Report on the Deliberation Results

November 16, 2016

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour, and Welfare

Brand Name	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg
Non-proprietary Name	Nivolumab (Genetical Recombination) (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	March 18, 2016

Results of Deliberation

In its meeting held on November 11, 2016, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Conditions of Approval

1. The applicant should formulate and properly implement a risk management plan.
2. Since the number of subjects enrolled in Japanese clinical studies was extremely limited, the applicant is required to conduct a use-results survey covering all patients treated with the product, until data from a certain number of patients are accumulated following commercial introduction, in order to understand the characteristics of patients treated with the product and compile the safety and efficacy data of the product in the early post-marketing period, thereby taking necessary measures to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

October 17, 2016
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.

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	March 18, 2016
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).
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	Orphan drug (Drug Designation No. 381 of 2016 [*28 yaku*]; PSEHB/ELD Notification No. 0316-3 dated March 16, 2016, by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour, and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate a certain level of efficacy of the product in the treatment of relapsed or refractory classical Hodgkin lymphoma and acceptable safety in view of the benefits indicated by the data submitted, as shown in 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 conditions. Interstitial lung disease, myasthenia gravis and myositis, colitis and severe diarrhoea, type 1 diabetes mellitus, hepatic function disorder, abnormal thyroid function, neurological disorder, renal disorder, adrenal disorder, encephalitis, severe skin disorder, venous thrombosis and embolism, infusion reaction, and cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles) should be further investigated via post-marketing surveillance.

Indications

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

(Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 after submission of the present application.)

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.

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, and relapsed or refractory classical Hodgkin lymphoma

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

(Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 after submission of the present application.)

Conditions of Approval

1. The applicant should formulate and properly implement a risk management plan.
2. Since the number of subjects enrolled in Japanese clinical studies was extremely limited, the applicant is required to conduct a use-results survey covering all patients treated with the product, until data from a certain number of patients are accumulated following commercial introduction, in order to understand the characteristics of patients treated with the product and compile the safety and efficacy data of the product in the early post-marketing period, thereby taking necessary measures to ensure the proper use of the product.

Attachment

Review Report (1)

September 8, 2016

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.

Product Submitted for Approval

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	March 18, 2016
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 Indications	1. Treatment of unresectable malignant melanoma 2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer 3. <u>Treatment of relapsed or refractory classical Hodgkin lymphoma</u> (Underline denotes additions.)
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. 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 <u>and relapsed or refractory classical Hodgkin lymphoma</u> The usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks. (Underline denotes additions.)

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List of Abbreviations

ABVD regimen	combination therapy of doxorubicin hydrochloride, bleomycin hydrochloride, vinblastine sulfate and dacarbazin
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALT	alanine aminotransferase
ASCT	autologous hematopoietic stem cell transplantation
AST	aspartate aminotransferase
Brentuximab	Brentuximab Vedotin (Genetical Recombination)
C_{avgss}	average serum concentration at steady state
C_{eoi}	serum concentration at the end of infusion
cHL	classical Hodgkin lymphoma
CI	confidence interval
CR	complete remission
EBV	Epstein-Barr virus
eGFR	estimated glomerular filtration rate
GVHD	graft versus host disease
HSCT	hematopoietic stem cell transplantation
ILD	interstitial lung disease
Japanese clinical practice guidelines	Hematological Malignancy Clinical Practice Guidelines 2013. Japanese Society of Hematology (Kanehara & Co., Ltd., 2013)
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Hodgkin Lymphoma
NCI-PDQ	National Cancer Institute Physician Data Query
NE	not estimated
NSCLC	non-small cell lung cancer
Partial change application	application for partial change approval
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PFS	progression free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Device Agency
PPK	population pharmacokinetics

PR	partial remission
PS	performance status
Q2W	quaque 2 weeks
RCC	renal cell carcinoma
Revised IWG criteria	Revised Response Criteria for Malignant Lymphoma
SD	stable disease
Study 15	Study ONO-4538-15
Study 39	Study CA209039
Study 205	Study CA209205
TMA	thrombotic microangiopathy
VC	central volume of distribution
VOD	veno-occlusive disease of the liver

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

1.1 Summary of the proposed product

Programmed cell death 1 ("PD-1") is a receptor belonging to the CD28 superfamily (a group of molecules that provide co-stimulatory signals which are involved in the control of T-cell activation) and is expressed on activated lymphocytes (including T cells, B cells, and natural killer T cells). PD-1 *in vivo* is thought to bind to PD-1 ligands expressed on antigen-presenting cells (PD-L1 and PD-L2) to suppress the immune response (*Immunol Rev*. 2010;236:219-42). PD-L1 and PD-L2 are also reported to be expressed on a wide range of tumor tissues (*Nat Rev Immunol*. 2008;8:467-77), suggesting that the PD-1/PD-1 ligand pathway is one of the mechanisms by which tumor cells avoid being attacked by antigen-specific T cells.

Nivolumab (genetical recombination) ("nivolumab"), a human monoclonal antibody against human PD-1 belonging to the immunoglobulin (Ig) G4 subclass, was developed by the applicant and by Medarex in the US (currently known as Bristol-Myers Squibb, BMS). Nivolumab binds to the extracellular domain of PD-1 (PD-1 ligand binding site) and blocks the interaction between PD-1 and PD-1 ligands, thereby enhancing the activation of cancer antigen-specific T cells and cytotoxic activation against cancer cells to inhibit tumor growth.

Nivolumab was approved in Japan for the indication of "unresectable malignant melanoma" in July 2014 and "unresectable, advanced or recurrent non-small cell lung cancer" in December 2015. The indications were expanded to include "unresectable or metastatic renal cell carcinoma" in August 2016 after submission of the present application.

1.2 Development history, etc.

Outside Japan, as part of the clinical development program of nivolumab for the treatment of classical Hodgkin lymphoma (cHL), Bristol-Myers Squibb initiated a phase I study in patients with relapsed or refractory hematologic malignancy (Study 39) in December 2012 and a phase II study in patients with relapsed or refractory cHL (Study 205) in August 2014. Based on the results of the pivotal Study 205, regulatory applications for nivolumab were filed in the US and EU in March 2016. In the US, nivolumab was granted accelerated approval in May 2016 for the treatment of cHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin ("brentuximab"). In the EU, the application is currently under review.

As of July 2016, nivolumab has been approved in 2 countries for the indication of cHL.

In Japan, the applicant started a phase II study in patients with relapsed or refractory cHL (Study 15) in March 2015.

The present partial change application for nivolumab has been filed for the additional indication of cHL, based on the results of pivotal Studies 15 and 205.

Nivolumab was designated as an orphan drug in March 2016 with an intended indication of cHL (Drug Designation No. 381 of 2016 [*28 yaku*]).

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

Since the present application is for a new indication, no data relating to the quality of nivolumab were submitted.

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

Although the present application is for a new indication, no new study data on non-clinical pharmacology were submitted because the non-clinical pharmacology of nivolumab had been evaluated at the initial application.

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

Although the present application is for a new indication, no new study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of nivolumab had been evaluated at the initial application.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for a new indication, no data relating to the toxicity of nivolumab 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 indication, no new data on biopharmaceutic studies or associated analytical methods were submitted because the biopharmaceutic studies and associated analytical methods for nivolumab had been evaluated at the initial application.

