Report on the Deliberation Results

August 17, 2016
Pharmaceutical Evaluation 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	December 11, 2015

Results of Deliberation

In its meeting held on August 5, 2016, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this results should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the product is the remainder of the ongoing re-examination period for the initial approval of nivolumab (until October 16, 2021).

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

July 22, 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	December 11, 2015
Dosage Form/Strength	Injection: Each via1 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	Priority review (PSEHB/ELD Notification No. 0204-2 dated February 4, 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 the efficacy of the product in the treatment of unresectable or metastatic renal cell carcinoma and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Post-marketing surveillance is required to further investigate 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).

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

(Single underline denotes new additions, and double-underline denotes additions made as of December 17, 2015 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, or unresectable or metastatic renal cell carcinoma

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 December 17, 2015 or February 29, 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)

June 14, 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	December 11, 2015
Dosage Form/Strength	Injection: Each via1 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 or metastatic renal cell carcinoma (Underline denotes additions.)

Proposed Dosage and Administration

1. Treatment of unresectable malignant melanoma

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

2. Treatment of unresectable or metastatic renal cell carcinoma

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

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMS	Bristol-Myers Squibb
C_{avgss}	Average serum concentration at steady state
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
Japanese clinical practice guideline	Renal Cancer Clinical Practice Guideline 2011 published by the Japanese Urological Association
KPS	Karnofsky Performance Status
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MSKCC risk criteria	Memorial Sloan-Kettering Cancer Center risk criteria
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Kidney Cancer
NCI-PDQ	National Cancer Institute Physician Data Query
NE	Not estimated
Nivolumab	Nivolumab (Genetical Recombination)
NSCLC	Non-small cell lung cancer
OS	Overall survival
Partial change application	Application for partial change approval
Pazopanib	Pazopanib Hydrochloride
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 Devices Agency
Post-study treatment	Treatment given after discontinuation of study treatment
PPK	Population pharmacokinetics
PS	Performance Status
QD	Quaque die (once daily)
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
Sorafenib	Sorafenib tosilate
Study 25	Study ONO-4538-03/CA209025
Sunitinib	Sunitinib malate
VC	Central volume of distribution

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

1.1 Summary of the product submitted for registration

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) (hereinafter referred to as "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 the PD-1 ligands, thereby enhancing the activation of cancer antigen-specific T cells and cytotoxic activities against cancer cells to inhibit tumor growth.

In Japan, nivolumab was approved for the indication of "unresectable malignant melanoma" in July 2014. The indication was expanded to include "unresectable, advanced or recurrent non-small cell lung cancer" in December 2015 after submission of the present application.

1.2 Development history, etc.

The clinical development of nivolumab for the treatment of renal cell carcinoma (RCC) began outside Japan in October 2012 with a phase III study in patients with unresectable or metastatic clear cell RCC who had received prior chemotherapy (Study 25), conducted by BMS. A marketing application for nivolumab was filed in September 2015 in the US and in October 2015 in the EU, both primarily based on the results of Study 25. In the US, the following indication was approved in November 2015: "Opdivo (Nivolumab) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy." In the EU, the following indication was approved in April 2016: "Opdivo (Nivolumab) is indicated for the treatment of patients with advanced renal cell carcinoma after prior therapy in adults."

As of April 2016, nivolumab has been approved for the indication of RCC in 37 countries.

In Japan, the applicant started a phase I study in patients with advanced solid tumors (Study ONO-4538-01) in February 2009. Subject enrollment in Study 25 began in January 2013.

The present partial change application was filed for the additional indication of RCC, based primarily on the results of Study 25.

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

The present application was filed for a new indication, and no data relating to the quality of nivolumab were submitted.

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

The present application was filed for a new indication, and 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

The present application was filed for a new indication, and 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

The present application was filed for a new indication, and 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

The present application was filed for a new indication, and no new data on biopharmaceutic studies and associated analytical methods were evaluated because such data had been evaluated at the initial application.

6.1 Clinical pharmacology studies

6.1.1 PPK analysis

PPK analyses were conducted with a nonlinear mixed effect model (Analytic software, NONMEM Version 7.3.0), based on the PK data of nivolumab (10,824 time points in 1484 patients) from Japanese clinical studies (Studies ONO-4538-01 and ONO-4538-02), foreign clinical studies (Studies CA209001, CA209003, CA209010, CA209063, CA209017, and CA209057), and a global study (Study 25). Nivolumab PK was described with a 2-compartment model.

The analysis was performed based on the data from 3 PPK analyses.[1] Candidate covariates for CL and central volume of distribution (VC) were cancer type (NSCLC, RCC, and others) and immunogenicity, and were investigated using a base model incorporating the effect of body weight, estimated glomerular filtration rate (eGFR), Eastern Cooperative Oncology Group Performance Status (ECOG PS), and serum albumin concentrations on CL, and the effect of body weight, sex, and NSCLC histological type on VC. Cancer type and immunogenicity were both selected as significant covariates for CL, but neither was selected as a significant covariate for VC.

The final model incorporated covariates of body weight, eGFR, ECOG PS, sex, serum albumin concentrations, NSCLC histological type, cancer type, and immunogenicity. The effects of these covariates on CL or VC of nivolumab were within the inter-individual variability (37.3% for CL and 30.6% for VC). The applicant explained that the effects of these covariates on nivolumab PK would be limited.

6.1.2 Relationship between nivolumab exposure and efficacy or safety

6.1.2.1 Relationship between nivolumab exposure and efficacy

Based on the results of a foreign phase II study in patients with unresectable or metastatic clear cell RCC (Study CA209010) and Study 25, the relationship between nivolumab exposure[2] (C_{avgss}) and prolonged overall survival (OS) was evaluated using a Cox proportional hazards model. No clear relationship was found between nivolumab exposure and prolonged OS.

6.1.2.2 Relationship between nivolumab exposure and safety

Based on the results of Study 25, a relationship between nivolumab exposure[3] (C_{avgss}) and time to the onset of adverse events leading to discontinuation or resulting in death was investigated using a Cox proportional hazards model. Increased nivolumab exposure (C_{avgss}) did not tend to correlate with reduced time to the onset of adverse events leading to discontinuation or resulting in death.

6.1.3 Effects of anti-nivolumab antibodies on the PK of nivolumab

In Study 25, 371 patients received 3 mg/kg of nivolumab intravenously every 2 weeks. The following are the findings on the expression of anti-nivolumab antibodies:

- Anti-nivolumab antibody-positive patients
  (a) In 1 patient (0.3%), anti-nivolumab antibodies were detected at ≥2 consecutive time points following treatment.

[1] (1) PPK analyses (software: NONMEM Version 7.2.0) were performed on PK data of nivolumab (6868 time points in 669 patients) obtained from Japanese clinical studies (Studies ONO-4538-01 and ONO-4538-02) and foreign clinical studies (Studies CA209001, CA209003, CA209010, and CA209063); (2) PPK analyses (software: NONMEM Version 7.2.0) were performed on PK data of nivolumab (7710 time points in 909 patients) obtained from the 6 studies in (1) and an foreign clinical study (Study CA209037); and (3) PPK analyses (software: NONMEM Version 7.1.2) were performed on PK data of nivolumab (9216 time points in 1314 patients) obtained from the 7 studies in (2) and 2 foreign clinical studies (Studies CA209017 and CA209057). In the PPK analyses (2) and (3), age, lactase dehydrogenase, liver function as assessed by National Cancer Institute Organ Dysfunction Working Group, race, and cancer type (malignant melanoma, NSCLC, and others) were not identified as influential factors for CL or VC.

[2] Estimated by the final model of PPK analyses [see Section 6.1.1]

[3] Estimated by the final model of PPK analyses [see Section 6.1.1]

(b) Other than the patient mentioned in (a), 7 patients (1.9%) were positive for anti-nivolumab antibody at the last measurement.

(c) Other than the patients mentioned in (a) and (b), 19 patients (5.1%) were positive for anti-nivolumab antibody.

- Anti-nivolumab neutralizing antibodies were not detected in any patients.

Further, the effects of anti-nivolumab antibodies on the PK of nivolumab were analyzed based on serum nivolumab concentrations in samples assayed for anti-nivolumab antibody in Study 25. The serum nivolumab concentrations in anti-nivolumab antibody-positive patients tended to be lower than those in anti-nivolumab antibody-negative patients, but the distributions of individual values were similar in both populations, showing no clear differences (Table 1).

Based on the above, the applicant explained that anti-nivolumab antibodies exhibited no clear effects on nivolumab PK.

