Review Report

February 22, 2017
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	July 27, 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	Priority review (PSEHB/ELD Notification No. 1006-2 dated October 6, 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 recurrent or distant metastatic head and neck cancer 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/myocarditis/myositis/rhabdomyolysis, colitis/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, immune thrombocytopenic purpura, and cardiac disorders (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
5. Treatment of recurrent or distant metastatic head and neck cancer

(Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 or December 2, 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, relapsed or refractory classical Hodgkin lymphoma, and recurrent or distant metastatic head and neck cancer

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

(Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 or December 2, 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)

January 17, 2017

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	July 27, 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 recurrent or distant metastatic head and neck cancer</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 recurrent or distant metastatic head and neck cancer</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

cHL	classical Hodgkin lymphoma
cetuximab	cetuximab (genetical recombination)
CI	confidence interval
DOC	docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
IC	investigator's choice
ILD	interstitial lung disease
Japanese clinical practice guidelines	Japanese Clinical Practice Guideline for Head and Neck Cancer 2013 by the Japan Society for Head and Neck Cancer
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MTX	methotrexate
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Head and Neck Cancer
NCI-PDQ	National Cancer Institute Physician Data Query
NE	not estimated
NSCLC	non-small cell lung cancer
OS	overall survival
Partial change application	application for partial change approval
PD-1	programmed cell death-1
PD-L	programmed cell death-ligand
PD-L1 negative	The percentage of cells expressing PD-L1 in the tumor tissue is below a cutoff value (<1%, <5%, or <10%)
PD-L1 positive	The percentage of cells expressing PD-L1 in the tumor tissue is at or above a cutoff value (≥1%, ≥5%, or ≥10%)
PFS	progression free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
Study 017	Study CA209017
Study 025	Study ONO-4538-03/CA209025
Study 037	Study CA209037

Study 057	Study CA209057
Study 066	Study CA209066
Study 15	Study ONO-4538-15
Study 141	Study ONO-4538-11/CA209141
Study 205	Study CA209205
VC	central volume of distribution

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. After submission of the present application, the indications were expanded to include "unresectable or metastatic renal cell carcinoma" in August 2016 and "relapsed or refractory classical Hodgkin lymphoma" in December 2016.

1.2 Development history, etc.

As the clinical development program of nivolumab for the treatment of head and neck cancer, the applicant and BMS initiated a phase III study in patients with recurrent or distant metastatic primary squamous cell carcinomas of the head and neck (oral cavity, oropharynx/hypopharynx, and larynx) that had progressed or recurred within 6 months after platinum-based chemotherapy (Study 141) in May 2014.

In the US and EU, regulatory applications of nivolumab, including the pivotal data from Study 141, were filed in May and June 2016, respectively. In the US, nivolumab was granted approval in November 2016 for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy. In the EU, the application is currently under review.

As of December 2016, nivolumab has been approved only in the US for the indication of head and neck carcinoma.

In Japan, patient enrollment in Study 141 started in [redacted], 20[redacted].

The present partial change application for nivolumab has been filed for the additional indication of head and neck cancer, based on the results of pivotal Study 141.

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 Population pharmacokinetics (PPK) analysis

PPK analysis was performed using a nonlinear mixed effect model based on the PK data (6227 sampling time points in 1035 subjects) collected from foreign clinical studies (Studies CA209001, CA209003, CA209063, 017, and 057) and a global study (Study 141) (NONMEM version 7.3.0). The PK of nivolumab was described by a 2-compartment model.

Based on the results of 2 PPK analyses,[1)] the base model included (a) the effects of body weight, estimated glomerular filtration rate (eGFR), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) on clearance (CL); and (b) the effects of body weight and sex on the central volume of distribution (CV). Using the base model, a full model was developed by incorporating cancer type (head and neck cancer, non-small cell lung cancer [NSCLC], and other cancer types) as covariates for CL.

