA concluded that a post-marketing surveillance in Japanese patients with malignant melanoma needs to be conducted to collect safety information on the adverse events regardless of severity and the actions taken for these events.

The proposed selection of colitis, diarrhoea, gastrointestinal perforation; and hepatic function disorder, cholangitis sclerosing as the safety specifications for the post-marketing surveillance is acceptable. The proposed target sample size and observation period should be reconsidered in view of the purpose of the surveillance.

7.2 Adverse events reported in clinical studies

Among the clinical study data submitted for safety evaluation, deaths are presented in Section "7.1 Evaluation data." Other frequently reported adverse events are presented in the following.

7.2.1 Japanese phase II study (Study 17)

Adverse events were reported in 30 of 30 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were also reported in 30 of 30 patients (100%). Table 13 shows the adverse events occurring at a ≥20% incidence.

Table 13. Adverse events with a ≥20% incidence

System Organ Class Preferred Term (MedDRA/J ver. 20.0)	n (%) N = 30	
	All Grades	Grade ≥3
All adverse events	30 (100)	23 (76.7)
Endocrine disorders		
Hypothyroidism	7 (23.3)	0
Gastrointestinal disorders		
Diarrhoea	16 (53.3)	1 (3.3)
Vomiting	6 (20.0)	1 (3.3)
General disorders and administration site conditions		
Malaise	7 (23.3)	1 (3.3)
Pyrexia	13 (43.3)	1 (3.3)
Hepatobiliary disorders		

System Organ Class Preferred Term (MedDRA/J ver. 20.0)	n (%) N = 30	
	All Grades	Grade ≥3
Hepatic function abnormal	7 (23.3)	4 (13.3)
Investigations		
ALT increased	11 (36.7)	3 (10.0)
AST increased	11 (36.7)	2 (6.7)
Lipase increased	12 (40.0)	7 (23.3)
Metabolism and nutrition disorders		
Hyponatraemia	6 (20.0)	5 (16.7)
Decreased appetite	9 (30.0)	1 (3.3)
Nervous system disorders		
Headache	6 (20.0)	1 (3.3)
Skin and subcutaneous tissue disorders		
Pruritus	10 (33.3)	0
Rash	18 (60.0)	2 (6.7)

Serious adverse events were reported in 20 of 30 patients (66.7%). The serious adverse events reported in ≥2 patients were hepatic function abnormal in 4 patients (13.3%), and liver disorder, decreased appetite, hyponatraemia, pyrexia, ILD, and hypophysitis in 2 patients (6.7%) each. For all of these events, a causal relationship to the study drug could not be ruled out.

Adverse events leading to drug discontinuation were reported in 10 of 30 patients (33.3%). The following adverse events leading to drug discontinuation in ≥2 patients: hyponatraemia, hepatic function abnormal, and ILD in 2 patients (6.7%) each. For all of these events, a causal relationship to the study drug could not be ruled out.

7.2.2 Foreign phase Ib study (Study 004)

7.2.2.1 Dose escalation phase

Adverse events were reported in 53 of 53 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 51 of 53 patients (96.2%). Pruritus, which was reported in 12 of 16 patients (75.0%) in Cohort 2a, was the only adverse event occurring at a ≥70% incidence in either cohort.

Serious adverse events were reported in 40 of 53 patients (75.5%). The serious adverse events reported in ≥3 patients in each cohort were: ALT increased and AST increased in 3 patients (21.4%) each in Cohort 1; vomiting, ALT increased, and AST increased in 3 patients (17.6%) each in Cohort 2; and, diarrhoea in 3 patients (18.8%) in Cohort 2a. Of these serious adverse events, a causal relationship to the study drug could not be ruled out for ALT increased and AST increased in 3 patients each in Cohort 1, ALT increased and AST increased in 3 patients each, and vomiting in 2 patients in Cohort 2, and diarrhoea in 3 patients in Cohort 2a.

Adverse events leading to drug discontinuation were reported in 16 of 53 patients (30.2%). Lipase increased, which was reported in 2 patients (12.5%) in Cohort 2a, was the only adverse event that led to drug discontinuation in ≥2 patients in either cohort. A causal relationship to the study drug could not be ruled out for the event.