6.1 Clinical pharmacology

6.1.1 Differences in the pharmacokinetics of nivolumab between cancer types

The effects of the difference in cancer type on the pharmacokinetics (PK) of nivolumab were evaluated based on the PK parameters of nivolumab obtained in Study 15 in patients with cHL and 2 Japanese phase II studies in patients with non-small cell lung cancer (NSCLC) (Studies ONO-4538-05 and ONO-4538-06) (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated November 18, 2015"). The population pharmacokinetic (PPK) analyses conducted for the approval application for the treatment of NSCLC and of renal cell carcinoma (RCC) revealed no significant differences in the PK of nivolumab in patients with different solid tumors, such as malignant melanoma, NSCLC, and RCC (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated November 18, 2015" and "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated July 22, 2016"). NSCLC, with a large number of patients, was selected as a solid tumor to be compared with cHL in this evaluation.

The results of the evaluation showed no significant differences in the C_{eoi} or C_{trough} following the first dose between patients with NSCLC and patients with cHL, while the C_{trough} following the 12th dose tended to be higher in patients with cHL than in patients with NSCLC (Table 1).

Table 1. Pharmacokinetic parameters (μg/mL) in patients receiving multiple doses of nivolumab 3 mg/kg

PK parameters	n	Patients with cHL	n	Patients with NSCLC
C_{eoi} after the first dose	16	48.2 ± 13.5	109	56.2 ± 11.1
C_{trough} after the first dose	16	18.7 ± 4.10	108	18.2 ± 5.24
C_{trough} after the 12th dose	5	106 ± 16.3	30	72.6 ± 21.8

Arithmetic mean ± standard deviation

The applicant's explanation:
The C_{trough} value following the 12th dose tended to be higher in patients with cHL than in patients with NSCLC. However, the results of PPK analysis [see "6.1.2 Population pharmacokinetic (PPK) analysis"] suggest that the difference in cancer type has a limited effect on the PK of nivolumab.

6.1.2 Population pharmacokinetic (PPK) analysis

PPK analysis was performed using a nonlinear mixed effect model based on the PK data (11,392 sampling time points in 1677 subjects) collected from Japanese clinical studies (Studies ONO-4538-01 and ONO-4538-02), foreign clinical studies (Studies CA209001, CA209003, 39, CA209010, CA209063, 205, CA209017, and CA209057), and a global study (Study CA209025) (NONMEM version 7.3.0). The PK of nivolumab was described by a 2-compartment model.

A base model was used based on the results of PPK analysis performed for the partial change application for the indication of RCC (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated July 22, 2016"). The base model included (a) the effects of body weight, estimated glomerular filtration rate (eGFR), performance status (PS), serum albumin concentration, immunogenicity, and cancer types (NSCLC, RCC, and other cancer types) on clearance (CL); and (b) the effects of body weight, sex, and the histology type of NSCLC on the central volume of distribution (VC). Based on the base model, a full model was developed by incorporating the following covariates: (a) cancer type (NSCLC, RCC, cHL, and other cancer types) and age for CL; and (b) cancer type for VC. In the full model, the significance of the covariates (cancer type, immunogenicity and age for CL, and cancer type for VC) was assessed by backward elimination. As a result, cancer type and immunogenicity were selected as significant covariates for CL.

The applicant's explanation:
In the final model, (a) body weight, eGFR, PS, serum albumin concentration, cancer type, and immunogenicity were covariates for CL, and (b) body weight, sex, and NSCLC histology were covariates for VC. The effects of these covariates on CL or VC were within the inter-individual variations (36.1% for CL and 30.1% for VC), suggesting that the effects of these covariates on the PK of nivolumab are limited.

6.1.3 Relationship between nivolumab exposure and efficacy/safety

6.1.3.1 Relationship between nivolumab exposure and efficacy

Based on the results of Studies 39 and 205, the relationship between nivolumab exposure[1)] (C_{avgss}) and centrally assessed response rate was evaluated using logistic regression analysis. A statistically significant relationship was found between exposure (C_{avgss}) and centrally assessed response rate. The applicant, however, explained that a definite conclusion cannot be drawn regarding the relationship between exposure (C_{avgss}) and centrally assessed response rate, because the sensitivity analysis showed no clear association between exposure (C_{avgss}) and investigator-assessed response rate.

6.1.3.2 Relationship between nivolumab exposure and safety

Based on the results of Studies 39 and 205, the relationship between nivolumab exposure[1)] (C_{avgss}) and the time to onset of Grade ≥3 adverse events for which a causal relationship to nivolumab cannot be ruled out was evaluated using the Cox proportional hazards model. No clear relationship was found between nivolumab exposure (C_{avgss}) and the time to the onset of Grade ≥3 adverse events for which a causal relationship to nivolumab cannot be ruled out.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in the pharmacokinetics of nivolumab between Japanese and non-Japanese patients with cHL

The applicant's explanation on the differences in the PK of nivolumab between Japanese and non-Japanese patients with cHL:

Table 2 shows the C_{trough} values in patients with cHL who received nivolumab 3 mg/kg in Studies 15 and 205. No clear differences in the PK of nivolumab exist between Japanese and non-Japanese patients.

Table 2. C_{trough} values (μg/mL) in patients with cHL receiving multiple doses of nivolumab 3 mg/kg

	n	Second dose	n	Sixth dose	n	12th dose
Japanese patients (Study 15)	16	31.7 ± 10.0	12	64.3 ± 18.5	5	106 ± 16.3
Non-Japanese patients (Study 205)	169	39.5 ± 11.3	113	76.7 ± 21.1	55	100 ± 27.2

Arithmetic mean ± standard deviation

PMDA's view:

C_{trough} is the only currently available parameter that can be used to compare the PK of nivolumab administered at the proposed dosage regimen between Japanese and non-Japanese patients with cHL, and it is therefore difficult to strictly evaluate the differences in PK between the populations. Nevertheless, PMDA considers that the data submitted do not reveal any clear tendency for the PK of nivolumab to differ between Japanese and non-Japanese patients with cHL.

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 result data from 4 clinical studies: a Japanese phase I study, a Japanese phase II study, a foreign phase I study, and a foreign phase II study (see Table 3). The results of Study ONO-4538-01 (a Japanese phase I study) were submitted and evaluated at the

[1)] It was estimated from the final model for PPK analysis [see "6.1.2 Population pharmacokinetic (PPK) analysis"].

initial application; therefore, these are not included in Table 3 or "7.1 Evaluation data" (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014").

Table 3. Summary of clinical studies on the efficacy and safety of nivolumab

Data type	Region	Study Identifier	Phase	Subjects	N	Dosage regimen	Main endpoints
Evaluation data	Japan	15	II	Patients with relapsed or refractory cHL	17	Intravenous nivolumab 3 mg/kg every 2 weeks	Efficacy Safety
	Foreign	39	I	Patients with relapsed or refractory hematologic malignancy	23 (cHL)	Intravenous nivolumab 1 or 3 mg/kg every 2 weeks	Efficacy Safety PK
		205	II	Patients with relapsed or refractory cHL	243	Intravenous nivolumab 3 mg/kg every 2 weeks	Efficacy Safety

These clinical studies are separately summarized below. Major adverse events other than death reported in each clinical study are detailed in "7.2 Adverse events reported in clinical studies."

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese phase II study (CTD 5.3.5.2-1, Study 15, ongoing since March 2015 [data cut-off, [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 13 sites in Japan to evaluate the efficacy and safety of nivolumab in patients with relapsed or refractory cHL who were resistant or intolerant[2)] to brentuximab (target sample size, 15 subjects).

Nivolumab was intravenously administered at 3 mg/kg every 2 weeks. The treatment was continued until disease progression was observed or until a withdrawal criterion was met.

Of the 17 patients enrolled in the study, 16 were included in the efficacy analysis population, excluding 1 patient who was diagnosed with non-Hodgkin lymphoma by centralized pathology review. All 17 patients received nivolumab and were included in the safety analysis population.

The primary endpoint was response rate[3)] assessed centrally according to the Revised Response Criteria for Malignant Lymphoma ("revised IWG criteria") (*J Clin Oncol*. 2007;25:579-86) (for results, see Table 4).