The applicant's explanation:

[1)] (a) PPK analysis based on PK data (6868 sampling time points in 669 subjects) collected from 2 Japanese clinical studies (Studies ONO-4538-01 and ONO-4538-02) and 4 foreign clinical studies (Studies CA209001, CA209003, CA209010, and CA209063) (NONMEM version 7.2.0)
(b) PPK analysis based on PK data (7710 sampling time points in 909 subjects) collected from the 6 studies used in the PPK analysis mentioned in (a) and a foreign clinical study (Study 037) (NONMEM version 7.2.0). In this PPK analysis, the following were not selected as significant covariates for CL: age, sex, cancer type (malignant melanoma, NSCLC, or other cancer types), lactate dehydrogenase, ethnicity, or liver functions according to the National Cancer Institute Organ Dysfunction Working Group criteria.

In the full model, the effects of these covariates on CL or VC were within the inter-individual variations (40.4% for CL and 23.9% for VC), suggesting that the effects of these covariates on the PK of nivolumab are limited.

6.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the applicant's explanation of PPK analysis for nivolumab is acceptable.

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 a global phase III study (Table 1).

Table 1. Summary of a clinical study on the efficacy and safety of nivolumab

Data type	Region	Study identifier	Phase	Subjects	N	Dosage regimen	Main endpoints
Evaluation data	Global	141	III	Patients with recurrent or distant metastatic head and neck cancer	361 (a) 240 (b) 121	(a) Intravenous nivolumab 3 mg/kg every 2 weeks (b) Investigator's choice of therapy • Intravenous cetuximab 400 mg/m^2 (Week 1) followed by 250 mg/m^2 (from Week 2 onward) once weekly • Intravenous MTX 40 mg/m^2 once weekly, or • Intravenous DOC 30 mg/m^2 once weekly	Efficacy Safety

A summary of the global phase III study is presented below. Major adverse events other than death reported in the clinical study are detailed in "7.2 Adverse events reported in a clinical study."

7.1 Evaluation data

7.1.1 Global clinical study

7.1.1.1 Global phase III study (CTD 5.3.5.1-1, Study 141, ongoing since May 29, 2014 [data cutoff, December 18, 2015])

An open-label, randomized, comparative study was conducted at 55 sites in 15 countries, including Japan, to evaluate the efficacy and safety of nivolumab and the investigator's choice of therapy (IC) in patients with recurrent or distant metastatic primary squamous cell carcinoma of the head and neck (oral cavity, oropharynx/hypopharynx, and larynx) that had progressed or recurred within 6 months after platinum-based chemotherapy[2)] (target sample size, 360 subjects).

Nivolumab was intravenously administered at 3 mg/kg every 2 weeks in the nivolumab group. Monotherapy with cetuximab, docetaxel hydrate (DOC), or methotrexate (MTX) was administered in the IC group. The treatment was continued until disease progression was observed or a withdrawal criterion was met.

All 361 patients enrolled and randomized in the study (240 in the nivolumab group and 121 in the IC group) were included in the efficacy analysis population. Of the 361 patients, 14 did not receive the study drug. The

2) Including curative-intent or adjuvant chemoradiotherapy

remaining 347 patients (236 in the nivolumab group and 111 in the IC group) were included in the safety analysis population.

In the original study protocol, overall survival (OS) and progression free survival (PFS) were the primary endpoints. [redacted]. Because the prolongation of PFS was expected to be smaller than had initially been assumed, the protocol was amended to use OS only as the single primary endpoint and to change the significance level of OS to 0.05, two-sided (Protocol version 2 [dated January 30, 2015]). In addition to the change in the primary endpoint, a new hypothesis concerning OS was formulated and the sample size required for the final analysis was increased from 180 to 360 based on [redacted].

An interim OS analysis was planned to be conducted at the earlier of the following: (1) when at least 195 events (approximately 70% of 278 events, the target number of events) have occurred; (2) at 6 months after the completion of enrollment of all subjects. The purpose of the interim analysis was to allow early termination due to good response. A Lan-DeMets α spending function of the O'Brien-Fleming type was used from the start of study, to adjust the probability of a type I error associated with the interim OS analysis.