Table 1 Serum nivolumab concentrations in repeated dose of 3 mg/kg nivolumab (μg/mL)

	n	Before second infusion	n	Before seventh infusion
Anti-nivolumab antibody (+) patients *	22	15.9 ± 7.51	4	42.4 ± 27.7
Anti-nivolumab antibody (-) patients	302	19.8 ± 6.47	268	58.9 ± 21.6

Mean ± SD

* Patients tested positive for an anti-nivolumab antibody before the second or seventh infusion of nivolumab

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA accepted the applicant's explanation on the PPK analyses, relationship between nivolumab exposure and efficacy or safety, and effects of anti-nivolumab antibodies on the PK of nivolumab.

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

The applicant submitted efficacy and safety evaluation data from 5 studies listed in Table 2 (a Japanese phase I study, a global phase III study, 2 foreign phase I studies, and a foreign phase II study). The results of the Japanese phase I study (Study ONO-4538-01) and the foreign phase I studies (Studies CA209001 and CA209003) were evaluated for the initial application, and thus are omitted from Table 2 and "7.1 Evaluation data" (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated on June 18, 2014").

Table 2 Clinical studies on efficacy and safety

Data classification	Area	Study	Phase	Population	Sample size	Summary of dosage regimen	Primary endpoints
Evaluation	Global	25	III	Patients with unresectable or metastatic clear cell RCC who had prior chemotherapy	821 (1) 410 (2) 411	(1) 3 mg/kg of nivolumab intravenously infused every 2 weeks (2) 10 mg of oral everolimus once daily	Efficacy Safety
	Foreign	CA209010	II	Patients with unresectable or metastatic clear cell RCC who had prior chemotherapy	168	0.3, 2 or 10 mg/kg of nivolumab intravenously infused every 3 weeks	Efficacy Safety

The results of both studies are summarized below. Major non-fatal adverse events in these studies are listed in "7.2 Adverse events observed in clinical studies."

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1-2, Study 25 [ongoing since October 2012] [data cut-off, June 18, 2015])

An open-label, randomized comparative study was conducted at 146 centers in 24 countries including Japan to investigate the efficacy and safety of nivolumab in patients with unresectable or metastatic clear cell RCC who received prior chemotherapy[4] (target sample size, 822).

In the nivolumab group, 3 mg/kg of nivolumab was administered intravenously every 2 weeks. In the everolimus group, 10 mg of everolimus was administered orally once daily. Treatment was continued until disease progression or until the withdrawal criteria were met.

The efficacy analysis set consisted of 821 patients who were enrolled and randomized (410 in the nivolumab group and 411 in the everolimus group). Of these, the safety analysis set consisted of 803 patients (406 in the nivolumab group and 397 in the everolimus group), excluding 18 patients who did not receive the study drug (4 in the nivolumab group and 14 in the everolimus group).

The primary endpoint of the study was OS. An interim analysis was planned to be conducted when a cumulative total of ≥398 adverse events (approximately 70% of the target number of events, 569) occurred, aiming at early termination of the study for efficacy. Type-I errors associated with the OS interim analysis were adjusted using the O'Brien-Fleming alpha spending function as per the Lan-DeMets method.

The interim efficacy analysis was performed when a cumulative total of 398 adverse events occurred (data cut-off, June 18, 2015). Table 3 and Figure 1 show the interim analysis results of OS and the Kaplan-Meier curve, respectively. At its meeting held on July 17, 2015, the independent data monitoring committee recommended early termination of the study.

[4] The study enrolled patients who had received prior chemotherapy consisting of 1 or 2 anti-angiogenic antineoplastic drugs (e.g., sunitinib, sorafenib, pazopanib, axitinib).

Table 3 Interim analysis results of OS (efficacy analysis set; data cut-off, June 18, 2015)

	Nivolumab	Everolimus
n	410	411
Deaths (%)	183 (44.6)	215 (52.3)
Median [95% CI] (months)	25.00 [21.75, NE]	19.55 [17.64, 23.06]
Hazard ratio [98.52% CI] [*1]	0.73 [0.57, 0.93]	
P value (2-sided) [*2]	0.0018	

[*1] Cox regression model stratified by region (US and Canada, Western Europe, and others), MSKCC risk criteria (favorable, intermediate, poor), and the number of prior treatment regimens (1, 2) consisting of anti-angiogenic antineoplastic drugs.
[*2] Log-rank test stratified by region (US and Canada, Western Europe, and others), MSKCC risk criteria (favorable, intermediate, poor), and the number of prior treatment regimens (1, 2) consisting of anti-angiogenic antineoplastic drugs, with a 2-sided significance level of 0.0148.

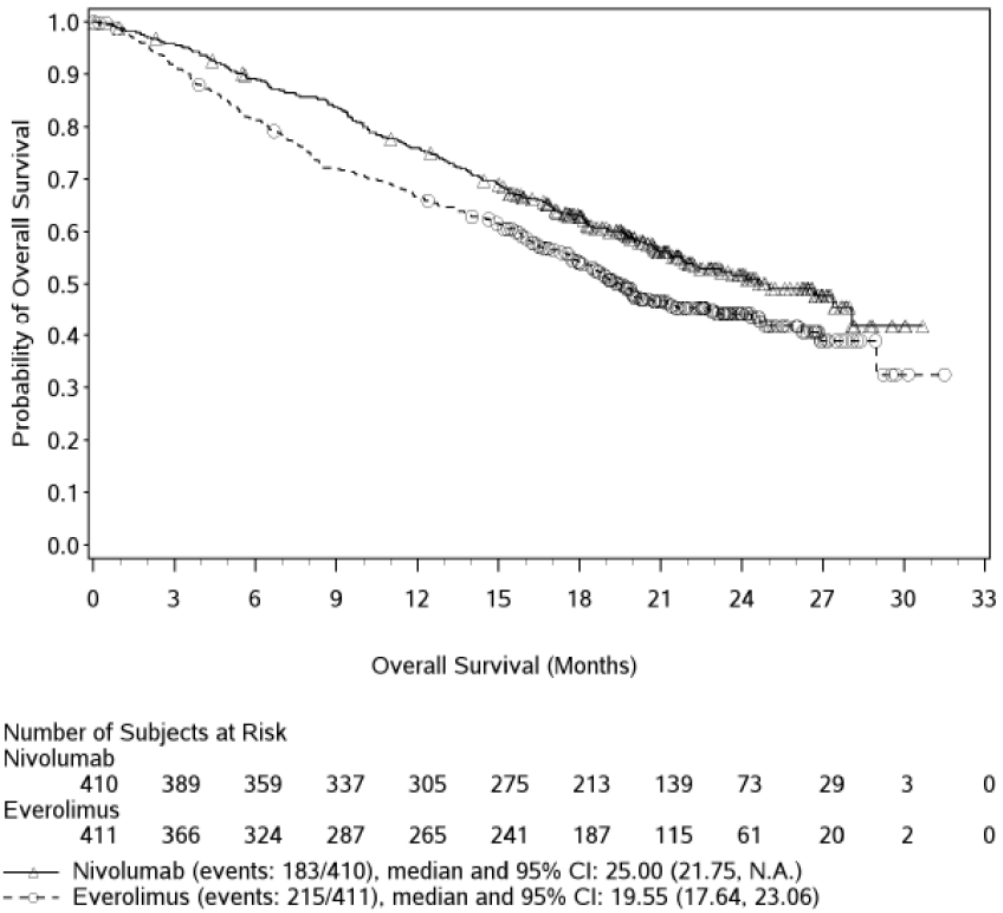

Figure 1 Kaplan-Meier curve for interim analysis of OS (efficacy analysis set; data cut-off, June 18, 2015)

The safety analysis revealed deaths of 19 of the 406 patients (4.7%) in the nivolumab group and 34 of the 397 patients (8.6%) in the everolimus group during the treatment period or within 30 days after the completion of treatment. Disease progression was the cause of death of 15 patients in the nivolumab group and 27 patients in the everolimus group. In the nivolumab group, other causes of death were ischaemic heart failure, myocardial infarction, pneumonia, and suicide (1 patient each). In the everolimus group, other causes of death were intestinal ischaemia, pneumonia, suicide, apoplectic fit, stroke, infection, and lower respiratory tract infection/pneumonia (1 patient each). A causal relationship of everolimus to intestinal ischaemia and pneumonia could not be ruled out.