[2)] In Study 15, patients clinically ineligible for brentuximab therapy were allowed to participate; however, no such patients were actually enrolled in the study.

[3)] The threshold response rate was determined to be 20%, based on that used in a clinical study of brentuximab in patients with relapsed or refractory cHL (*J Clin Oncol*. 2012;30:2183-9).

Table 4. Best overall response and response rate
(Centrally assessed, efficacy analysis population [data cutoff, [redacted], 20[redacted]])

	n (%), N = 16
Complete response (CR)	4 (25.0)
Partial response (PR)	8 (50.0)
Stable disease (SD)	2 (12.5)
Progressive disease (PD)	1 (6.3)
Not evaluable (NE)	1 (6.3)
Response (CR + PR)	12
(Response rate [95%CT*])	(75.0% [47.6%, 92.7%])

*: Clopper-Pearson method

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

7.1.2 Foreign clinical studies

7.1.2.1 Foreign phase I study (CTD 5.3.3.2-3, Study 39, ongoing since December 2012 [data cut-off, [redacted], 20[redacted][4)]])

An open-label, uncontrolled study was conducted at 7 sites outside Japan to evaluate the tolerability and safety of nivolumab in patients with relapsed or refractory hematologic malignancy (target sample size, 315 subjects). This study was composed of 3 cohorts.[5)] The data submitted for the present partial change application were the results of the interim analysis of efficacy and safety data from 23 patients[6)] with cHL who were allocated to nivolumab monotherapy and received nivolumab 3 mg/kg every 2 weeks.

Nivolumab was intravenously administered at 3 mg/kg every 2 weeks.[7)] The treatment was continued until disease progression was observed or until a withdrawal criterion was met.

All 23 patients who were allocated to nivolumab monotherapy and received nivolumab 3 mg/kg every 2 weeks were included in the efficacy and safety analysis populations.

In patients with cHL who received nivolumab 3 mg/kg every 2 weeks, response rate assessed by investigators according to the revised IWG criteria was 87.0% (95% confidence interval [CI], 66.4%, 97.2%) (20 of 23 patients).

No deaths occurred during the treatment period or within 100 days after the last dose.

[4)] Safety data collected by [redacted], 20[redacted] were submitted after the submission of the present partial change application.
[5)] The 3 cohorts consist of a cohort receiving nivolumab monotherapy (planned sample size, 110); a cohort receiving nivolumab and ipilimumab (genetical recombination) (off-label use in Japan) (planned sample size, 75); and a cohort receiving nivolumab and lirilumab (not approved in Japan) (planned sample size, 130)
[6)] The nivolumab monotherapy cohort consisted of a dose escalation phase and a dose expansion phase. Two patients with cHL were enrolled in the nivolumab 3 mg/kg Q2W group in the dose escalation phase, and 21 patients with cHL in the dose expansion phase. (During the dose expansion phase, nivolumab 3 mg was administered every 2 weeks, as determined in the dose escalation phase.)
[7)] Only the second dose was intravenously administered 3 weeks after the first dose, in order to evaluate PK, etc.

7.1.2.2 Foreign phase II study (CTD 5.3.5.2-2, Study 205, ongoing since August 2014 [data cut-off, [redacted], 20[redacted][8)]])

An open-label, uncontrolled study was conducted at 34 sites outside Japan to evaluate the efficacy and safety of nivolumab in patients with relapsed or refractory cHL after autologous hematopoietic stem cell transplantation (ASCT) (target sample size, 320 subjects). This study was composed of Cohorts A to C[9)] and analysis of each cohort was scheduled at a predefined time point.[10)] The following data were submitted for the present partial change application: (1) efficacy data from Cohort B, in which the predefined analysis had been completed; and (2) the safety data from all cohorts.

Nivolumab was intravenously administered at 3 mg/kg every 2 weeks. The treatment was continued until disease progression was observed or until a withdrawal criterion was met.

All 80 patients who were allocated to Cohort B and received nivolumab were included in the efficacy analysis population for the present partial change application. The safety analysis population included all 243 patients (Cohort A, 63; Cohort B, 80; and Cohort C, 100) who were enrolled in the study and received nivolumab.

The primary endpoint was response rate[3)] assessed centrally according to the revised IWG criteria. The results in Cohort B are shown in Table 5.

Table 5. Best overall response and response rate (Centrally assessed, efficacy analysis population [data cutoff, [redacted], 20[redacted]])

	n (%), N = 80
Complete response (CR)	7 (8.8)
Partial response (PR)	46 (57.5)
Stable disease (SD)	18 (22.5)
Progressive disease (PD)	6 (7.5)
Not evaluable (NE)	3 (3.8)
Response (CR + PR)	53
(Response rate [95%CT*])	(66.3% [54.8%, 76.4%])

*: Clopper-Pearson method

Death occurred in 8 of 243 patients (3.3%) during the treatment period or within 100 days after the last dose. Of the 8 patients, 4 died of disease progression. Other causes of death were atypical pneumonia, EBV test positive, cardiac arrest, and graft versus host disease (GVHD) in 1 patient each; a causal relationship to nivolumab was ruled out for all the events.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

The evaluation data submitted included the Japanese phase II study (Study 15) and the foreign phase II study (Study 205), both of which enrolled patients with relapsed or refractory cHL who were resistant or intolerant

[8)] Safety data collected by [redacted], 20[redacted] were submitted after the submission of the present partial change application.
[9)] Cohort A, patients without prior brentuximab therapy; Cohort B, patients who have received brentuximab therapy after ASCT; and Cohort C, patients with prior brentuximab therapy
[10)] Interim analysis was scheduled at 6 months after the first dose in the last patient in Cohort B, and [redacted] in Cohorts A and C.

to brentuximab. PMDA decided that the 2 clinical studies were most important for evaluating the efficacy and safety of nivolumab, and therefore focused its review on the studies.

7.R.2 Efficacy

PMDA concluded that a certain level of efficacy of nivolumab has been demonstrated in patients with relapsed or refractory cHL who were resistant or intolerant to brentuximab, based on the following reviews.

7.R.2.1 Efficacy endpoint and evaluation results

Both in Study 15 and Cohort B of Study 205, the response rates were significantly higher than the predefined threshold response rate [see "7.1.1.1 Japanese phase II study" and "7.1.2.2 Foreign phase II study"]. The response rates [95%CI] assessed by the investigator according to the revised IWG criteria (a secondary endpoint) were 56.3% [29.9%, 80.2%] in Study 15 and 72.5% [61.4%, 81.9%] in Cohort B of Study 205. The centrally assessed median response duration [95%CI] (months) was "not estimated (NE)" [3.71, NE] in Study 15 and 7.79 [6.64, NE] in Cohort B of Study 205. Overall survival, a secondary endpoint, did not reach the median in Study 15 or Cohort B of Study 205, with a survival rate of 98.7% at 6 months in Cohort B of Study 205.

The applicant's explanation of the use of response rate as the primary efficacy endpoint in Study 15 and Cohort B of Study 205:

Since no therapies have been demonstrated to prolong overall survival in patients with relapsed or refractory cHL who are resistant or intolerant to brentuximab, achieving response in this patient population is considered to be of clinically significance.

PMDA's view:

Based on the above-mentioned results, PMDA concluded that a certain level of efficacy of nivolumab has been demonstrated in patients with relapsed or refractory cHL who are resistant or intolerant to brentuximab.