7.2.2.2 Extension phase

Adverse events were reported in 41 of 41 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 40 of 41 patients (97.6%). The adverse events with a ≥60% incidence were rash in 27 patients (65.9%) and fatigue in 26 patients (63.4%).

Serious adverse events were reported in 26 of 41 patients (63.4%). Diarrhoea in 7 patients (17.1%) was the only serious adverse event reported in ≥5 patients. A causal relationship to the study drug could not be ruled out in all of the 7 patients.

Adverse events leading to drug discontinuation were reported in 13 of 41 patients (31.7%). The following adverse events led to drug discontinuation in ≥2 patients: colitis, diarrhoea, ALT increased, and AST increased in 2 patients (4.9%) each. Of these adverse events, a causal relationship to the study drug could not be ruled out for diarrhoea, ALT increased, and AST increased in 2 patients each, and colitis in 1 patient.

7.2.3 Foreign phase II study (Study 069)

Adverse events were reported in 94 of 94 patients (100%) in the NIVO/IPI group, and 45 of 46 patients (97.8%) in the IPI group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 86 of 94 patients (91.5%) in the NIVO/IPI group and 43 of 46 patients (93.5%) in the IPI group. The adverse events occurring at a ≥50% incidence in each group were fatigue in 50 patients (53.2%) and diarrhoea in 47 patients (50.0%) in the NIVO/IPI group, and fatigue in 30 patients (65.2%) in the IPI group.

Serious adverse events were reported in 59 of 94 patients (62.8%) in the NIVO/IPI group and 18 of 46 patients (39.1%) in the IPI group. Colitis in 16 patients (17.0%) in the NIVO/IPI group was the only serious adverse event reported in ≥10 patients in either group. A causal relationship to the study drug could not be ruled out in all of the 16 patients.

Adverse events leading to drug discontinuation were reported in 41 of 94 patients (43.6%) in the NIVO/IPI group and 5 of 46 patients (10.9%) in the IPI group. Colitis in 15 patients (16.0%) in the NIVO/IPI group was the only adverse event that led to drug discontinuation in ≥10 patients in either group. A causal relationship to the study drug could not be ruled out in all of the 15 patients.

7.2.4 Foreign phase III study (Study 067)

Adverse events were reported in 312 of 313 patients (99.7%) in the NIVO/IPI group, 312 of 313 patients (99.7%) in the NIVO group, and 308 of 311 patients (99.0%) in the IPI group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 300 of 313 patients (95.8%) in the NIVO/IPI group, 270 of 313 patients (86.3%) in the NIVO group, and 268 of 311 patients

(86.2%) in the IPI group. Table 14 shows the adverse events occurring at a ≥20% incidence in any treatment group.