7.1.2 Foreign clinical study

7.1.2.1. Foreign phase II study (CTD 5.3.5.1-1, Study CA209010 [ongoing since May 2011] [data cut-off, [redacted], 20[redacted]])

A double-blind, randomized, comparative study was conducted at 39 centers outside Japan to investigate the efficacy and safety of nivolumab in patients with unresectable or metastatic clear cell RCC who had received prior chemotherapy[5] (target sample size, 150).

Patients received 0.3, 2 or 10 mg/kg of nivolumab intravenously every 3 weeks until disease progression or meeting the withdrawal criteria.

The efficacy analysis set consisted of 168 patients who were enrolled and randomized (60 in the 0.3 mg/kg group, 54 in the 2 mg/kg group, and 54 in the 10 mg/kg group). Of these, 167 patients (59 in the 0.3 mg/kg group, 54 in the 2 mg/kg group, and 54 in the 10 mg/kg group) were included in the safety analysis set, excluding 1 patient (the 0.3 mg/kg group) who did not receive the study drug.

The primary endpoint of this study was progression free survival (PFS). A primary analysis was planned to be conducted when a cumulative total of approximately 116 adverse events occurred. Table 4 shows the results of the primary analysis of PFS, showing no significant differences among the 3 groups.

Table 4 Primary analysis of PFS (efficacy analysis set; data cut-off, May 15, 2013)

		0.3 mg/kg	2 mg/kg	10 mg/kg
n		60	54	54
Death or exacerbation (%)		48 (80.0)	43 (79.6)	45 (83.3)
Median [80% CI] (months)		2.69 [1.94, 3.02]	4.04 [2.76, 4.24]	4.17 [2.79, 5.49]
Hazard ratio [80% CI] [*1]	2 mg/kg vs. 0.3 mg/kg		0.98 [0.74, 1.29]	
	10 mg/kg vs. 0.3 mg/kg		0.98 [0.75, 1.29]	
	10 mg/kg vs. 2 mg/kg		1.01 [0.75, 1.34]	
P value (two-sided) [*2]			0.924	

[*1] Cox regression model stratified by MSKCC risk criteria (favorable, intermediate, poor) and the number of prior treatment regimens (1, ≥2).

[*2] Log-rank test stratified by MSKCC risk criteria (favorable, intermediate, poor) and the number of prior treatment regimens (1, ≥2), with a 2-sided significance level of 0.2.

The safety analysis revealed deaths of 5 of the 59 patients (8.5%) in the 0.3 mg/kg group, 3 of the 54 patients (5.6%) in the 2 mg/kg group, and 2 of the 54 patients (3.7%) in the 10 mg/kg group during the treatment with nivolumab or within 30 days after the completion of treatment. Disease progression was the cause of death of 5 patients in the 0.3 mg/kg group, 3 patients in the 2 mg/kg group, and 1 patient in the 10 mg/kg group. The other cause of death was multiple organ failure in 1 patient in the 10 mg/kg group. The causal relationship between the study drug and all deaths was ruled out.

[5] The study enrolled patients who had received prior chemotherapy consisting of 1 or 2 anti-angiogenic antineoplastic drugs (e.g., sunitinib, sorafenib, pazopanib, axitinib).

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

The global phase III study (Study 25) was conducted to assess the efficacy and safety of nivolumab in patients with unresectable or metastatic clear cell RCC who had received prior chemotherapy. PMDA considered Study 25 was the most important clinical study for evaluating the efficacy and safety of nivolumab in the evaluation data submitted. PMDA therefore decided to review the data focusing on Study 25. The efficacy of nivolumab in Japanese patients was investigated based on the consistency between the Japanese population and the entire study population of Study 25, in accordance with "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and "Basic principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012). The efficacy of nivolumab in Japanese patients was examined based on both the primary and secondary endpoints, in view of the number of Japanese patients enrolled.

7.R.2 Efficacy

PMDA concluded the efficacy of nivolumab was demonstrated in patients with unresectable or metastatic clear cell RCC who had received prior chemotherapy (see below for a detailed discussion).

7.R.2.1 Control group

The applicant's rationale for using everolimus as the control in Study 25:

When Study 25 began, NCCN guidelines (ver.1. 2012) and Japanese clinical guidelines recommended everolimus for patients with unresectable or metastatic clear cell RCC who had received prior chemotherapy.

PMDA accepted the applicant's explanation.

7.R.2.2 Endpoints and assessment results

PMDA's view:

Treatments for patients with unresectable or metastatic clear cell RCC who had received prior chemotherapy is aimed to prolong survival. Thus, OS was the appropriate primary endpoint of Study 25.

Study 25 demonstrated the superiority of nivolumab to everolimus in OS [see Section 7.1.1.1], showing the efficacy of nivolumab in patients included in Study 25.

7.R.2.3 Efficacy in Japanese patients

The applicant's explanation on the efficacy of nivolumab in Japanese patients:

Study 25 enrolled 63 Japanese patients (37 in the nivolumab group and 26 in the everolimus group). Table 5 summarizes the results of the OS interim analysis in the Japanese patients. Figure 2 shows the Kaplan-Meier curve.

Table 5 Interim analysis results of OS in Japanese patients (data cut-off, June 18, 2015)

	Nivolumab	Everolimus
n	37	26
Death (%)	11 (29.7)	5 (19.2)
Median [95% CI] (months)	27.37 [23.62, NE]	NE [NE, NE]
Hazard ratio [95% CI] [*1]	1.50 [0.49, 4.54]	
P value (two-sided) [*2]	0.4752	

[*1] Cox regression model stratified by MSKCC risk criteria (favorable, intermediate, poor) and the number of prior treatment regimens (1, 2) consisting of anti-angiogenic antineoplastic drugs.
[*2] Log-rank test stratified by MSKCC risk criteria (favorable, intermediate, poor) and the number of prior treatment regimens (1, 2) consisting of anti-angiogenic antineoplastic drugs.

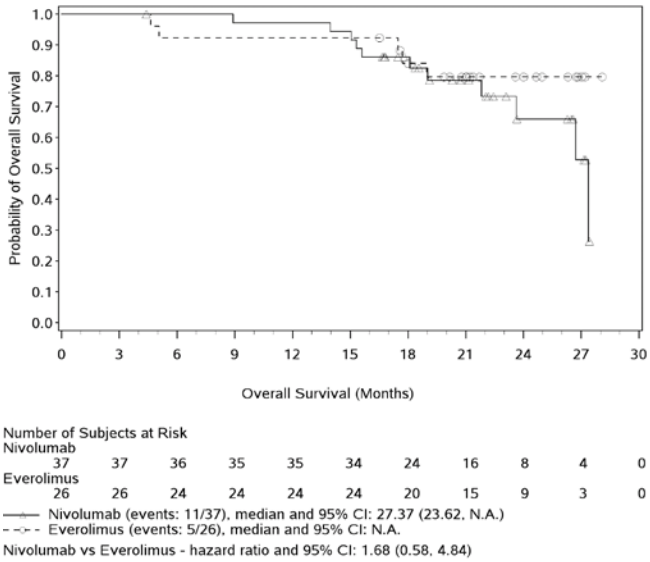

Figure 2 Kaplan-Meier curve for interim analysis of OS in Japanese patients (data cut-off, June 18, 2015)

Patients with unresectable or metastatic RCC responding to the treatment are expected to have improved QOL (*J Clin Oncol*. 2009;27:1280-9). Table 6 summarizes the secondary endpoint of Study 25, response rates [95% CI (%)] assessed by investigators based on RECIST v1.1.

Table 6 Best overall response and response rates (efficacy analysis set, RECIST v1.1, investigator-assessed)

Best overall responses	N (%)			
	Japanese		Entire study	
	Nivolumab n = 37	Everolimus n = 26	Nivolumab n = 410	Everolimus n = 411
Complete response (CR)	0	1 (3.8)	4 (1.0)	2 (0.5)
Partial response (PR)	16 (43.2)	1 (3.8)	99 (24.1)	20 (4.9)
Stable disease (SD)	15 (40.5)	20 (76.9)	141 (34.4)	227 (55.2)
Progressive disease (PD)	6 (16.2)	4 (15.4)	143 (34.9)	114 (27.7)
Not evaluable	0	0	23 (5.6)	48 (11.7)
Response (CR＋PR) rate [95% CI] (%)	43.2 [27.1, 60.5]	7.7 [0.9, 25.1]	25.1 [21.0, 29.6]	5.4 [3.4, 8.0]

PMDA asked the applicant to explain the reason for inconsistency between the entire study population and the Japanese population in the interim analysis results of OS, the primary endpoint of Study 25.