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

PMDA's view as a result of its review [for review summary, see 7.R.3.1 and 7.R.3.2]:

Special attention should be paid to the following adverse events when administering nivolumab to patients with relapsed or refractory cHL; these events were identified as requiring attention at the regulatory reviews for the previously approved indications: interstitial lung disease (ILD), hepatic function disorder, abnormal thyroid function, infusion reaction, skin disorder, colitis and severe diarrhoea, myasthenia gravis and myositis, neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, encephalitis, type 1 diabetes mellitus, and cardiac disorder (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated June 18, 2014," "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated November 18, 2015," "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated January 22, 2016," and "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated July 22, 2016"). The

occurrence of these adverse events should be carefully monitored in patients with relapsed or refractory cHL as well as in those receiving nivolumab for the other indications.

The above-mentioned adverse events require careful attention in the use of nivolumab. Nevertheless, PMDA has concluded that nivolumab is tolerable in patients with cHL as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis and patient management in anticipation of an adverse reaction caused by excessive immune responses, drug interruption, or other appropriate actions.

7.R.3.1 Safety profile of nivolumab

The applicant's explanation on the safety profile of nivolumab based on the safety data from Studies 15 and 205:

The safety data from Studies 15 and 205 are summarized in Table 6.

Table 6. Safety summary (Studies 15 and 205)

	n (%)	
	Study 15 N = 17	Study 205 N = 243
All adverse events	17 (100)	238 (97.9)
Grade ≥3 adverse events	2 (11.8)	84 (34.6)
Adverse events resulting in death	0	8 (3.3)
Serious adverse events	1 (5.9)	60 (24.7)
Adverse events leading to drug discontinuation	1 (5.9)	15 (6.2)
Adverse events leading to drug interruption	4 (23.5)	81 (33.3)

The adverse events reported with an incidence of ≥20% in Study 15 were pyrexia (41.2%, 7 of 17 patients), pruritis (29.4%, 5 of 17 patients), headache (23.5%, 4 of 17 patients), and rash (23.5%, 4 of 17 patients), and those in Study 205 were fatigue (30.9%, 75 of 243 patients), diarrhoea (28.0%, 68 of 243 patients), pyrexia (25.5%, 62 of 243 patients), and cough (23.0%, 56 of 243 patients). The Grade ≥3 adverse events reported with an incidence of ≥2% in Study 15 were anaemia (5.9%, 1 of 17 patients), lymphocytopenia (5.9%, 1 of 17 patients), hyponatraemia (5.9%, 1 of 17 patients), and ILD (5.9%, 1 of 17 patients), and those in Study 205 were lipase increased (4.9%, 12 of 243 patients), anaemia (2.9%, 7 of 243 patients), neutropenia (2.9%, 7 of 243 patients), ALT increased (2.9%, 7 of 243 patients), pneumonia (2.5%, 6 of 243 patients), AST increased (2.1%, 5 of 243 patients), and malignant neoplasm progression (2.1%, 5 of 243 patients). The serious adverse events reported with an incidence of ≥2% in Study 15 were hyponatraemia (5.9%, 1 of 17 patients) and ILD (5.9%, 1 of 17 patients), and those in Study 205 were pneumonia (2.5%, 6 of 243 patients), infusion related reaction (2.1%, 5 of 243 patients), and malignant neoplasm progression (2.1%, 5 of 243 patients). The only adverse event leading to drug discontinuation with an incidence of ≥1% in Study 15 was ILD (5.9%, 1 of 17 patients), and that in Study 205 was AST increased (1.2%, 3 of 243 patients). The adverse events leading to drug interruption with an incidence of ≥2% in Study 15 were enterocolitis (5.9%, 1 of 17 patients), pneumonia (5.9%, 1 of 17 patients), lymphocytopenia (5.9%, 1 of 17 patients), bronchitis (5.9%, 1 of 17 patients), and hyponatraemia (5.9%, 1 of 17 patients), and those in Study 205 were diarrhoea (2.9%, 7 of 243 patients), pneumonia (2.5%, 6 of 243 patients), anaemia (2.1%, 5 of 243 patients), neutropenia (2.1%, 5 of 243 patients),

pyrexia (2.1%, 5 of 243 patients), ALT increased (2.1%, 5 of 243 patients), and lipase increased (2.1%, 5 of 243 patients).

The applicant explained the differences in the safety profile of nivolumab between the previously approved indications (unresectable malignant melanoma, unresectable, advanced or recurrent NSCLC, and unresectable or metastatic RCC) and the currently proposed indication (relapsed or refractory cHL).

The applicant's explanation:
The incidences of the adverse events reported in Studies 15, 205, and 39 were compared with those in patients who received nivolumab 3 mg/kg every 2 weeks in the following studies: (1) foreign phase III studies in patients with unresectable malignant melanoma (Studies CA209066 and CA209037); (2) foreign phase III studies in patients with unresectable, advanced or recurrent NSCLC (Studies CA209017 and CA209057); and (3) the global phase III study in patients with unresectable or metastatic RCC (Study CA209025) (474 patients with malignant melanoma, 418 patients with NSCLC, and 406 patients with RCC). The results of the comparison are shown in Table 7.

Table 7. Safety summary in patients with cHL, malignant melanoma, NSCLC, or RCC

	n (%)			
	cHL N = 283	Malignant melanoma N = 474	NSCLC N = 418	RCC N = 406
All adverse events	278 (98.2)	457 (96.4)	407 (97.4)	397 (97.8)
Grade ≥3 adverse events	101 (35.7)	218 (46.0)	222 (53.1)	230 (56.7)
Adverse events resulting in death	10 (3.5)	44 (9.3)	65 (15.6)	23 (5.7)
Serious adverse events	69 (24.4)	206 (43.5)	195 (46.7)	194 (47.8)
Adverse events leading to drug discontinuation	18 (6.4)	48 (10.1)	62 (14.8)	72 (17.7)
Adverse events leading to drug interruption	85 (30.0)	146 (30.8)	118 (28.2)	177 (43.6)

The following adverse events occurred with a ≥5% higher incidence in patients with cHL than in any of the other patient populations (i.e., patients with malignant melanoma, NSCLC, or RCC): pyrexia (cHL, 28.3%; malignant melanoma, 15.2%; NSCLC, 13.4%; RCC, 16.5%), upper respiratory tract infection (cHL, 16.6%; malignant melanoma, 3.8%; NSCLC, 6.0%; RCC, 7.4%), infusion related reaction (cHL, 12.7%; malignant melanoma, 3.0%; NSCLC, 2.2%; RCC, 3.2%), neuropathy peripheral (cHL, 8.1%; malignant melanoma, 2.5%; NSCLC, 3.1%; RCC, 3.0%), thrombocytopenia (cHL, 8.1%; malignant melanoma, 1.3%; NSCLC, 1.4%; RCC, 1.0%), lipase increased (cHL, 7.8%; malignant melanoma, 2.7%; NSCLC, 0.2%; RCC, 1.0%), and neutropenia (cHL, 7.1%; malignant melanoma, 0.2%; NSCLC, 1.0%, RCC, 0.5%). No Grade ≥3 adverse events, serious adverse events, adverse events resulting in death, adverse events leading to drug discontinuation, or adverse events leading to drug interruption occurred with a ≥5% higher incidence in patients with cHL than in any of the other patient populations (i.e., patients with malignant melanoma, NSCLC, or RCC).

The applicant's explanation on the differences in the safety of nivolumab between Japanese and non-Japanese patients:

No adverse events occurred with a ≥20% higher incidence in Study 15 (involving Japanese patients with cHL) than in Study 205 (involving non-Japanese patients with cHL). Similarly, no Grade ≥3 adverse events, adverse events resulting in death, serious adverse events, or adverse events leading to drug discontinuation occurred with a ≥10% higher incidence in Study 15 than in Study 205.