Table 14. Adverse events occurring with a ≥20% incidence in any treatment group

System Organ Class Preferred Term (MedDRA/J ver. 19.0)	n (%)					
	NIVO/IPI N = 313		NIVO N = 313		IPI N = 311	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	312 (99.7)	241 (77.0)	312 (99.7)	164 (52.4)	308 (99.0)	192 (61.7)
Gastrointestinal disorders						
Diarrhoea	169 (54.0)	35 (11.2)	112 (35.8)	1 (0.3)	146 (46.9)	23 (7.4)
Nausea	137 (43.8)	12 (3.8)	95 (30.4)	2 (0.6)	95 (30.5)	6 (1.9)
Vomiting	98 (31.3)	12 (3.8)	63 (20.1)	3 (1.0)	52 (16.7)	5 (1.6)
Constipation	60 (19.2)	1 (0.3)	67 (21.4)	1 (0.3)	70 (22.5)	0
Abdominal pain	58 (18.5)	5 (1.6)	53 (16.9)	3 (1.0)	63 (20.3)	6 (1.9)
General disorders and administration site conditions						
Fatigue	162 (51.8)	20 (6.4)	150 (47.9)	4 (1.3)	133 (42.8)	6 (1.9)
Pyrexia	125 (39.9)	5 (1.6)	50 (16.0)	0	56 (18.0)	2 (0.6)
Investigations						
ALT increased	65 (20.8)	29 (9.3)	24 (7.7)	4 (1.3)	16 (5.1)	7 (2.3)
Metabolism and nutrition disorders						
Decreased appetite	92 (29.4)	6 (1.9)	70 (22.4)	0	73 (23.5)	4 (1.3)
Musculoskeletal and connective tissue disorders						
Arthralgia	67 (21.4)	1 (0.3)	66 (21.1)	3 (1.0)	51 (16.4)	1 (0.3)
Nervous system disorders						
Headache	80 (25.6)	2 (0.6)	69 (22.0)	1 (0.3)	75 (24.1)	3 (1.0)
Respiratory, thoracic, and mediastinal disorders						
Cough	76 (24.3)	1 (0.3)	86 (27.5)	2 (0.6)	65 (20.9)	0
Dyspnoea	72 (23.0)	9 (2.9)	45 (14.4)	4 (1.3)	42 (13.5)	2 (0.6)
Skin and subcutaneous tissue disorders						
Pruritus	122 (39.0)	6 (1.9)	83 (26.5)	1 (0.3)	124 (39.9)	1 (0.3)
Rash	103 (32.9)	10 (3.2)	93 (29.7)	1 (0.3)	81 (26.0)	8 (2.6)

Serious adverse events were reported in 223 of 313 patients (71.2%) in the NIVO/IPI group, 133 of 313 patients (42.5%) in the NIVO group, and 171 of 311 patients (55.0%) in the IPI group. The serious adverse events reported in ≥20 patients in each group were diarrhoea in 33 patients (10.5%), colitis in 31 patients (9.9%), and pyrexia in 26 patients (8.3%) in the NIVO/IPI group, malignant neoplasm progression in 25 patients (8.0%) in the NIVO group, and malignant neoplasm progression in 33 patients (10.6%), colitis in 26 patients (8.4%), and diarrhoea in 25 patients (8.0%) in the IPI group. A causal relationship to the study drug could not be ruled out for colitis in 30 patients, diarrhoea in 28 patients, and pyrexia in 13 patients in the NIVO/IPI group, and colitis in 26 patients and diarrhoea in 23 patients in the IPI group.

Adverse events leading to drug discontinuation were reported in 147 of 313 patients (47.0%) in the NIVO/IPI group, 57 of 313 patients (18.2%) in the NIVO group, and 78 of 311 patients (25.1%) in the IPI group. The following adverse events leading to drug discontinuation in ≥20 patients in each group: colitis in 30 patients (9.6%) and diarrhoea in 25 patients (8.0%) in the NIVO/IPI group, and colitis in 22 patients (7.1%) in the IPI group. A causal relationship to the study drug could not be ruled out for all of the events.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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 review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.2.1) 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 review based on the application documents submitted. However, the inspection revealed the following finding at some of the study sites used by the applicant, despite its minor impact on the overall assessment of the studies. The heads of the relevant medical institutions were notified of the issue as a finding requiring improvement.

Finding(s) requiring corrective action

Study sites

- Protocol deviations (noncompliance with the dosing regimen of the study drug)

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

On the basis of the data submitted, PMDA has concluded that NIVO/IPI therapy has efficacy in the treatment of unresectable malignant melanoma, and that NIVO/IPI therapy has acceptable safety in view of its benefits. NIVO/IPI therapy is clinically meaningful because it offers a therapeutic option for patients with unresectable malignant melanoma. PMDA also considers that the clinical positioning, dosage, and administration, etc. should be further discussed.

PMDA concluded that NIVO/IPI therapy may be approved for the treatment of unresectable malignant melanoma if NIVO/IPI therapy is not considered to have any particular problems, based on comments from the Expert Discussion.