The applicant's response:

The applicant investigated possible effect of the differences in prognostic factors or post-study treatment on the OS analyses in the Japanese population.

In Study 25, biases in prognostic factors (Memorial Sloan-Kettering Cancer Center [MSKCC] risk criteria, Karnofsky Performance Status [KPS], number of metastasized organs) in the Japanese patients were investigated both in the nivolumab and everolimus groups. The investigation revealed a biased distribution of the prognostic factors between the 2 groups: the nivolumab group had a higher percentage of patients with factors probably related to poor prognoses than the everolimus group (Table 7).

Table 7 Summary of prognostic factors

Prognostic factors		N (%)			
		Entire study		Japanese	
		Nivolumab n = 410	Everolimus n = 411	Nivolumab n = 37	Everolimus n = 26
MSKCC risk criteria	poor risk	64 (15.6)	60 (14.6)	3 (8.1)	1 (3.8)
	favorable/intermediate risk	346 (84.4)	351 (85.4)	34 (91.9)	25 (96.2)
KPS	<90%	134 (32.7)	147 (35.8)	5 (13.5)	2 (7.7)
	≥90%	276 (67.3)	264 (64.2)	32 (86.5)	24 (92.3)
Liver metastasis	With	100 (24.4)	87 (21.2)	8 (21.6)	2 (7.7)
	Without	310 (75.6)	324 (78.8)	29 (78.4)	24 (92.3)
Number of metastasized organs	≥2	341 (83.2)	338 (82.2)	31 (83.8)	19 (73.1)
	<2	69 (16.8)	73 (17.8)	6 (16.2)	7 (26.9)
History of diabetes mellitus	With	59 (14.4)	63 (15.3)	7 (18.9)	4 (15.4)
	Without	351 (85.6)	348 (84.7)	30 (81.1)	22 (84.6)

The applicant investigated effect of the biases in the prognostic factors on the OS analyses in the Japanese population, using a Cox regression model stratified by the above-mentioned prognostic factors (Table 8). The hazard ratio of OS in the nivolumab group against the everolimus group tended to become closer to 1.0.

Table 8 Hazard ratio of OS with prognostic factors as stratification factors

Combinations of stratification factors	Hazard ratio [95% CI]
None	1.68 [0.58, 4.84]
(a), (b), and (c)	1.00 [0.30, 3.35]
(a), (b), and (d)	1.33 [0.40, 4.36]
(a), (b), and (e)	1.11 [0.35, 3.51]
(a), (b), and (f)	1.52 [0.45, 5.17]

(a) MSKCC risk criteria, (b) number of prior treatment regimens using anti-angiogenic antineoplastic drugs, (c) KPS, (d) liver metastasis, (e) number of metastasized organs, and (f) history of diabetes mellitus

The applicant investigated the effect of the differences in post-study treatment on the OS analyses in the Japanese population. Table 9 summarizes patients receiving post-study treatment. When the effect of post-study treatment was taken into account in the OS analyses in the Japanese patients using the inverse probability censoring weighting method, etc., the hazard ratio of the nivolumab group against the everolimus group was >1.0, the same result without the effect of post-study treatment taken into account.

Table 9 Summary of post-study treatments

Post-study treatment	N (%)			
	Entire study		Japanese	
	Nivolumab n = 410	Everolimus n = 411	Nivolumab n = 37	Everolimus n = 26
With	276 (67.3)	284 (69.1)	23 (62.2)	21 (80.8)
Without	134 (32.7)	127 (30.9)	14 (37.8)	5 (19.2)

These results, despite a small number of adverse events in the Japanese population that precluded adequate discussion, indicate that the inconsistency in the interim OS analysis results between the entire study population and the Japanese population may be attributable to the bias in prognostic factors in the Japanese population.

PMDA's view:

According to the applicant, the inconsistency between the entire population and the Japanese population in the OS analysis results in Study 25 may be attributable to the bias in prognostic factors, and this explanation is understandable to a certain degree. However, the efficacy of nivolumab in the Japanese population could not be determined based solely on the study results, because (a) the small number of events occurring in the Japanese patients precludes the evaluation of the effect of the biased distribution of the prognostic factors, and because (b) the estimation of therapeutic effect based on the multivariate analysis did not clearly demonstrate the efficacy of nivolumab in the Japanese population when the effect of prognostic factors was taken into account.

However, nivolumab is expected to be effective in Japanese patients as well, according to the explanation in "7.R.1 Data for review" and the findings presented below. The OS analysis data in the Japanese population of Study 25 are important in deciding the use of nivolumab in clinical settings, and therefore should be communicated appropriately to healthcare professionals through the package insert, etc.

- Response rates assessed by RECIST v1.1, the secondary endpoint of Study 25 (Table 6), were consistent between the entire study population and the Japanese population, indicating the efficacy of nivolumab in Japanese patients.
- No clear differences have been noted in the efficacy of nivolumab for the approved indications (unresectable malignant melanoma and unresectable, advanced or recurrent NSCLC) between Japanese and non-Japanese populations.
- There are no clear differences in the diagnostic and therapeutic systems for the treatment of RCC between Japan and other countries.
- Cancer is characterized by disease progression with the accumulation of genetic mutations. No clear differences have been reported in genes involved in the progression of RCC between Japanese and non-Japanese populations.

7.R.3 Safety

PMDA's view:

After the reviews in the following subsections, PMDA concluded that nivolumab should be used in patients with unresectable or metastatic RCC while paying special attention to the following adverse events (these events were identified as requiring attention at the regulatory reviews for the approved indications): interstitial lung disease, 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 on June 18, 2014," "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated on November 18, 2015," and "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated on January 22, 2016"). Patients with unresectable or metastatic RCC should be carefully monitored for these adverse events during treatment with nivolumab, as with patients receiving nivolumab for the approved indications.

The above-mentioned adverse events require careful attention in the use of nivolumab. Nevertheless, PMDA concluded that nivolumab will be tolerated by patients with RCC 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

The applicant's explanation on the safety profile of nivolumab based on the safety data obtained in Study 25.

Table 10 summarizes safety data from Study 25.

Table 10 Summary of the safety of nivolumab (Study 25)

	N (%)	
	Nivolumab n = 406	Everolimus n = 397
All adverse events	397 (97.8)	386 (97.2)
Grade ≥3 adverse events	230 (56.7)	251 (63.2)
Adverse events resulting in death	23 (5.7)	34 (8.6)
Serious adverse events	194 (47.8)	173 (43.6)
Adverse events leading to drug discontinuation	72 (17.7)	82 (20.7)
Adverse events leading to drug interruption or dose reductiom*	177 (43.6)	222 (55.9)

* The treatment was interruptedonly in the nivolumab group.

The following adverse events (any grade) occurred at an incidence ≥5% higher in the nivolumab group than in the everolimus group: back pain (nivolumab, 21.4% vs. everolimus, 15.6%), arthritis (19.7% vs. 14.4%), pruritus (18.5% vs. 12.6%), muscle pain (9.6% vs. 3.5%), and hypothyroidism (6.9% vs. 1.5%). Grade ≥3 adverse events occurring at an incidence ≥2% higher in the nivolumab group than in the everolimus group were hypercalcaemia (3.0% vs. 0.5%) and alanine aminotransferase (ALT) increased (3.0% vs. 0.3%). Serious adverse events occurring at an incidence ≥2% higher in the nivolumab group

than in the everolimus group was hypercalcaemia (2.5% vs. 0.5%). Adverse events leading to drug discontinuation occurring at an incidence ≥2% higher in the nivolumab group than in the everolimus group was malignant neoplasm progression (3.9% vs. 1.0%).

The applicant's explanation on the difference in the safety profile of nivolumab between the approved indications (unresectable malignant melanoma and unresectable, advanced or recurrent NSCLC) and unresectable or metastatic RCC:
Table 11 shows a comparison of adverse events in patients receiving nivolumab between Study 25 (unresectable or metastatic RCC) and foreign phase III Studies CA209066 and CA209037 (unresectable malignant melanoma) or foreign phase III Studies CA209017 and CA209057 (unresectable, advanced or recurrent NSCLC).