PMDA's view:

The adverse events frequently reported in Studies 15 and 205 require special attention when administering nivolumab to patients with cHL; information on the occurrence of the events should be appropriately provided to healthcare professionals. Since all of these events are known adverse events of nivolumab, the drug is tolerable also in patients with cHL as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis and patient management in anticipation of an adverse reaction caused by excessive immune responses, drug interruption, or other appropriate actions.

Because of a small number of Japanese patients who have received nivolumab, there is a limitation in making a rigorous comparison of the safety of nivolumab between Japanese and non-Japanese patients. Nonetheless, PMDA concluded that nivolumab is tolerable in Japanese patients as well as in non-Japanese patients, because there were no tendencies for adverse events resulting in death, serious adverse events, or adverse events leading to drug discontinuation to develop more frequently in Japanese patients than in non-Japanese patients.

7.R.3.2 Others

7.R.3.2.1 Serious complications of allogeneic hematopoietic stem cell transplantation (HSCT) after treatment with nivolumab

A precaution regarding the possible occurrence of serious complications of allogeneic HSCT in patients who have received prior treatment with nivolumab was added to the U.S. label in May 2016. PMDA asked the applicant to explain the incidences of complications of allogeneic HSCT in patients who have received prior treatment with nivolumab.

The applicant's response:

Data on GVHD-related adverse events were collected from 17 patients in Study 205 (12 patients) and Study 39 (5 patients) who underwent allogeneic HSCT after treatment with nivolumab.[11)] Acute GVHD occurred in 14 of 17 patients (82.4%) (Grade 1, 3 patients; Grade 2, 5 patients; Grade 3, 1 patient; Grade 4, 4 patients; and Grade unknown, 1 patient). Transplant-related death occurred in 6 of 17 patients (35.3%). Table 8 provides detailed information on the patients who experienced Grade ≥3 acute GVHD and died of transplant-related toxicity (transplant-related death). In patients undergoing allogeneic HSCT after nivolumab therapy, the median number of nivolumab doses was 9 (range, 4 to 16).

[11)] Questionnaires regarding the occurrence and details of transplant-related complications (acute GVHD, hyperacute GVHD [defined as acute GVHD occurring within 14 days after HSCT], transplant-related death, veno-occlusive disease [VOD], steroid-responsive fever syndrome [defined as "fever responsive to steroids, without infection"], and other transplant-related complications) were sent to 10 study sites that performed allogeneic HSCT between [redacted], 20[redacted] and [redacted], 20[redacted] in patients participating in Studies 205 or 39. All the 10 sites provided information on transplant-related complications. The grade of acute GVHD was evaluated according to the 1994 Consensus Conference on Acute GVHD Grading (*Bone Marrow Transplant.* 1995;15:825-8).

Table 8. Patients with Grade ≥3 acute GVHD and transplant-related death (Studies 205 and 39)

Age	Sex	Number of doses[*1]	Time to HSCT[*2] (days)	Acute GVHD			Steroid-responsive non-infectious pyrexia	VOD	Other transplant-related complications	Cause of death
				Time to onset[*3] (days)	Grade	Site(s)				
20	Woman	4	63	30	4	Skin Gastrointestinal Liver	Absent	Absent	Sepsis/multi-organ failure	Transplant-related (multi-organ failure)
34	Man	16	22	17	4	Skin Gastrointestinal Liver	Absent	Present	Septic shock	Transplant-related (GVHD)
28	Woman	8	11	22	4	Skin Gastrointestinal Liver	Present	Absent	Thrombotic microangiopathy (TMA)	Transplant-related (GVHD, infection)
31	Woman	9	94	13	4	Skin Gastrointestinal Liver	Present	Absent	Diffuse pulmonary alveolar haemorrhage	Transplant-related death

*1, Number of doses administered until HSCT occurred; *2, Period from the last dose of nivolumab to the onset of HSCT;
*3, Period from HSCT to the onset of GVHD

In patients with relapsed or refractory Hodgkin lymphoma, the incidence of acute GVHD (Grade ≥3) after allogeneic HSCT is 9.9% to 12.3%, and the incidence of transplant-related death within 100 days after allogeneic HSCT is 6% to 28% (*J Clin Oncol.* 2008;26:455-62; *Haematologica.* 2008;94:230-8). As compared with these data, Studies 205 and 39 showed a tendency toward higher incidences of Grade ≥3 acute GVHD and transplant-related death, although only a limited number of patients in the studies underwent allogeneic HSCT after treatment with nivolumab. In addition, a non-clinical study in mice after allogeneic HSCT suggested that inhibition of the PD-1/PD-1 ligand pathway may induce GVHD (e.g., *J Immunol.* 2003;171:1272-7). Thus, attention should be paid to the occurrence of serious acute GVHD when performing allogeneic HSCT in patients who have received prior treatment with nivolumab.

PMDA's view:

At present, a definitive conclusion cannot be drawn regarding the association between prior nivolumab therapy and serious complications of allogeneic HSCT because of a small number of patients who underwent allogeneic HSCT after nivolumab therapy and the limited available information on the risk factors of acute GVHD in such patients. Since allogeneic HSCT could be performed in patients with relapsed or refractory cHL (e.g., *Blood.* 2016;127:287-95; *Semin Hematol.* 2016;53:180-5), the information presented above (e.g., the fact that serious complications of allogeneic HSCT occurred in several patients who had received prior nivolumab therapy) should be appropriately provided to healthcare professionals using an information leaflet or other materials.

7.R.4 Clinical positioning and indication

The proposed indication of nivolumab was "treatment of patients with relapsed or refractory classical Hodgkin lymphoma." The following statement was included in the proposed "Precautions for Indication" section:

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

As a result of the review described in "7.R.2 Efficacy" and "7.R.3 Safety" and the following subsections (7.R.4.1 and 7.R.4.2), PMDA concluded that the proposed indication and the proposed precautionary statement in "Precautions for Indications" are acceptable.

7.R.4.1 Clinical positioning

Foreign clinical practice guidelines and a major textbook of oncology contain the following statements on nivolumab for the treatment of relapsed or refractory cHL. Currently, there is no mention of nivolumab in the Japanese clinical practice guidelines.

Clinical practice guidelines

- NCCN guidelines (ver. 3. 2016): Nivolumab is a treatment option for relapsed or refractory cHL after ASCT and brentuximab therapy (Category 2A[12)]).

- The US National Cancer Institute's Physician Data Query (NCI-PDQ) (updated on March 4, 2016): Study 39 showed the following results regarding nivolumab: (1) In patients with relapsed or refractory cHL who had received ≥2 prior treatment regimens, the response rate was 87% and complete response (CR) rate was 17%; most of the patients had a >1 year duration of response or CR. (2) The PFS rate [95%CI] at week 24 was 86% [62%, 95%] in these patients.

Oncology textbook

- Williams Hematology, ninth edition (McGraw-Hill Education. 2016, USA): Study 39 showed that the response rate of nivolumab was 87% in patients with relapsed or refractory cHL who had received ≥2 prior treatment regimens.

The applicant's explanation of the clinical positioning of nivolumab:
In Japan, treatment of cHL is performed according to the Japanese clinical practice guidelines, etc.; the standard therapy for treatment-naive patients with cHL is as follows: (1) for patients with localized stages (stage I or II), 4 cycles of a combination regimen with doxorubicin, bleomycin, vinblastine sulfate, and dacarbazine (ABVD regimen) plus regional radiation; (2) for patients with advanced stages (stage III or IV), 6 to 8 cycles of the ABVD regimen. Patients with relapsed or refractory cHL after the initial therapy receive rescue therapy with combination chemotherapy and then, if eligible, undergo ASCT. Patients with relapsed or refractory cHL who have received prior combination chemotherapy and ASCT receive brentuximab therapy or combination chemotherapy with a regimen that has never been used, although there are no standard therapies proven to prolong survival in those patients.