Review Report (2)

April 13, 2018

Products Submitted for Approval

(a)	**Brand Name**	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg
	Non-proprietary Name	Nivolumab (Genetical Recombination)
	Applicant	Ono Pharmaceutical Co., Ltd.
	Date of Application	September 29, 2017
(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	September 29, 2017

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

As a result of its review described in Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of nivolumab (genetical recombination) (hereinafter referred to as "NIVO")/ipilimumab (genetical recombination) (hereinafter referred to as "IPI") therapy has been demonstrated in the treatment of chemotherapy-naïve patients with unresectable malignant melanoma. This conclusion is based on the results of a foreign phase III study (Study 067) designed to compare the efficacy and safety of NIVO/IPI therapy or NIVO monotherapy with those of IPI monotherapy (the control therapy), which demonstrated that NIVO/IPI therapy resulted in the prolongation of overall survival, the primary endpoint, in chemotherapy-naïve patients with unresectable malignant melanoma.

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

1.2 Safety

As a result of its review, described in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that particular attention should be paid to the following adverse events when NIVO/IPI therapy is provided to patients with unresectable malignant melanoma. These events were identified as requiring attention at the regulatory reviews for the approved indications for (a) NIVO and (b) IPI:

(a) 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

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

Although attention should be paid to the above adverse events, NIVO/IPI therapy is tolerable in patients with unresectable 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 or IPI.

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

1.3 Clinical positioning and indications

As a result of its review, described in Section "7.R.4 Clinical positioning and indications," PMDA concluded that no changes from or modifications to the approved indications of NIVO and IPI, namely, "unresectable malignant melanoma," are necessary. PMDA also concluded that the proposed precautionary statements in the "Precautions for Indications" sections for NIVO and IPI should be modified, as follows:

NIVO

- 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.

IPI

- The efficacy and safety of IPI in postoperative adjuvant chemotherapy 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. In particular when administrating IPI as monotherapy to chemotherapy-naïve patients, other therapeutic options should also be carefully considered.

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 Sections "7.R.4 Clinical positioning and indications" and "7.R.5 Dosage and administration," PMDA concluded that the efficacy of NIVO/IPI therapy evaluated by PD-L1 expression status in Study 067 should be included in the "Clinical Studies" sections of the package inserts for NIVO and IPI, and that the statements presented in the table below should be included in the "Dosage and Administration" and "Precautions for Dosage and Administrations" sections.

	Dosage and Administration		Precautions for Dosage and Administration
	Chemotherapy-naïve patients	Chemotherapy-treated patients	
NIVO	The usual adult dosage of NIVO is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks. In combination therapy with IPI, the usual adult dosage of NIVO is 1 mg/kg body weight, administered as an intravenous infusion every 3 weeks for 4 doses, followed by NIVO 3 mg/kg body weight as an intravenous infusion every 2 weeks.	The usual adult dosage of NIVO 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.	• The dosing regimen of NIVO must be selected based on a careful review of the content of the "Clinical Studies" section. • The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy. • Preparation method for injection solution and the duration of infusion ➢ 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. ➢ NIVO should be intravenously infused over at least 1 hour. • An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion.
IPI	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.	The usual adult dosage is 3 mg/kg (body weight) of IPI administered intravenously every 3 weeks for a total of 4 times.	• The criteria for interruption or discontinuation of treatment in the event of adverse reactions (omitted, because they are identical to those at the initial approval). • The add-on effect of IPI to NIVO 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, NIVO monotherapy should also be carefully considered before initiating NIVO/IPI therapy. • IPI should be administered intravenously over a period of 90 minutes. When necessary, IPI should be diluted with normal saline or 5% glucose solution for injection.

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

Based on the above, PMDA instructed the applicant to include the statements presented in the above table in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections. The applicant agreed.

1.5 Risk management plan (draft)

The applicant selected colitis, diarrhoea, gastrointestinal perforation; and hepatic function disorder, cholangitis sclerosing as safety specifications and plans to conduct a post-marketing surveillance primarily to evaluate the incidence of events of Grade ≥3 and the actions taken for such events in clinical practice. The target sample size is 100 patients. The observation period is 13 weeks.