Table 11 Summary of the safety of nivolumab in patients with RCC, malignant melanoma, and NSCLC

	N (%)				
	25	CA209066 (chemotherapy-naïve malignant melanoma)	CA209037 (malignant melanoma with prior chemotherapy)	CA209017 (squamous cell NSCLC)	CA209057 (non-squamous cell NSCLC)
	n = 406	n = 206	n = 268	n = 131	n = 287
All adverse events	397 (97.8)	192 (93.2)	265 (98.9)	127 (96.9)	280 (97.6)
Grade ≥3 adverse events	230 (56.7)	76 (36.9)	142 (53.0)	67 (51.1)	155 (54.0)
Adverse events resulting in death	23 (5.7)	13 (6.3)	31 (11.6)	19 (14.5)	46 (16.0)
Serious adverse events	194 (47.8)	64 (31.1)	142 (53.0)	61 (46.6)	134 (46.7)
Adverse events leading to drug discontinuation	72 (17.7)	14 (6.8)	34 (12.7)	14 (10.7)	48 (16.7)
Adverse events leading to drug interruption	177 (43.6)	50 (24.3)	96 (35.8)	36 (27.5)	82 (28.6)

Adverse events occurring at an incidence ≥10% higher in Study 25 than in Study CA209066 were fatigue (Study 25, 48.0% vs. Study CA209066, 31.6%), cough (31.8% vs. 11.7%), dyspnoea (23.2% vs. 8.3%), anaemia (19.2% vs. 9.2%), and blood creatinine increased (13.8% vs. 2.4%). Grade ≥3 adverse events occurring at an incidence ≥3% higher in Study 25 than in Study CA209066 were anaemia (5.9% vs. 1.0%) and fatigue (4.4% vs. 1.0%). In contrast, the adverse event occurring at an incidence ≥10% higher in Study CA209066 than in Study 25 was vitiligo (Study 25, 0% vs. Study CA209066, 10.7%). The Grade ≥3 adverse event occurring at an incidence ≥3% higher in Study CA209066 than in Study 25 was gamma-glutamyltransferase increased (0.7% vs. 3.9%).

The adverse event occurring at an incidence ≥10% higher in Study 25 than in Study CA209037 was cough (Study 25, 31.8% vs. Study CA209037, 20.9%). None of the Grade ≥3 adverse events occurred at an incidence ≥3% higher in Study 25 than in Study CA209037. No adverse events occurred at an incidence ≥10% higher in Study CA209037 than in Study 25. The Grade ≥3 adverse event occurring at an incidence ≥3% higher in Study CA209037 than in Study 25 was malignant neoplasm progression (4.9% vs. 13.1%).

Adverse events occurring at an incidence ≥10% higher in Study 25 than in Study CA209017 were fatigue (Study 25, 48.0% vs. Study CA209017, 30.5%), nausea (28.3% vs. 15.3%), back pain (21.4% vs. 9.9%), and pruritus (18.5% vs. 7.6%). None of the Grade ≥3 adverse events occurred at an incidence ≥3% higher in Study 25 than in Study CA209017. The adverse event occurring at an incidence ≥10% higher

in Study CA209017 than in Study 25 was dyspnoea (23.2% vs. 36.6%). Grade ≥3 adverse events occurring at an incidence ≥3% higher in Study CA209017 than in Study 25 were malignant neoplasm progression (4.9% vs. 10.7%) and pneumonia (2.2% vs. 6.9%).

Adverse events occurring at an incidence ≥10% higher in Study 25 than in Study CA209057 were fatigue (Study 25, 48.0% vs. Study CA209057, 31.7%) and blood creatinine increased (13.8% vs. 3.8%). The Grade ≥3 adverse event occurring at an incidence ≥3% higher in Study 25 than in Study CA209057 was anaemia (5.9% vs. 1.7%). The adverse event occurring at an incidence ≥10% higher in Study CA209057 than in Study 25 was asthenia (8.9% vs. 20.6%). The Grade ≥3 adverse events occurring at an incidence ≥3% higher in Study CA209057 than in Study 25 was malignant neoplasm progression (4.9% vs. 8.7%).

PMDA's view:

In Study 25, the incidences of some adverse events were higher in the nivolumab group than in the everolimus group. Some also occurred more frequently in patients with RCC than in patients with malignant melanoma or NSCLC, approved indications. Most of these adverse events were, however, Grade ≤2 and known adverse events of nivolumab. PMDA concluded that nivolumab is tolerated by patients with RCC 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 adverse reactions caused by excessive immune responses, drug interruption, or other appropriate actions. However, special attention should be paid to the adverse events occurring more frequently following treatment with nivolumab than with everolimus. Data on the occurrence of these adverse events should be communicated appropriately to healthcare professionals using written materials.

7.R.3.2 Differences in safety between Japanese and non-Japanese patients

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

Table 12 summarizes the safety of the nivolumab in Japanese and non-Japanese patients included in Study 25.

Table 12 Summary of the safety of nivolumab (Study 25)

	N (%)	
	Japanese n = 37	Non-Japanese n = 369
Adverse events	36 (97.3)	361 (97.8)
Grade ≥3 adverse events	22 (59.5)	208 (56.4)
Adverse events resulting in death	1 (2.7)	22 (6.0)
Serious adverse events	13 (35.1)	181 (49.1)
Adverse events leading to drug discontinuation	5 (13.5)	67 (18.2)
Adverse events leading to drug interruption	18 (48.6)	159 (43.1)

The adverse event of any grades occurring in Japanese patients at an incidence ≥20% higher than in non-Japanese patients was nasopharyngitis (Japanese, 32.4% vs. non-Japanese, 6.8%). Grade ≥3 adverse events occurring in Japanese patients at an incidence ≥5% higher than in non-Japanese patients were

lymphocyte count decreased (8.1% vs. 0.5%), cancer pain (8.1% vs. 0.3%), amylase increased (5.4% vs. 0.3%), and lipase increased (5.4% vs. 0.3%). The serious adverse event occurring in Japanese patients at an incidence ≥5% higher than in non-Japanese patients was cancer pain (8.1% vs. 0.3%). None of the adverse events leading to drug discontinuation or resulting in death occurred in Japanese patients at an incidence ≥5% higher than in non-Japanese patients.

PMDA's view:
A limited number of Japanese patients having been treated with nivolumab precludes a precise comparison of the safety of nivolumab between Japanese and non-Japanese patients. However, the adverse events occurring more frequently in Japanese patients than in non-Japanese patients are known adverse events of nivolumab, and none of them led to death or the discontinuation of treatment. Nivolumab is therefore tolerable in Japanese patients. Nevertheless, using written materials, the applicant should appropriately inform healthcare professionals about the adverse events occurring more frequently in Japanese patients than in non-Japanese patients.

7.R.4 Clinical positioning and indication

The proposed indication of nivolumab was "treatment of unresectable or metastatic renal cell carcinoma."
In the proposed package insert, the "Precautions for Indications" section included the following advice:

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

As a result of its review (see "7.R.2 Efficacy" and "7.R.3 Safety" and subsections 7.R.4.1 to 7.R.4.3), PMDA concluded that the proposed indication of nivolumab, "treatment of unresectable or metastatic renal cell carcinoma," is appropriate, provided that the following precautionary advice is given in the "Precautions for Indications":

- The efficacy and safety of nivolumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of nivolumab have not been established in patients who have received cytokine therapy as the only prior treatment.
- The efficacy and safety of nivolumab 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 nivolumab.

7.R.4.1 Clinical positioning of Nivolumab

Nivolumab is mentioned as a treatment for unresectable or metastatic RCC in foreign clinical practice guidelines and a standard textbook of oncology (see below for detailed description). At present, Japanese clinical practice guidelines do not mention nivolumab.

Clinical practice guidelines

- NCCN guidelines (ver.2. 2016): Study 25 showed that nivolumab is a therapeutic option for patients with unresectable or metastatic clear cell RCC who received prior chemotherapy with axitinib, pazopanib, sorafenib, or sunitinib.
- US NCI-PDQ (updated on April 18, 2016): Nivolumab is a treatment option for unresectable or metastatic RCC previously treated with chemotherapy with axitinib, pazopanib, sorafenib or sunitinib.

Textbook

- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition* (Lippincott Williams & Wilkins, 2015, USA): In a phase I study, the response rate to nivolumab monotherapy was 30% in patients with unresectable or metastatic RCC. Phase II and III studies are currently underway.

The applicant's explanation on the clinical positioning of nivolumab:
Nivolumab was shown to be superior in efficacy to everolimus in Study 25 in patients with unresectable or metastatic clear cell RCC who had received prior chemotherapy. Nivolumab is a therapeutic option for this patient population.

Because no clinical study data are available regarding the efficacy of nivolumab in chemotherapy-naïve patients with RCC, the efficacy of nivolumab in this patient population is unclear at present. A global phase III study (Study ONO-4538-16/CA209214) is ongoing to compare the efficacy and safety of sunitinib monotherapy and combination therapy with nivolumab plus ipilimumab (genetical recombination) in chemotherapy-naïve patients with RCC, [redacted].