Under these circumstances, the results of Study 15 and Cohort B of Study 205 demonstrated the clinical usefulness of nivolumab in the treatment of patients with relapsed or refractory cHL who are resistant or intolerant to brentuximab; thus, nivolumab is a therapeutic option for those patients.

PMDA accepted the applicant's explanation.

[12)] Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

7.R.4.2 Intended population

The applicant explained that the intended population of nivolumab is patients with relapsed or refractory cHL who are resistant or intolerant to brentuximab, corresponding to the patient populations of Study 15 and Cohort B of Study 205.

PMDA asked the applicant to explain treatment with nivolumab in patients excluded from Study 15 or Cohort B of Study 205, that is, (a) patients with relapsed or refractory cHL who are eligible for ASCT and (b) patients with relapsed or refractory cHL who are eligible for brentuximab.

The applicant's response:

Treatment with nivolumab in patient populations (a) and (b) are not recommended for the reasons below. The characteristics, such as a history of prior treatment, of the patients enrolled in Studies 15 and 205 will be described in the "Clinical Studies" section of the package insert. The "Precautions for indications" section of the package insert will include a precautionary statement to the effect that 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 nivolumab.

- There have been no clinical data from patients with relapsed or refractory cHL who are eligible for ASCT, although the results of the studies mentioned below indicated no clear differences in the efficacy of nivolumab between patients with and without prior ASCT.
  - In 17 patients with relapsed or refractory cHL enrolled in Study 15, the response rates [95%CI] of nivolumab were 63.6% [30.8%, 89.1%] (7 of 11 patients) in those who had not received prior ASCT because of ineligibility for ASCT, and 100% [47.8%, 100%] (5 of 5 patients) in those with prior ASCT.
  - In 23 patients with relapsed or refractory cHL enrolled in Study 39, the response rates [95%CI] of nivolumab were 80.0% [28.4%, 99.5%] (4 of 5 patients) in those who had not received prior ASCT because of ineligibility for ASCT, and 55.6% [30.8%, 78.5%] (10 of 18 patients) in those with prior ASCT.
- In 23 patients with relapsed or refractory cHL enrolled in Study 39, the response rates [95%CI] of nivolumab were 60.0% [14.7%, 94.7%] (3 of 5 patients) in those without prior brentuximab therapy and 61.1% [35.7%, 82.7%] (11 of 18 patients) in those with prior brentuximab therapy, showing no clear differences in the efficacy of nivolumab between patients with and without prior brentuximab therapy. Nevertheless, there have been no clinical data from patients with relapsed or refractory cHL who are eligible for brentuximab.

PMDA's view:

Based on the above applicant's explanation and considering that nivolumab will be used by physicians with sufficient knowledge and experience in cancer chemotherapy, PMDA concluded that the proposed indication "relapsed or refractory classical Hodgkin lymphoma" is acceptable, provided that the characteristics, such as a history of prior treatment, of the patients enrolled in Study 15 and Cohort B of Study 205 are described in the "Clinical Studies" section of the package insert, and that the following statement is included in the "Precautions for Indication" section.

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

7.R.5 Dosage and administration

The proposed dosage and administration was "The usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight administered as an intravenous infusion every 2 weeks." The following precautionary advice was included in the proposed "Precautions for Dosage and Administration" section:

- Preparation method for the injection solution and the duration of infusion
- An in-line filter (pore size, 0.2 or 0.22 μm) should be used for infusion.
- The efficacy and safety of nivolumab in combination with other antineoplastic drugs have not been established.

As a result of the review described below, PMDA concluded that the proposed dosage and administration of nivolumab are appropriate and that the proposed precautionary statement should be included in the "Precautions for Dosage and Administration" section.

7.R.5.1 Dosage and administration of nivolumab

The applicant's explanation on the rationale for the dosage and administration of nivolumab selected for patients with relapsed or refractory cHL:

Based on the results of the foreign phase I study (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated November 18, 2015") and other data, a dosing regimen of 3 mg/kg every 2 weeks was selected for Studies 15 and 205, and the studies demonstrated the clinical usefulness of nivolumab for the treatment of patients with relapsed or recurrent cHL. The proposed dosage and administration of nivolumab is based on the dosing regimen employed in these 2 studies.

PMDA accepted the applicant's explanation.

7.R.5.2 Concomitant use of other antineoplastic drugs

The applicant's explanation:

Nivolumab has been administered only as monotherapy to patients with relapsed or refractory cHL in clinical studies, and the efficacy and safety of nivolumab in combination with other antineoplastic drugs are unknown. The "Precautions for Dosage and Administration" section of the package insert will include a precautionary statement to the effect that the efficacy and safety of nivolumab in combination with other antineoplastic drugs have not been established.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation on their post-marketing surveillance plan:

The applicant plans to conduct post-marketing surveillance covering all patients treated with nivolumab to evaluate the safety of brentuximab in clinical practice in patients with relapsed or refractory cHL.

Since the safety profile observed in Studies 15, 205 and 39 was comparable with the safety profile found with the previously approved indications [see "7.R.3.1 Safety profile of nivolumab"], the following events have been selected as the key survey items in the post-marketing surveillance, because they are key survey items in the post-marketing surveillance in patients with unresectable malignant melanoma, unresectable advanced or recurrent NSCLC, and unresectable or metastatic RCC:
ILD, myasthenia gravis and myositis, colitis and severe diarrhoea, type 1 diabetes mellitus, hepatic function disorder, abnormal thyroid function, neurological disorder, renal disorder, adrenal disorder, encephalitis, severe skin disorder, venous thrombosis and embolism, infusion reaction, and cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles).

The target sample size was determined as 200, focusing on ILD based on (1) the incidence of ILD in Study 15 and (2) the ILD events reported in patients with NSCLC treated with nivolumab after the market launch in and out of Japan.

The follow-up period is 12 months, because in Studies 205 and 39, 96.2% of the events included in the key survey items occurred within 12 months after the start of treatment and no new events were reported thereafter.

PMDA's view:
The safety data from Japanese patients with cHL treated with nivolumab are limited and the results of the ongoing post-marketing surveillance for the previously approved indications (i.e., unresectable malignant melanoma, unresectable, advanced or recurrent NSCLC, and unresectable or metastatic RCC) have not been obtained. Therefore, safety information should be collected from all patients with relapsed or refractory cHL treated with nivolumab in a timely and unbiased manner for a certain period after the launch, and the collected information should be promptly provided to healthcare professionals.

The key survey items and follow-up period for the post-marketing surveillance proposed by the applicant are acceptable. The target sample size should be reconsidered, focusing on not only ILD but also other key survey items.

7.R.7 Development of nivolumab in pediatric patients

PMDA asked the applicant to explain the status of development of nivolumab in pediatric patients with relapsed or refractory cHL in and out of Japan.

The applicant's response:
At present, the applicant has no plan to develop nivolumab in pediatric patients with relapsed or refractory cHL either in or out of Japan.

PMDA's view:

In order to appropriately develop nivolumab for pediatric patients with relapsed or refractory cHL, the applicant should collect and analyze information on development demand for pediatric patients, and take appropriate actions such as the conduct of a clinical study in Japan.

7.2 Adverse events reported in clinical studies

Among the clinical study data submitted for safety evaluation, data on death are presented in "7.1 Evaluation data." The subsections below explain other major adverse events, but do not include the results of the Japanese phase I study (Study ONO-4538-01) or a foreign phase I study (Study CA209001) because they were evaluated at the initial application for nivolumab (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014").

7.2.1 Japanese phase II study (Study 15)

All patients experienced adverse events. All patients also experienced adverse events for which a causal relationship to nivolumab could not be ruled out. The adverse events with an incidence of ≥10% are shown in Table 9.