PMDA's conclusion as a result of its review, described in Section "7.R.6 Post-marketing investigations" in the Review Report (1):
Since only limited safety data are available from Japanese patients with malignant melanoma receiving NIVO/IPI therapy, the applicant should conduct a post-marketing surveillance to collect information on the incidences of adverse events of all grades and the actions taken for them in clinical practice. The proposed safety specifications for the surveillance are acceptable; however, the target sample size and the observation period should be reconsidered to collect data regarding the events selected as the safety specifications regardless of severity.

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

In view of the above review, PMDA instructed the applicant to reconsider the plan of the post-marketing surveillance.

The applicant's response:

- The target sample size for the post-marketing surveillance is set at 100 patients based on the incidences of the adverse events selected as the safety specifications, which required any actions such as a dose reduction of NIVO or IPI in Study 067.
- The observation period for the post-marketing period is set at 13 weeks based on the timing of the onset of the adverse events selected as the safety specifications, which required any actions such as a dose reduction of NIVO or IPI in Study 067.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plans (drafts) for NIVO and IPI should include the safety and efficacy specifications presented in Tables 15 and 17, respectively, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 16, 18, and 19.

Table 15. Safety and efficacy specifications in the risk management plan (draft) for NIVO

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 (hematologic malignancies)	None
Efficacy specification (relating to the present partial change application)		
None		

*, No changes made for the present partial change application

Table 16. Summary of additional pharmacovigilance activities, efficacy investigation/studies, and additional risk minimization activities included under the risk management plan (draft) for NIVO

Additional pharmacovigilance activities	Efficacy investigations/studies (Items related to the present change application)	Additional risk minimization activities
• 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, NIVO monotherapy) • Specified use-results survey in patients with unresectable malignant melanoma (NIVO/IPI therapy) • 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 • Post-marketing clinical study in patients with unresectable malignant melanoma (extension study of Study ONO-4538-02) • Post-marketing clinical study in patients with unresectable, advanced or recurrent SQ-NSCLC (extension study of Study ONO-4538-05) • Post-marketing clinical study in patients with unresectable, advanced or recurrent NSQ-NSCLC (extension study of Study ONO-4538-06) • Post-marketing clinical study in patients with chemotherapy-naïve, 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 patients with advanced or metastatic clear cell RCC and prior chemotherapy (extension study of Study ONO-4538-03/CA209025) • Post-marketing clinical study in patients with relapsed or refractory cHL (extension study of Study ONO-4538-15) • Post-marketing clinical study in patients with unresectable, advanced or recurrent gastric cancer who have received ≥2 chemotherapy regimens (extension study of Study ONO-4538-12)	None	• Disseminate data gathered during the early post-marketing phase vigilance in patients with unresectable malignant melanoma (NIVO/IPI therapy) • Preparation and provision of materials for healthcare professionals • Preparation and provision of materials for patients

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

Table 17. Safety and efficacy specifications in the risk management plan (draft) for IPI

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 • Interstitial lung disease • Infusion reaction • Myositis	• Excessive immune response • Reproductive and developmental toxicity • Sepsis	None
Efficacy specification (relating to the present partial change application)		
None		

*, No changes made for the present partial change application

Table 18. Summary of additional pharmacovigilance activities, efficacy investigation/studies, and additional risk minimization activities included under the risk management plan (draft) for IPI

Additional pharmacovigilance activities	Efficacy investigations/studies (Items related to the present change application)	Additional risk minimization activities
• Early post-marketing phase vigilance (NIVO/IPI therapy) • Specified use-results survey in patients with unresectable malignant melanoma (IPI monotherapy) • Specified use-results survey in patients with unresectable malignant melanoma (NIVO/IPI therapy)	None	• Disseminate data gathered during the early post-marketing phase vigilance (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 dosage and administration is added.

Table 19. Outline of post-marketing surveillance (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 with unresectable malignant melanoma who receive NIVO/IPI therapy
Observation period	13 weeks
Planned sample size	100 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. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved for the following indications and dosage and administration, 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 an emergency response. The re-examination periods for the present application are the remainder of the ongoing re-examination periods for the initial approval of NIVO and IPI (NIVO, until July 3, 2024; IPI, until July 2, 2025).

Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg

Indications (No change)

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

Dosage and Administration (Underline denotes addition.)

1. Treatment of unresectable malignant melanoma

   Chemotherapy-naïve patients:

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

   In combination therapy with ipilimumab (genetical recombination), the usual adult dosage of nivolumab (genetical recombination) is 1 mg/kg body weight, administered as an intravenous infusion every 3 weeks for 4 doses, followed by nivolumab (genetical recombination) 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, and unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy

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

Condition of Approval

The applicant should formulate and properly 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 (shortness of breath, dyspnoea, coughing, and fatigue) and examined by chest X-rays. 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 (No change)

(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 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 in adjuvant chemotherapy have not been established.
(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.

Precautions for Dosage and Administration (Underline denotes addition. Strikethrough denotes deletion.)

(1) The dosing regimen of Opdivo for ~~patients with~~ unresectable malignant melanoma ~~who have received prior chemotherapy~~ must be selected based on a careful review of the content of the "Clinical Studies" section.
(2) Preparation method for injection solution and the duration of infusion
    1) Prior to treatment, the required volume of the solution should be withdrawn from a vial(s) to achieve a single dose of 3<u>,</u>~~or~~ 2~~ mg/kg~~<u>, or 1 mg/kg</u> 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 1 hour.
(3) An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion.
(4) The efficacy and safety of Opdivo in combination with other antineoplastic drugs (including cytokines) have not been established <u>in the treatment of non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, head and neck cancer, or gastric cancer</u>.
<u>(5) The add-on effect of ipilimumab (genetical recombination) 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)/ipilimumab (genetical recombination) therapy.</u>

Yervoy Injection 50 mg (for intravenous use)

Indications (No change)

Unresectable malignant melanoma

Dosage and Administration (Underline denotes addition.)

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.

Condition of Approval

The applicant is required to establish 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, resulting in 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 (Underline denotes addition. Strikethrough denotes deletion.)

1 Eligibility of patients for treatment with ipilimumab 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 administrating Yervoy as monotherapy to ~~for previously~~ ~~untreated~~ chemotherapy-naïve patients, other therapeutic options should also be carefully considered.

2 The efficacy and safety of Yervoy in postoperative adjuvant chemotherapy have not been established.

Precautions for Dosage and Administration (Underline denotes addition. Strikethrough denotes deletion.)

~~1 Yervoy should not be used in combination with other antineoplastic agents.~~

~~2~~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 The add-on effect of ipilimumab (genetical recombination) 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/ipilimumab (genetical recombination) therapy.

3 Yervoy should be administered intravenously over a period of 90 minutes. When necessary, Yervoy should be diluted with normal saline or 5% glucose solution for injection.

Appendix

List of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CI	confidence interval
CR	complete response
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
Dabrafenib/trametinib	combination of dabrafenib mesilate and trametinib dimethyl sulfoxide
DLT	dose limiting toxicity
eGFR	estimated glomerular filtration rate
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IPI	ipilimumab (genetical recombination)
ITT	intention-to-treat
Japanese clinical practice guidelines	Evidence-based guidelines for the diagnosis and treatment of skin cancer 2015, edited by the Japanese Dermatological Association and the Japanese Skin Cancer Society, and Guidance on Melanoma Pharmacotherapy Version 1, 2017, edited by the Japanese Skin Cancer Society
LDH	lactate dehydrogenase
MedDRA/J	Medical Dictionary for Regulatory Activities, Japanese version
MTD	maximal tolerated dose
NA	not available
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Melanoma
NE	not evaluable
NIVO	nivolumab (genetical recombination)
NIVO/IPI	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
Pembrolizumab	pembrolizumab (genetical recombination)
PFS	progression free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	small cell lung cancer
SD	stable disease

SOC	system organ class
SQ-NSCLC	squamous non-small cell lung cancer
Study 004	Study CA209004
Study 067	Study CA209067
Study 069	Study CA209069
Study 17	Study ONO-4538-17
VC	central volume of distribution