Besides everolimus, axitinib and sorafenib have been approved for use in patients with RCC who had received prior chemotherapy. PMDA asked the applicant to explain how to differentiate when to use nivolumab and when to use axitinib or sorafenib in clinical practice.

The applicant's response:
How to differentiate when to use nivolumab and when to use axitinib or sorafenib is unclear because of the lack of clinical study data on the efficacy and safety of nivolumab in comparison with axitinib or sorafenib. However, the appropriate drug will be selected based on the safety profile of each drug on a patient-by-patient basis, because the drugs have different safety profiles.

PMDA accepted the applicant's response.

7.R.4.2 Intended population of nivolumab

The applicant's explanation:

The present application proposes nivolumab therapy for patients with unresectable or metastatic clear cell RCC who received prior chemotherapy, because Study 25 demonstrated the clinical benefit of nivolumab in this population.

PMDA asked the applicant to explain the use of nivolumab in the following populations excluded from Study 25: (a) patients with RCC of histological types other than clear cell; and (b) patients with RCC who have received cytokine therapy as the only prior treatment.

The applicant's explanation:
For the reasons indicated below, the use of nivolumab will be accepted in (a) but not in (b) at present. Thus, the "Clinical Studies" section of the package insert should highlight that Study 25 enrolled patients with clear cell RCC but did not include patients who had received cytokine therapy as the only prior treatment. Additionally, the "Precautions for Indications" section should mention that eligible patients for nivolumab therapy should 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.

(a) There are no clinical study data on the efficacy or safety of nivolumab in patients with RCC of any histological types other than clear cell. Because Japanese clinical practice guidelines do not provide therapeutic options by histological type, therapies for clear cell RCC are used for the treatment of non-clear cell RCC as well. Nivolumab is therefore a therapeutic option even for patients with non-clear cell RCC.

(b) In Study CA209003, nivolumab was administered, at a dosage different from the proposed dosage and administration, to 9 patients with RCC who had received cytokine therapy as the only prior treatment (8 patients with interleukin-2 and 1 patient with interferon). Of these, 1 patient previously treated with interleukin-2 responded to nivolumab. However, Japanese and foreign clinical practice guidelines recommend axitinib or sorafenib therapy to patients previously treated cytokine therapy, and the drugs should be prioritized over nivolumab.

PMDA's view:
Because nivolumab is expected to be used by physicians who have sufficient knowledge and experience in cancer chemotherapy, the applicant's explanation is generally acceptable. The proposed indication of nivolumab (treatment of unresectable or metastatic renal cell carcinoma) is appropriate, provided that the population characteristics of Study 25 (i.e., patients with clear cell RCC) are mentioned in the "Clinical Studies" section of the package insert, and provided that the following precautionary advice is given in the "Precautions for Indications" section:

- The efficacy and safety of nivolumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of nivolumab have not been established in patients who have received cytokine therapy as the only prior treatment.
- 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.4.3 Efficacy and safety of nivolumab in adjuvant chemotherapy

The applicant explained that no clinical study data are currently available on the efficacy and safety of nivolumab in adjuvant chemotherapy, and that this point will be mentioned in the "Precautions for indications" section.

PMDA accepted the applicant's explanation.

7.R.5 Dosage and administration

The proposed dosage and administration of nivolumab was "the usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks." The proposed precautions for dosage and administration included the following:

- 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 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.

Based on the discussions below, PMDA concluded that the dosage and administration of nivolumab should be defined as proposed: "The usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks." PMDA concluded that the "Precautions for Dosage and Administration" section should give the following advice:

- 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 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 (including cytokines) have not been established.

7.R.5.1 Dosage and administration of nivolumab

The applicant's justification for the proposed dosage and administration of nivolumab for the treatment of unresectable or metastatic RCC:

Based on the results of foreign phase I studies (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated November 18, 2015"), the dosing regimen of nivolumab in Study 25 was defined as 3 mg/kg of nivolumab intravenously every 2 weeks. Because Study 25 demonstrated the clinical benefit of nivolumab in patients with unresectable or metastatic RCC who had received prior chemotherapy, the proposed dosage and administration of nivolumab were defined based on the dosing regimen of Study 25.

PMDA accepted the applicant's explanation.

7.R.5.2 Concomitant use with other anti-malignant tumor agents (including cytokines)

No clinical study data are available on the efficacy or safety of nivolumab coadministered with other anti-malignant tumor agents (including cytokines). The applicant explained that this fact will be highlighted in the "Precautions for Dosage and Administration" section.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation on post-marketing investigations:

To investigate the safety of nivolumab in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients with unresectable or metastatic RCC who receive nivolumab.

The safety profile of the nivolumab group in Study 25 was comparable to that for the approved indications. Therefore, the following events have been selected as the key survey items in the surveillance on unresectable or metastatic RCC, because they are key survey items in the post-marketing surveillance on unresectable malignant melanoma and unresectable advanced or recurrent NSCLC:

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).

The target sample size was determined as 500 based on the incidence of interstitial lung disease in Study 25. Interstitial lung disease, one of the key survey items, led to death of some patients in Study 25. In light of the incidences of the above-mentioned key survey items in the entire study population of Study 25, the sample size of 500 patients will allow the collection of data on not only interstitial lung disease but also other key survey items.

The observation period is 12 months. Most adverse events included in the key survey items occurred within 12 months after the start of treatment with nivolumab in Study 25. After 12 months after the start of treatment, there was no new onset of an adverse event with obvious increasing trend.

PMDA's view:

Safety data of nivolumab in Japanese patients with RCC are limited, and results of the post-marketing surveillance for the approved indications, unresectable malignant melanoma and unresectable advanced or recurrent NSCLC, are yet to be available. Therefore, the survey should be continued for a certain period following marketing approval, covering all patients with unresectable or metastatic RCC receiving nivolumab to gather safety data promptly and in an unbiased manner. Collected safety findings should be promptly communicated to healthcare professionals.

The proposed key survey items, target sample size, and observation period of the survey are acceptable.

7.2 Adverse events observed in clinical studies

Among the clinical study data submitted for safety evaluation, data on death are presented in "7.1 Evaluation data." The following subsections 7.2.1 and 7.2.2 summarize other major adverse events, but do not include the results of the Japanese phase I study (Study ONO-4538-01) and foreign phase I studies (Studies CA209001 and CA209003) because they were evaluated during the regulatory review for the initial approval (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated on June 18, 2014").

7.2.1 Global phase III study (Study 25)

Adverse events were observed in 397 of 406 patients (97.8%) in the nivolumab group and 386 of 397 patients (97.2%) in the everolimus group. A causal relationship between an adverse event and the study drug could not be ruled out in 319 of 406 patients (78.6%) in the nivolumab group and 349 of 397 patients (87.9%) in the everolimus group. Table 13 lists adverse events occurring at an incidence of ≥20% in either of the two groups.

Table 13 Adverse events occurring at an incidence of ≥20% in either group

System organ class Preferred term (MedDRA/J ver.18.0)	N (%)			
	Nivolumab n = 406		Everolimus n = 397	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	397 (97.8)	230 (56.7)	386 (97.2)	251 (63.2)
Blood and lymphatic system disorders				
Anaemia	78 (19.2)	24 (5.9)	139 (35.0)	52 (13.1)
Gastrointestinal disorders				
Nausea	115 (28.3)	2 (0.5)	114 (28.7)	5 (1.3)
Diarrhoea	96 (23.6)	5 (1.2)	124 (31.2)	6 (1.5)
Constipation	92 (22.7)	2 (0.5)	73 (18.4)	2 (0.5)
Stomatitis	20 (4.9)	0	126 (31.7)	18 (4.5)
General disorders and administration site conditions				
Fatigue	195 (48.0)	18 (4.4)	178 (44.8)	19 (4.8)
Oedema peripheral	58 (14.3)	2 (0.5)	102 (25.7)	4 (1.0)
Mucosal inflammation	15 (3.7)	0	82 (20.7)	14 (3.5)
Pyrexia	67 (16.5)	3 (0.7)	80 (20.2)	3 (0.8)
Metabolism and nutrition disorders				
Decreased appetite	93 (22.9)	5 (1.2)	121 (30.5)	6 (1.5)
Musculoskeletal and connective tissue disorders				
Back pain	87 (21.4)	14 (3.4)	62 (15.6)	11 (2.8)
Respiratory, thoracic, and mediastinal disorders				
Cough	129 (31.8)	0	141 (35.5)	2 (0.5)
Dyspnoea	94 (23.2)	11 (2.7)	106 (26.7)	8 (2.0)
Skin and subcutaneous tissue disorders				
Rash	64 (15.8)	3 (0.7)	92 (23.2)	3 (0.8)