Table 9. Adverse events with an incidence of ≥10%

System Organ Class Preferred Term (MedDRA/J ver.18.1)	n (%), N = 17	
	All Grades	Grade ≥3
All adverse events	17 (100)	2 (11.8)
Endocrine disorders		
Hypothyroidism	3 (17.6)	0
General disorders and administration site conditions		
Fatigue	2 (11.8)	0
Malaise	2 (11.8)	0
Oedema	2 (11.8)	0
Pyrexia	7 (41.2)	0
Musculoskeletal and connective tissue disorders		
Back pain	2 (11.8)	0
Myalgia	2 (11.8)	0
Nervous system disorders		
Headache	4 (23.5)	0
Respiratory, thoracic and mediastinal disorders		
Upper respiratory tract inflammation	2 (11.8)	0
Skin and subcutaneous tissue disorders		
Dermatitis acneiform	2 (11.8)	0
Pruritus	5 (29.4)	0
Rash	4 (23.5)	0

Serious adverse events were reported in 1 of 17 patients (5.9%). The reported serious adverse events were hyponatraemia and ILD in 1 patient (5.9%) each. A causal relationship to nivolumab could not be ruled out for both events.

Adverse event leading to drug discontinuation was ILD, reported in 1 of 17 patients (5.9%). A causal relationship to nivolumab could not be ruled out for the event.

7.2.2 Foreign phase I study (Study 39)

Adverse events were reported in all patients. In total, 21 of 23 patients (91.3%) experienced adverse events for which a causal relationship to nivolumab could not be ruled out. The adverse events with an incidence of ≥20% are shown in Table 10.

Table 10. Adverse events with an incidence of ≥20%

System Organ Class Preferred Term (MedDRA/J ver.18.1)	n (%), N = 23	
	All Grades	Grade ≥3
All adverse events	23 (100)	15 (65.2)
Blood and lymphatic system disorders		
Lymphocytopenia	5 (21.7)	3 (13.0)
Thrombocytopenia	9 (39.1)	4 (17.4)
Endocrine disorders		
Hypothyroidism	5 (21.7)	0
Gastrointestinal disorders		
Diarrhoea	11 (47.8)	1 (4.3)
Nausea	7 (30.4)	0
Vomiting	7 (30.4)	0
General disorders and administration site conditions		
Fatigue	12 (52.2)	1 (4.3)
Pyrexia	11 (47.8)	0
Infections and infestations		
Upper respiratory tract infection	6 (26.1)	0
Investigations		
ALT increased	6 (26.1)	1 (4.3)
AST increased	5 (21.7)	1 (4.3)
Metabolism and nutrition disorders		
Hyperglycaemia	9 (39.1)	0
Hypokalaemia	6 (26.1)	3 (13.0)
Hypophosphataemia	6 (26.1)	2 (8.7)
Musculoskeletal and connective tissue disorders		
Back pain	6 (26.1)	1 (4.3)
Nervous system disorders		
Headache	5 (21.7)	0
Neuropathy peripheral	5 (21.7)	0
Respiratory, thoracic and mediastinal disorders		
Cough	14 (60.9)	0
Nasal congestion	6 (26.1)	0
Skin and subcutaneous tissue disorders		
Pruritus	9 (39.1)	0
Rash	10 (43.5)	0

Serious adverse events were reported in 8 of 23 patients (34.8%). The reported serious adverse events were febrile neutropenia and GVHD in 2 patients (8.7%) each, and lymph node pain, thrombotic microangiopathy (TMA), bacteraemia, encephalitis, pneumonia mycoplasmal, skin infection, pancreatitis, small intestinal obstruction, postoperative pyrexia, liver function test abnormal, myelodysplastic syndrome, acute renal failure, and haemoptysis in 1 patient (4.3%) each. A causal relationship to nivolumab could not be ruled out for lymph node pain, pancreatitis, and myelodysplastic syndrome in 1 patient each.

Adverse events leading to discontinuation of nivolumab were reported in 2 of 23 patients (8.7%): pancreatitis and myelodysplastic syndrome in 1 patient (4.3%) each. A causal relationship to nivolumab could not be ruled out for both events.

7.2.3 Foreign phase II study (Study 205)

Adverse events were reported in 238 of 243 patients (97.8%). In total, 185 of 243 patients (76.1%) experienced adverse events for which a causal relationship to nivolumab could not be ruled out. The adverse events with an incidence of ≥20% are shown in Table 11.

Table 11. Adverse events with an incidence of ≥20%

System Organ Class Preferred Term (MedDRA/J ver.18.1)	n (%), N = 243	
	All Grades	Grade ≥3
All adverse events	238 (97.9)	84 (34.6)
Gastrointestinal disorders		
Diarrhoea	68 (28.0)	2 (0.8)
General disorders and administration site conditions		
Fatigue	75 (30.9)	4 (1.6)
Pyrexia	62 (25.5)	1 (0.4)
Respiratory, thoracic and mediastinal disorders		
Cough	56 (23.0)	0

Serious adverse events were reported in 60 of 243 patients (24.7%). Serious adverse events reported in ≥2 patients were pneumonia in 6 patients (2.5%); infusion related reaction and malignant neoplasm progression in 5 patients (2.1%) each; pyrexia, pleural effusion, and pneumonitis in 4 patients (1.6%) each; diarrhoea and dyspnoea in 3 patients (1.2%) each; and arrhythmia, pericardial effusion, meningitis, sepsis, parainfluenzae virus infection, respiratory tract infection, hypercalcaemia, seizure, and rash in 2 patients (0.8%) each. A causal relationship to nivolumab could not be ruled out for infusion related reaction in 5 patients, pneumonitis in 4 patients, pyrexia, pleural effusion, and diarrhoea in 2 patients each, and pneumonia, pericardial effusion, meningitis, sepsis, hypercalcaemia, seizure, and rash in 1 patient each.

In total, 15 of 243 patients (6.2%) experienced adverse events leading to drug discontinuation: AST increased in 3 patients (1.2%); pneumonia, ALT increased, and pneumonitis in 2 patients (0.8%) each; and pericardial effusion, colitis, pyrexia, autoimmune hepatitis, hepatitis, atypical pneumonia, EBV test positive, malignant neoplasm progression, syncope, autoimmune nephritis, and pleural effusion in 1 patient (0.4%) each. A causal relationship to nivolumab could not be ruled out for AST increased in 3 patients, ALT increased and pneumonitis in 2 patients each, and pneumonia, pericardial effusion, colitis, autoimmune hepatitis, hepatitis, syncope, autoimmune nephritis, and pleural effusion in 1 patient each.

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. The inspection and assessment revealed no noteworthy issues. PMDA thus 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. As a result, PMDA concluded that the clinical studies have generally been conducted in compliance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. During the inspection, however, PMDA identified the following matter that had to be corrected at a study site, and notified the head of the site of the matter, although it did not substantially affect the overall evaluation.

The matter to be corrected:
Study site
• Blood samples for genetic testing were collected from a patient who did not consent to the testing.

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

PMDA has concluded that the data submitted demonstrate a certain level of efficacy of nivolumab in the treatment of relapsed or refractory cHL and acceptable safety in view of the benefits indicated by the data submitted. Nivolumab is clinically meaningful because it offers a new therapeutic option for patients with relapsed or refractory cHL. PMDA considers that the indication and post-marketing issues should be further discussed.