The interim analysis of efficacy was performed (data cutoff, December 18, 2015). The results of the interim OS analysis (Table 2) and Kaplan-Meier curves (Figure 1) are shown below. Based on these results, the independent data-monitoring committee recommended the early termination of the study at the meeting held on [redacted], [redacted] 20[redacted].

Table 2. Interim OS analysis (efficacy analysis population [data cutoff, December 18, 2015])

	Nivolumab	IC
N	240	121
Number of events (%)	133 (55.4)	85 (70.2)
Median [95% CI] (months)	7.49 [5.49, 9.10]	5.06 [4.04, 6.05]
Hazard ratio [97.73% CI][*1]	0.70 [0.51, 0.96]	
P-value (2-sided)[*2]	0.0101	

*1, Cox proportional hazards model stratified by prior cetuximab therapy (yes/no)
*2, Log-rank test stratified by prior cetuximab therapy (yes/no), with a 2-sided significance level of 0.0227

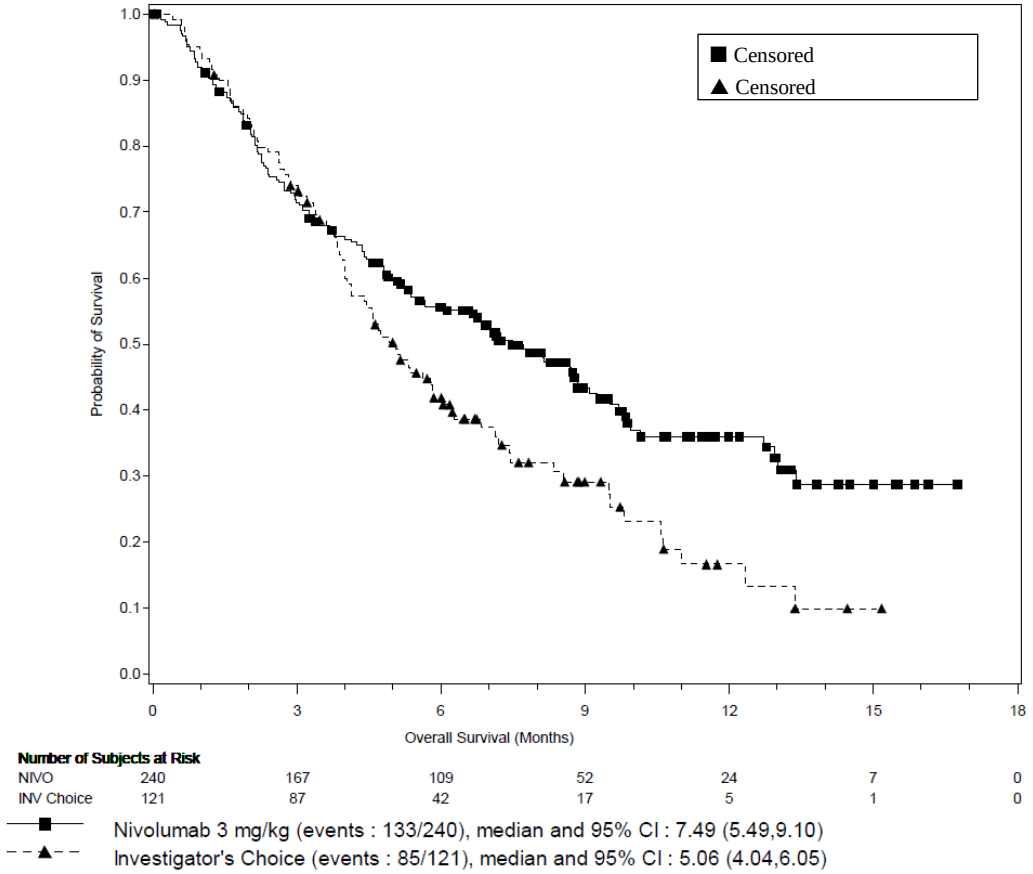

Figure 1. Kaplan-Meier curves for interim OS analysis (efficacy analysis population [data cutoff, December 18, 2015])