Serious adverse events were observed in 194 of 406 patients (47.8%) in the nivolumab group and 173 of 397 patients (43.6%) in the everolimus group. The following serious adverse events were observed in ≥3 patients: In the nivolumab group, malignant neoplasm progression in 22 patients (5.4%), pleural effusion in 14 patients (3.4%), pneumonia in 11 patients (2.7%), hypercalcaemia in 10 patients (2.5%), pneumonitis, spinal cord compression, and acute renal failure in 8 patients each (2.0%), back pain and

anaemia in 7 patients each (1.7%), metastases to central nervous system, dyspnoea, diarrhoea, myocardial infarction in 6 patients each (1.5%), sepsis, constipation, and renal failure in 5 patients each (1.2%), cancer pain, metastatic renal cell carcinoma, haemoptysis, pulmonary embolism, abdominal pain, pain, pyrexia, and hyperglycaemia in 4 patients each (1.0%), basal cell carcinoma, urinary tract infection, bone pain, pain in extremity, pathological fracture, angina pectoris, heart failure, and adrenal insufficiency in 3 patients each (0.7%); in the everolimus group, malignant neoplasm progression in 24 patients (6.0%), pneumonia in 15 patients (3.8%), pleural effusion in 13 patients (3.3%), pneumonitis and anaemia in 12 patients each (3.0%), pulmonary embolism in 7 patients (1.8%), small intestinal obstruction, back pain, pyrexia, general physical health deterioration, hyperglycaemia, and acute renal failure in 5 patients each (1.3%), dyspnea in 4 patients (1.0%), interstitial lung disease, sepsis, urinary tract infection, abdominal pain, muscular weakness, dehydration, and cerebrovascular accident in 3 patients each (0.8%). In the nivolumab group, a causal relationship to the study drug could not be ruled out for pneumonitis (7 patients), diarrhoea (5 patients), pyrexia and anaemia (3 patients each), hyperglycaemia, acute renal failure, and adrenal insufficiency (2 patients each), pleural effusion, dyspnoea, haemoptysis, pneumonia, back pain, hypercalcaemia, and renal failure (1 patient each). In the everolimus group, a causal relationship to the study drug could not be ruled out for pneumonitis (12 patients), pneumonia and anaemia (5 patients each), interstitial lung disease and pyrexia (3 patients each), hyperglycaemia and acute renal failure (2 patients each), pleural effusion, dyspnoea, sepsis, urinary tract infection, and small intestinal obstruction (1 patient each).

Adverse events led to the discontinuation of the study drug in 72 of 406 patients (17.7%) in the nivolumab group and 82 of 397 patients (20.7%) in the everolimus group. The following adverse events led to drug discontinuation in ≥2 patients: in the nivolumab group, malignant neoplasm progression (16 patients, 3.9%), pneumonitis (6 patients, 1.5%), ALT increased (5 patients, 1.2%), spinal cord compression, aspartate aminotransferase (AST) increased, and colitis (3 patients each, 0.7%), diarrhoea, acute renal failure, and tubulointerstitial nephritis (2 patients each, 0.5%); in the everolimus group, pneumonitis (13 patients, 3.3%), pneumonia and fatigue (5 patients each, 1.3%), malignant neoplasm progression and cough (4 patients each, 1.0%), dyspnoea, cerebrovascular accident, nausea, vomiting, acute renal failure, asthenia, and hypertriglyceridaemia (3 patients each, 0.8%), pleural effusion, weight decreased, diarrhoea, stomatitis, rash, anaemia, mucosal inflammation, and pyrexia (2 patients each, 0.5%). In the nivolumab group, a causal relationship to the study drug could not be ruled out for pneumonitis (5 patients), ALT increased (4 patients), AST increased and colitis (3 patients each), diarrhoea, acute renal failure, and tubulointerstitial nephritis (2 patients each). In the everolimus group, a causal relationship to the study drug could not be ruled out for pneumonitis (12 patients), cough and fatigue (4 patients each), nausea, vomiting, pneumonia, and hypertriglyceridaemia (3 patients each), diarrhoea, stomatitis, rash, anaemia, asthenia, mucosal inflammation, and pyrexia (2 patients each), dyspnoea, weight decreased, and acute renal failure (1 patient each).

7.2.2 Foreign phase II clinical study (Study CA209010)

Adverse events were observed in 58 of 59 patients (98.3%) in the 0.3 mg/kg group, 54 of 54 (100%) patients in the 2 mg/kg group, 53 of 54 patients (98.1%) in the 10 mg/kg group. A causal relationship between an adverse event and the study drug could not be ruled out in 45 of 59 patients (76.3%) in the 0.3 mg/kg group, 36 of 54 patients (66.7%) in the 2 mg/kg group, and 41 of 54 patients (75.9%) in the 10 mg/kg group. Table 14 lists adverse events occurring at an incidence of ≥20% in any group.

Table 14 Adverse events occurring at an incidence of ≥20% in any group

System organ class Preferred term (MedDRA/J ver.17.1)	N (%)					
	0.3 mg/kg n = 59		2 mg/kg n = 54		10 mg/kg n = 54	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	58 (98.3)	31 (52.5)	54 (100)	38 (70.4)	53 (98.1)	29 (53.7)
Gastrointestinal disorders						
Nausea	16 (27.1)	2 (3.4)	16 (29.6)	2 (3.7)	13 (24.1)	0
Constipation	13 (22.0)	1 (1.7)	19 (35.2)	0	10 (18.5)	0
Vomiting	11 (18.6)	0	8 (14.8)	0	11 (20.4)	0
Diarrhoea	8 (13.6)	0	10 (18.5)	0	16 (29.6)	1 (1.9)
General disorders and administration site conditions						
Fatigue	24 (40.7)	4 (6.8)	24 (44.4)	3 (5.6)	28 (51.9)	2 (3.7)
Oedema peripheral	13 (22.0)	0	12 (22.2)	2 (3.7)	10 (18.5)	1 (1.9)
Infections and infestations						
Upper respiratory tract infection	7 (11.9)	0	11 (20.4)	0	8 (14.8)	0
Metabolism and nutrition disorders						
Decreased appetite	6 (10.2)	0	15 (27.8)	0	11 (20.4)	0
Musculoskeletal and connective tissue disorders						
Back pain	10 (16.9)	1 (1.7)	16 (29.6)	2 (3.7)	17 (31.5)	0
Arthritis	8 (13.6)	0	16 (29.6)	1 (1.9)	15 (27.8)	1 (1.9)
Pain in extremity	5 (8.5)	0	15 (27.8)	1 (1.9)	5 (9.3)	0
Respiratory, thoracic and mediastinal disorders						
Cough	19 (32.2)	1 (1.7)	20 (37.0)	0	11 (20.4)	0
Dyspnoea	16 (27.1)	5 (8.5)	11 (20.4)	3 (5.6)	13 (24.1)	3 (5.6)
Skin and subcutaneous tissue disorders						
Rash	8 (13.6)	0	6 (11.1)	0	12 (22.2)	0

Serious adverse events occurred in 28 of 59 patients (47.5%) in the 0.3 mg/kg group, 35 of 54 patients (64.8%) in the 2 mg/kg group, and 22 of 54 patients (40.7%) in the 10 mg/kg group. The following serious adverse events were observed in ≥2 patients in any group: in the 0.3 mg/kg group, malignant neoplasm progression, hypercalcaemia, and anaemia (3 patients each, 5.1%), pulmonary embolism, RCC, spinal cord compression, convulsion, nausea, constipation, pain, and acute renal failure (2 patients each, 3.4%); in the 2 mg/kg group, spinal cord compression (4 patients, 7.4%), malignant neoplasm progression (3 patients, 5.6%), haemoptysis, pleural effusion, paraesthesia, pancreatitis, oedema peripheral, pneumonia, dehydration, hyperglycaemia, anaemia, acute renal failure, and hypotension (2 patients each, 3.7%); in the 10 mg/kg group, pulmonary embolism and dyspnoea (3 patients each, 5.6%), malignant neoplasm progression, metastases to central nervous system, abdominal pain, and pneumonia (2 patients each, 3.7%). A causal relationship to the study drug could not be ruled out for pancreatitis, hyperglycaemia, and anaemia (1 patient each) in the 2 mg/kg group and dyspnoea (1 patient) in the 10 mg/kg group.