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

Review Report (2)

October 14, 2016

Product Submitted for Approval

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	March 18, 2016

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

1.1 Efficacy

As a result of the review described in "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that a certain level of efficacy of nivolumab (genetical recombination) ("nivolumab") has been demonstrated in the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who are resistant or intolerant to brentuximab vedotin (genetical recombination) ("brentuximab"). This conclusion was drawn from the following findings: Patients with relapsed or refractory cHL who were resistant or intolerant to brentuximab were enrolled in a Japanese phase II study (Study ONO-4538-15 [Study 15]) and in Cohort B of a foreign phase II study (Study CA209205 [Study 205]). The response rates [95%CI] assessed centrally according to the Revised Response Criteria for Malignant Lymphoma (the primary endpoint) were 75.0% [47.6%, 92.7%] in Study 15 and 66.3% [54.8%, 76.4%] in Cohort B of Study 205; both values are significantly higher than 20%, the predefined threshold response rate.

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

1.2 Safety

As a result of the review described in "7.R.3 Safety" of the Review Report (1), PMDA concluded that the following adverse events should be closely monitored when nivolumab is administered to patients with relapsed or refractory cHL; these events were identified as requiring attention at the regulatory reviews for the previously approved indications (unresectable malignant melanoma, unresectable, advanced or recurrent non-small-cell lung cancer [NSCLC], and unresectable or metastatic renal cell carcinoma [RCC]): interstitial lung

disease (ILD), hepatic function disorder, abnormal thyroid function, infusion reaction, skin disorder, colitis and severe diarrhoea, myasthenia gravis and myositis, neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, encephalitis, type 1 diabetes mellitus, and cardiac disorder.

PMDA concluded that nivolumab is tolerable in patients with cHL as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, differential diagnosis and patient management in anticipation of an adverse reaction caused by excessive immune responses, drug interruption, or other appropriate actions.

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

1.3 Clinical positioning and indication

PMDA's conclusion:

As a result of the review described in "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA concluded that nivolumab is positioned as a new therapeutic option for the patient populations of Studies 15 and Cohort B of Study 205. The proposed indication "relapsed or refractory classical Hodgkin lymphoma" is thus appropriate, provided that the characteristics, such as the history of prior treatment, of the patients enrolled in Study 15 and Cohort B of Study 205 are described in the "Clinical Studies" section of the package insert and that the following statement is included in the "Precautions for Indications" section.

Precautions for Indications

- 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 nivolumab.

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

PMDA instructed the applicant to include the indication and the statement for "Precautions for Indications" in the package insert. The applicant agreed.

1.4 Dosage and administration

As a result of the review described in "7.R.5 Dosage and administration" of the Review Report (1), PMDA concluded that the proposed dosage and administration, "The usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks," is acceptable, along with the following precautionary advice in the "Precautions for Dosage and Administration" section of the package insert:

Precautions for dosage and administration

- Preparation method for the injection solution and the duration of infusion
  - Prior to treatment, the required volume of nivolumab should be withdrawn from a vial(s) to achieve a single dose of 3 mg/kg.

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

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

PMDA instructed the applicant to include the statements above in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections. The applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance covering all patients with relapsed or refractory cHL who receive nivolumab, to evaluate the safety of nivolumab in clinical practice. The observation period is 12-months, and the planned sample size is 200 patients. The key survey items are ILD, myasthenia gravis and myositis, colitis and severe diarrhoea, type 1 diabetes mellitus, hepatic function disorder, abnormal thyroid function, neurological disorder, renal disorder, adrenal disorder, encephalitis, severe skin disorder, venous thrombosis and embolism, infusion reaction, and cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles).

In view of the discussions presented in "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA concluded that the applicant should conduct post-marketing surveillance covering all patients receiving nivolumab in clinical practice to collect safety information in a timely and unbiased manner for a certain period of time after the market launch, and promptly provide the collected information to healthcare professionals. PMDA also reached the following conclusions:

- The key survey items and observation period for the post-marketing surveillance proposed by the applicant are acceptable.
- The planned sample size should be reconsidered, focusing on not only ILD but also the other key survey items.

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

PMDA instructed the applicant to reconsider the plan for the post-marketing surveillance based on the above review.

The applicant's response:

The planned sample size for the post-marketing surveillance is changed to 250, which would allow a comparison between the incidences of adverse events classified as the key survey items in the surveillance and those in Study 205.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for nivolumab should include the safety and efficacy specifications presented in Table 12, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 13.

Table 12. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Myasthenia gravis and myositis • Colitis and severe diarrhoea • Type 1 diabetes mellitus • Hepatic function disorder • 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	• Excessive immune response • Embryonic/fetal toxicity • Cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles)	• None
Efficacy specification (relating to the present partial change application)		
• Efficacy in the treatment of patients with relapsed or refractory cHL in clinical practice		

Table 13. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (unresectable or metastatic RCC) • Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Specified use-results survey in patients with unresectable, advanced or recurrent NSCLC (all-case surveillance) • Specified use-results survey in patients with unresectable or metastatic RCC (all-case surveillance) • Specified use-results survey in patients with relapsed or refractory cHL (all-case surveillance) • 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 15)	• Provision of data from early post-marketing phase vigilance (unresectable or metastatic RCC) • Preparation and provision of materials for healthcare professionals • Preparation and provision of materials for patients

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

Table 14. Outline of use-results survey (draft)

Objective	To evaluate the safety etc. of nivolumab in clinical practice after the market launch
Survey method	All-case surveillance using a central registration system
Population	Patients with relapsed or refractory cHL
Observation period	12 months
Planned sample size	250 patients
Main survey items	Key survey items: ILD, myasthenia gravis and myositis, colitis and severe diarrhoea, type 1 diabetes mellitus, hepatic function disorder, abnormal thyroid function, neurological disorder, renal disorder, adrenal disorder, encephalitis, severe skin disorder, venous thrombosis and embolism, infusion reaction, and cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles) Other main survey items: patient characteristics (e.g., performance status, timing of diagnosis, disease stage classification, prior treatments), exposure to nivolumab, concomitant drugs, laboratory data, antitumor effect, patient outcome, adverse events, and other relevant items

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the following indications and dosage and administration with the conditions of approval shown below, provided that the necessary precautionary statements are included in the package insert and information on the proper use of the product is properly disseminated after the market launch, and provided that the product is used under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions capable of emergency response. The product is designated as an orphan drug for the proposed indication “Hodgkin lymphoma”; therefore, the re-examination period is 10 years.

Indications (Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 after submission of the present application.)

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

Dosage and Administration (Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 after submission of the present application.)

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.

   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, and relapsed or refractory classical Hodgkin lymphoma

   The usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight, administered as

an intravenous infusion every 2 weeks.

Conditions of Approval

1. The applicant should formulate and properly implement a risk management plan.
2. Since the number of subjects enrolled in Japanese clinical studies was extremely limited, the applicant is required to conduct a use-results survey covering all patients treated with the product, until data from a certain number of patients are accumulated following commercial introduction, in order to understand the characteristics of patients treated with the product and compile the safety and efficacy data of the product in the early post-marketing period, thereby taking necessary measures to ensure the proper use of the product.

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 (Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 after submission of the present application.)

(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 or chemotherapy-naïve patients with <u>unresectable or metastatic renal cell carcinoma</u>.

(2) The efficacy and safety of Opdivo in adjuvant chemotherapy have not been established <u>in patients with unresectable malignant melanoma, patients with unresectable, advanced or recurrent non-small cell lung cancer, or patients with unresectable or metastatic renal cell carcinoma.</u>

(3) 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.

(4) <u>The efficacy and safety of Opdivo have not been established in patients with unresectable or metastatic renal cell carcinoma who have received cytokine therapy as the only prior treatment.</u>

Precautions for Dosage and Administration (Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 after submission of the present application.)

(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 or 2 mg/kg for the treatment of malignant melanoma and a single dose of 3 mg/kg for the treatment of non-small cell lung cancer, renal cell carcinoma, or classical Hodgkin lymphoma.

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.