Safety analysis revealed that 50 of 236 patients (21.2%) died in the nivolumab group and 21 of 111 patients (18.9%) in the IC group during the treatment period or within 30 days after the last dose. The causes of death in the nivolumab group were disease progression in 31 patients, and disease progression/ischaemic stroke, disease progression/cancer pain, disease progression/bone pain, disease progression/cardiac failure, disease progression/dysphagia, disease progression/speech disorder, disease progression/pneumonia, shock haemorrhagic, pneumonia, acute respiratory failure, hydrocephalus, tumour haemorrhage, ulcer haemorrhage, superior vena cava syndrome, cerebrovascular accident, hypercalcaemia, infection, cardiopulmonary failure, and cardio-respiratory arrest in 1 patient each. The causes of death in the IC group were disease progression in 15 patients, and disease progression/respiratory distress, disease progression/vertigo, disease progression/leukopenia/pneumonia, cardiac arrest, lung infection, and sepsis in 1 patient each. A causal relationship to study drug could not be ruled out for the hypercalcaemia that occurred in 1 patient in the nivolumab group.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

As a result of the review below, PMDA concluded that nivolumab has demonstrated efficacy in patients with recurrent or distant metastatic primary squamous cell carcinoma of the head and neck (oral cavity, oropharynx/hypopharynx, and larynx) that has progressed or recurred within 6 months after platinum-based chemotherapy.

7.R.1.1 Rationale for the control group

The applicant's explanation of the rationale for the control group:

When Study 141 was planned, there were no established standard treatments for the target patient population of the study, but cetuximab, DOC, and MTX had been recommended by the NCCN guidelines (ver. 2, 2013) as treatment options for the population. In Study 141, therefore, cetuximab, DOC, or MTX was used as the active comparator at the discretion of the investigator.

PMDA's view:

PMDA accepted the applicant's explanation in general. Since the difference in the drugs selected in the control group may affect the efficacy evaluation of nivolumab, the efficacy evaluation of nivolumab should include comparisons between nivolumab and individual comparators.

7.R.1.2 Efficacy endpoint and evaluation results

PMDA's view:

Patients with recurrent or distant metastatic head and neck cancer receive treatment to prolong survival. OS is therefore the appropriate primary endpoint for Study 141.

PMDA concluded that the efficacy of nivolumab has been demonstrated in the target patient population of Study 141, based on the following findings.

• In Study 141, nivolumab was superior to IC in OS [see 7.1.1.1 "Global phase III study"].

• The OS hazard ratios (95% confidence intervals [CI]) between nivolumab and IC were 0.54 [0.30, 0.98] (cetuximab), 0.84 [0.58, 1.23] (DOC), and 0.60 [0.41, 0.86] (MTX), indicating no differences (between the 3 comparators) that affect the efficacy evaluation of nivolumab.

7.R.1.3 Efficacy in Japanese patients

The results of interim OS analysis (Table 3) and Kaplan-Meier curves (Figure 2) in Japanese patients in Study 141 are shown below.

Table 3. Interim OS analysis (Japanese patients [data cutoff, December 18, 2015])

	Nivolumab	IC
N	18	9
Number of deaths (%)	5 (27.8)	6 (66.7)
Median [95% CI] (months)	NE [9.10, NE]	4.70 [2.20, NE]
Hazard ratio [95% CI]*	0.32 [0.10, 1.05]	