Adverse events led to the discontinuation of the study drug in 4 of 59 patients (6.8%) in the 0.3 mg/kg group, 12 of 54 patients (22.2%) in the 2 mg/kg group, and 8 of 54 patients (14.8%) in the 10 mg/kg group. The following adverse events led to the discontinuation of study drug: in the 0.3 mg/kg group, pericarditis, arthritis, central nervous system lesion, dyspnoea, and pleural effusion (1 patient each, 1.7%); in the 2 mg/kg group, pneumonitis (2 patients, 3.7%), enteritis, nausea, pancreatitis, small intestine ulcer, adrenal insufficiency, hypothyroidism, adverse event, fatigue, paraesthesia, spinal cord compression, cough, wheezing, AST increased, back pain, and rash (1 patient each, 1.9%); in the 10 mg/kg group, dyspnoea, pleural effusion, pneumonitis, pulmonary embolism, balance disorder, intracranial haemorrhage, neuropathy peripheral, multiple organ failure, temperature intolerance, ALT increased, AST increased, and blood alkaline phosphatase (ALP) increased (1 patient each, 1.9%). Of these, a causal relationship to the study drug could not be ruled out for the following events: in the 0.3 mg/kg group, pericarditis and arthritis (1 patient each); in the 2 mg/kg group, pneumonitis (2 patients), enteritis, pancreatitis, adrenal insufficiency, hypothyroidism, cough, wheezing, AST increased, and rash (1 patient each); in the 10 mg/kg group, pleural effusion, pneumonitis, balance disorder, neuropathy peripheral, temperature intolerance, blood ALP increased, AST increased, and ALT increased (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 inspection and assessment are ongoing. The results and PMDA's conclusion are reported in Review Report (2).

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

The inspection is ongoing. The results and PMDA's conclusion are reported in Review Report (2).

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

PMDA has concluded that the data submitted demonstrate the efficacy of nivolumab in the treatment of unresectable or metastatic renal cell carcinoma and acceptable safety in view of the benefits indicated by the data submitted. Nivolumab is clinically meaningful as a therapeutic option for unresectable or metastatic RCC. The efficacy of nivolumab and post-marketing investigation items 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)

July 21, 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	December 11, 2015

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

PMDA's conclusion:

The global phase III study (Study ONO-4538-03/CA209025, i.e., Study 25) was conducted to investigate the efficacy and safety of nivolumab (genetical recombination) ("nivolumab" hereinafter) in patients with unresectable or metastatic clear cell renal cell carcinoma (RCC) who received prior chemotherapy.[6] PMDA has concluded that nivolumab was shown to be effective for patients with unresectable or metastatic clear cell RCC, because in Study 25 overall survival (the primary endpoint) was significantly longer in the nivolumab group than in the everolimus group (control) [see Section 7.R.2 in Review Report (1)]. PMDA accepted, though not completely, the applicant's explanation that nivolumab is expected to be effective in Japanese patients with unresectable or metastatic clear cell RCC.

This conclusion was supported by the expert advisors at the Expert Discussion.

1.2 Safety

PMDA's conclusion:

Based on the discussions in "7.R.3. Safety" in Review Report (1), PMDA concluded that the following adverse events require attention during the treatment with nivolumab for unresectable or metastatic RCC; these events were identified as requiring attention at the regulatory reviews for the approved

[6] The study enrolled patients who had received prior chemotherapy consisting of 1 or 2 anti-angiogenic antineoplastic drugs (e.g., sunitinib malate, sorafenib tosilate, pazopanib hydrochloride, axitinib).

indications (unresectable malignant melanoma; unresectable, advanced or recurrent non-small-cell lung cancer [NSCLC]):

Interstitial lung disease, 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

There are no other adverse events requiring attention during nivolumab therapy.

Nivolumab is tolerated by patients with RCC 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 adverse reactions caused by excessive immune responses, drug interruption, and other appropriate actions.

This conclusion was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

PMDA's conclusion:

Based on the discussions in "7.R.4 Clinical positioning and indication" in Review Report (1), PMDA concluded that the proposed indication for nivolumab (treatment of unresectable or metastatic renal cell carcinoma), is appropriate. However, the fact that the subjects of Study 25 were patients with clear cell RCC should be highlighted in the "Clinical Studies" section of the package insert along with the following advice in the "Precautions for Indications" section:

Precautions for indications

- The efficacy and safety of nivolumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of nivolumab have not been established in patients who have received cytokine therapy as the only prior treatment.
- The efficacy and safety of nivolumab 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 nivolumab.

This conclusion was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to amend the "Precautions for Indications" section as per above. The applicant agreed to follow the instruction.

1.4 Dosage and administration

PMDA's conclusion:

Based on the discussions in "7.R.5 Dosage and administration" in Review Report (1), PMDA concluded that the dosage and administration of nivolumab should be defined as "The usual adult dosage of

nivolumab (genetical recombination) is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks," along with the following precautionary advice in the "Precautions for Dosage and Administration" section:

Precautions for dosage and administration

- 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 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 (including cytokines) have not been established.

This conclusion was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to amend the "Precautions for Dosage and Administration" section as per above. The applicant agreed to follow the instruction.

1.5 Risk management plan (draft)

The applicant plans to conduct, all-case, post-marketing surveillance (the survey) to investigate the safety of nivolumab in post-marketing clinical use in patients with unresectable or metastatic RCC who receive nivolumab. The target sample size is 500 patients. The observation period is 12 months. The key survey items are 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).

PMDA's conclusion:

Based on the discussions in "7.R.6 Post-marketing investigations" in Review Report (1), PMDA concluded that, for a certain period following marketing approval, a survey of all patients with unresectable or metastatic RCC receiving nivolumab should be conducted to gather unbiased safety data promptly and provide available safety findings to healthcare professionals. PMDA concluded that the proposed key survey items, target sample size, and observation period of the survey are acceptable.

This conclusion was supported by the expert advisors at the Expert Discussion.

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 15, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 16.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
• 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 (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 patietns with unresectable or metastatic RCC in clinical practice		

Table 16 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, advanced or recurrent NSCLC) • 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) • 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 25 [Study ONO-4538-03/CA209025])	• Provision of data from the early post-marketing phase vigilance (unresectable, advanced or recurrent NSCLC) • Provision of data from the 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 17 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 unresectable or metastatic RCC
Observation period	12 months
Planned sample size	500 patients
Main survey items	Key survey items: 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). 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. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

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

The new drug application data were subjected to a document-based inspection and 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/assessment revealed that the sponsor's electronic data processing system was operated in a way that did not allow investigators to confirm some changes or modifications made to the data in case report forms. Despite this problem requiring improvement, the final case report data were inspected and confirmed by the investigators. PMDA concluded that there were no obstacles to conducting its regulatory review of the application documents submitted.

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

The new drug application data (CTD5.3.5.1-2.1) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The clinical studies were generally performed in accordance with GCP. As a result, PMDA concluded that there were no obstacles to conducting its regulatory review of the application documents submitted. However, the inspection revealed a problem that should be corrected in a study site, despite its minor impact on the overall assessment of the studies. The head of the site was notified of the problem (see below for details).

Problem that should be corrected

A study site

- Study drug management failure (a wrong dose of the study drug was administered to some patients)

3. Overall Evaluation

Based on the above review, PMDA has concluded that the product may be approved for indications and dosage and administration with the conditions of approval shown below, provided that 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 re-examination period for the product is the remainder of the ongoing re-examination period for the initial approval of nivolumab (October 16, 2021).

Indications (Single underline denotes new additions, and double-underline denotes additions made as of December 17, 2015 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

Dosage and Administration (Single underline denotes new additions, and double underline denotes additions made as of December 17, 2015 or February 29, 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 or unresectable or metastatic renal cell carcinoma

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.

Contraindications (No change)

Patients with a history of hypersensitivity to the ingredients of Opdivo

Precautions for Indications (Single underline denotes new additions. Double-underline denotes additions made as of December 17, 2015 or February 29, 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 unresectable or metastatic renal cell carcinoma.

(2) The efficacy and safety of Opdivo in adjuvant chemotherapy have not been established.

(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) 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.

Precautions for Dosage and Administration (Single underline denotes new additions. Double-underline denotes additions made as of December 17, 2015 or February 29, 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 and renal cell carcinoma.

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.