* Non-stratified Cox proportional hazards model

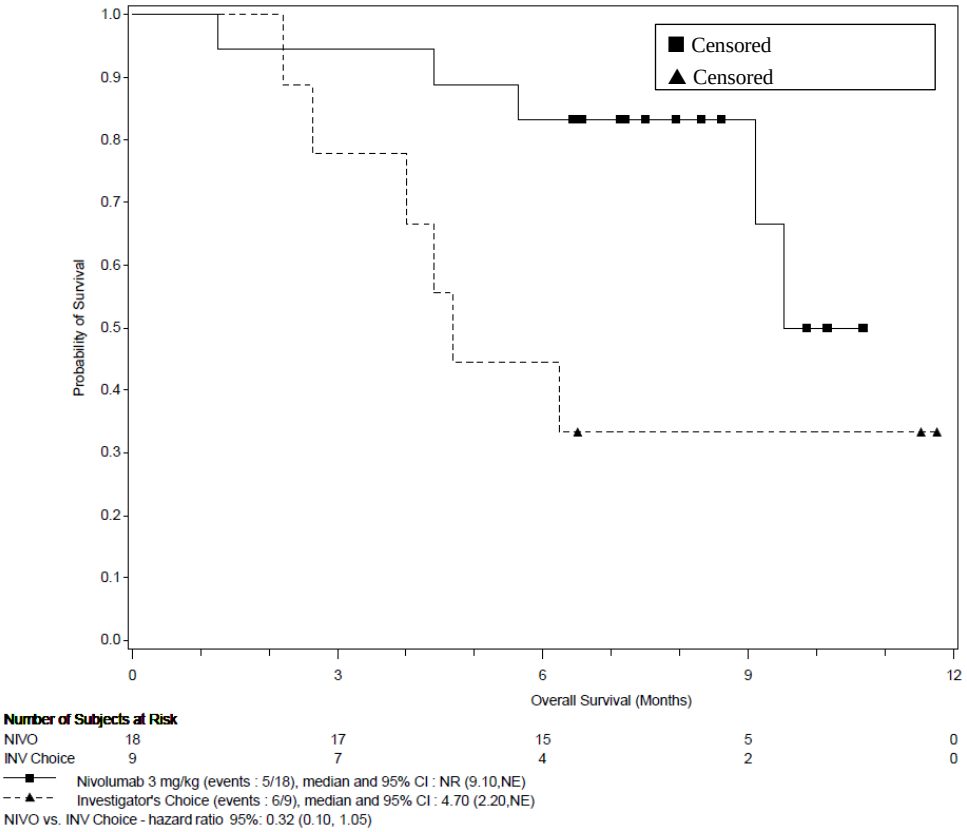

Figure 2. Kaplan-Meier curves for interim OS analysis (Japanese patients [data cutoff, December 18, 2015])

PMDA's view:

The efficacy of nivolumab in Japanese patients cannot be fully evaluated based solely on the results from the Japanese population in Study 141 because of the small number of Japanese patients enrolled and the few events occurring in the patients. Nonetheless, in view of the study results presented above, PMDA concluded that the efficacy of nivolumab can be expected in Japanese patients with recurrent or distant metastatic head and neck cancer.

7.R.2 Safety [for adverse events, see "7.2 Adverse events reported in a clinical study"]

PMDA's view as a result of its review:

Special attention should be paid to the following adverse events when administering nivolumab to patients with recurrent or distant metastatic head and neck cancer; 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/severe diarrhoea, myasthenia gravis/myocarditis/rhabdomyolysis/myositis, neurological disorder, renal disorder, venous thrombosis and

embolism, adrenal disorder, encephalitis, type 1 diabetes mellitus, immune thrombocytopenic purpura, and cardiac disorder (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated October 17, 2016," "Package Insert for Opdivo Intravenous Infusion," etc.). These adverse events should be carefully monitored in patients receiving nivolumab for recurrent or distant metastatic head and neck cancer as for the previously approved indications.

PMDA's conclusion:
Although attention should be paid to the above events, nivolumab is tolerable in patients with head and neck cancer 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.2.1 Safety profile of nivolumab

The applicant's explanation on the safety profile of nivolumab based on the safety data from Study 141:
The safety data from Study 141 are summarized in Table 4.

Table 4. Safety summary (Study 141)

	n (%)	
	Nivolumab N = 236	IC N = 111
All adverse events	229 (97.0)	109 (98.2)
Grade ≥3 adverse events	143 (60.6)	83 (74.8)
Adverse events resulting in death	54 (22.9)	26 (23.4)
Serious adverse events	127 (53.8)	66 (59.5)
Adverse events leading to drug discontinuation	51 (21.6)	27 (24.3)
Adverse events leading to drug interruption or dose reduction*	56 (23.7)	49 (44.1)

* Only adverse events leading to drug interruption in the nivolumab group

Adverse events of any grade reported with a ≥5% higher incidence in the nivolumab group than in the IC group were headache (8.9% [21 of 236 patients] in the nivolumab group; 3.6% [4 of 111 patients] in the IC group), pruritus (8.5% [20 of 236 patients]; 0%), and back pain (5.9% [14 of 236 patients]; 0%). Grade ≥3 adverse events reported with a ≥2% higher incidence in the nivolumab group than in the IC group were dyspnoea (5.5% [13 of 236 patients]; 1.8% [2 of 111 patients]) and pneumonia (3.8% [9 of 236 patients]; 0.9% [1 of 111 patients]). Serious adverse events with a ≥2% higher incidence in the nivolumab group than in the IC group were pneumonia (4.2% [10 of 236 patients]; 0.9% [1 of 111 patients]) and dyspnoea (3.8% [9 of 236 patients]; 0.9% [1 of 111 patients]). The adverse event leading to drug discontinuation with a ≥2% higher incidence in the nivolumab group than in the IC group was malignant neoplasm progression (7.6% [18 of 236 patients]; 5.4% [6 of 111 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, unresectable or metastatic renal cell carcinoma [RCC], and relapsed or refractory classical Hodgkin lymphoma [cHL]) and the currently proposed indication (recurrent or distant metastatic head and neck cancer).

The applicant's explanation:

The incidences of the adverse events reported in the nivolumab group of Study 141 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 066 and 037); (2) foreign phase III studies in patients with unresectable, advanced or recurrent NSCLC (Studies 017 and 057); (3) a global phase III study in patients with unresectable or metastatic RCC (Study 025); and (4) Japanese phase II study (Study 15) and foreign phase II study (Study 205) in patients with relapsed or refractory cHL. The results of the comparison are shown in Table 5.

Table 5. Safety summary in patients with head and neck cancer, malignant melanoma, NSCLC, RCC, or cHL

	n (%)				
	Head and neck cancer N = 236	Malignant melanoma N = 474	NSCLC N = 418	RCC N = 406	cHL N = 260
All adverse events	229 (97.0)	457 (96.4)	407 (97.4)	397 (97.8)	255 (98.1)
Grade ≥3 adverse events	143 (60.6)	218 (46.0)	222 (53.1)	230 (56.7)	83 (31.9)
Adverse events resulting in death	54 (22.9)	44 (9.3)	65 (15.6)	23 (5.7)	5 (1.9)
Serious adverse events	127 (53.8)	206 (43.5)	195 (46.7)	194 (47.8)	55 (21.2)
Adverse events leading to drug discontinuation	51 (21.6)	48 (10.1)	62 (14.8)	72 (17.7)	13 (5.0)
Adverse events leading to drug interruption	56 (23.7)	146 (30.8)	118 (28.2)	177 (43.6)	85 (32.7)

Adverse events of any grade reported with a ≥5% higher incidence in patients with head and neck cancer than in any of the other patient populations were malignant neoplasm progression (head and neck cancer, 18.2%; malignant melanoma, 10.3%; NSCLC, 10.5%; RCC, 5.4%; cHL, 1.5%) and dysphagia (head and neck cancer, 12.3%; malignant melanoma, 1.5%; NSCLC, 2.6%; RCC, 1.0%; cHL, 1.2%). Grade ≥3 adverse events reported with a ≥5% higher incidence in patients with head and neck cancer were malignant neoplasm progression (head and neck cancer, 18.2%; malignant melanoma, 9.5%; NSCLC, 9.3%; RCC, 4.9%; cHL, 1.5%). The adverse event resulting in death reported with a ≥5% higher incidence in patients with head and neck cancer was malignant neoplasm progression (head and neck cancer, 16.9%; malignant melanoma, 7.4%; NSCLC, 7.9%; RCC, 3.4%; cHL, 0.8%). The serious adverse event with a ≥5% higher incidence in patients with head and neck cancer was malignant neoplasm progression (head and neck cancer, 18.2%; malignant melanoma, 9.9%; NSCLC, 9.8%; RCC, 5.4%; cHL, 1.5%). No adverse events leading to drug discontinuation or drug interruption were reported with a ≥5% higher incidence in patients with head and neck cancer than in any of the other patient populations (i.e., patients with malignant melanoma, NSCLC, RCC, or cHL).

PMDA's view:

Some adverse events occurred more frequently in patients with head and neck cancer receiving nivolumab in Study 141 than in the IC group in the study or in patients receiving nivolumab for the previously approved indications. However, most of the adverse events were attributed to the underlying illness, or were of Grade ≤2 severity. All of the adverse events not attributable to the underlying illness were known adverse events of nivolumab. PMDA concluded that nivolumab is tolerable in patients with head and neck cancer 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.2.2 Differences in the safety of nivolumab between Japanese and non-Japanese patients

The applicant's explanation:

Table 6 shows the safety summary in Japanese and non-Japanese patients receiving nivolumab in Study 141.

Table 6. Safety summary (Study 141)

	n (%)	
	Japanese N = 18	Non-Japanese N = 218
All adverse events	18 (100)	211 (96.8)
Grade ≥3 adverse events	9 (50.0)	134 (61.5)
Adverse events resulting in death	2 (11.1)	52 (23.9)
Serious adverse events	9 (50.0)	118 (54.1)
Adverse events leading to drug discontinuation	1 (5.6)	50 (22.9)
Adverse events leading to drug interruption	5 (27.8)	51 (23.4)

Adverse events of any grade reported with a ≥20% higher incidence in Japanese patients than in non-Japanese patients were decreased appetite (Japanese, 38.9% [7 of 18 patients]; non-Japanese, 17.0% [37 of 218 patients]) and malaise (Japanese, 22.2% [4 of 18 patients]; non-Japanese, 0.9% [2 of 218 patients]). The Grade ≥3 adverse event reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients was constipation (Japanese, 11.1% [2 of 18 patients]; non-Japanese, 0%). No adverse events resulting in death, serious adverse events, or adverse events leading to drug discontinuation were reported with a ≥10% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:

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 with head and neck cancer as in non-Japanese patients, based on the following findings.

- Most of the adverse events with a higher incidence in Japanese patients than in non-Japanese patients were of Grade ≤2 severity.
- No significant differences were noted in the incidences of adverse events resulting in death, serious adverse events, or adverse events leading to drug discontinuation.

7.R.3 Clinical positioning and indication

The proposed indication of nivolumab was "treatment of patients with recurrent or distant metastatic head and neck cancer." The following statements were included in the proposed "Precautions for Indications" section:

- Nivolumab should be administered to patients who have received prior platinum-based chemotherapy (including chemoradiotherapy), in consideration of their sensitivity to platinum antineoplastic agents.
- The efficacy and safety of nivolumab in adjuvant chemotherapy have not been established.

- Eligible patients must be selected based on 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 reviews described in "7.R.1 Efficacy" and "7.R.2 Safety" and in the following subsections (7.R.3.1 to 7.R.3.3), PMDA concluded that the proposed indication is appropriate and that the precautionary statements below should be included in the "Precautions for Indications" sections.

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

7.R.3.1 Intended population

The NCCN guidelines (ver. 2. 2016), a foreign clinical practice guideline, contain the following statement on nivolumab for the treatment of recurrent or distant metastatic head and neck cancer. Currently, nivolumab is not mentioned in the Japanese clinical practice guidelines, the US National Cancer Institute Physician Data Query (NCI-PDQ) (dated May 20, 2016), or major textbooks of oncology in and outside Japan.

- Based on the results of Study 141, treatment with nivolumab is strongly recommended for patients with recurrent or distant metastatic head and neck cancer that has progressed after platinum-based chemotherapy.

The applicant's explanation on the clinical positioning and indication of nivolumab:

Nivolumab is a therapeutic option for the patient population of Study 141, that is, patients with recurrent or distant metastatic primary squamous cell carcinoma of the head and neck (oral cavity, oropharynx/hypopharynx, and larynx) that has progressed or recurred within 6 months after platinum-based chemotherapy. The following populations were not enrolled in Study 141: (a) patients with primary squamous cell carcinoma of the nasal cavity, paranasal cavity, or nasopharynx; (b) patients with nonsquamous cell carcinoma. Although no clinical study results are available in these populations, nivolumab therapy is also acceptable to the populations, for the following reasons:

- (a) Patients with primary squamous cell carcinoma of the nasal cavity, paranasal cavity, or nasopharynx account for approximately 7% of all patients with head and neck cancer, and it is difficult to obtain evidence to establish the standard treatment for such patients; therefore, these patients are currently treated in clinical practice according to the treatment regimens for primary squamous cell carcinoma of the oral cavity, oropharynx/hypopharynx, or larynx (e.g., NCCN guidelines, ver.2. 2016 and other guidelines).
- (b) Patients with nonsquamous cell carcinoma account for approximately 10% of all patients with head and neck cancer, and it is difficult to obtain evidence to establish the standard treatment for such patients; therefore, these patients are currently treated in clinical practice according to the treatment regimens for squamous cell carcinoma (New Clinical Oncology, revised fourth edition, Nankodo 2015).

In consideration of the above-mentioned circumstances, the proposed indication was determined to be "recurrent or distant metastatic head and neck cancer," provided that the characteristics of the patients enrolled

in Study 141 are described in the “Clinical Studies” section of the package insert and that the following statements are included in the “Precautions for Indications” section.

- Nivolumab should be administered to patients who have received prior platinum-based chemotherapy (including chemoradiotherapy), in consideration of their sensitivity to platinum antineoplastic agents.
- 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.

PMDA’s view:

PMDA accepted the applicant’s explanation in general, taking into consideration that nivolumab is an antineoplastic drug prescribed and administered by physicians with sufficient knowledge and experience in cancer chemotherapy. However, the statement “sensitivity to platinum antineoplastic agents” included in the proposed “Precautions for Indications" section is not appropriate, since its meaning is ambiguous and the Japanese and foreign clinical practice guidelines for head and neck cancer do not contain such a description.

PMDA’ conclusion

The indication should be “recurrent or distant metastatic head and neck cancer” as proposed by the applicant. The proposed statements for the “Precautions for Indications” section should be modified as follows:

- The efficacy and safety of nivolumab have not been established in platinum-based chemotherapy-naïve patients.
- 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.3.2 Efficacy and safety of nivolumab by PD-L1 expression status

Nivolumab is an antibody to human PD-1. PMDA asked the applicant to explain the efficacy and safety of nivolumab by PD-L1 expression status and to describe the intended patient population of nivolumab.

The applicant’s response:

In Study 141, the PD-L1 expression levels in tumor samples were determined by the PD-L1 IHC 28-8 pharmDx “Dako” assay (Dako Japan, presently known as Agilent Technologies) to evaluate the association between PD-L1 expression and (a) the efficacy or (b) safety of nivolumab.

(a) Efficacy:

The percentage of cells expressing PD-L1 in the tumor tissue could be evaluated in 161 of 240 patients (67.1%) in the nivolumab group and 99 of 121 patients (81.8%) in the IC group. Table 7 and Figures 3, 4, and 5 show the OS in these patients by PD-L1 expression status (cutoff value; 1%, 5%, or 10%) (data cutoff, February 3, 2016). At each cutoff value, a higher efficacy of nivolumab was observed in PD-L1 positive patients than in PD-L1 negative patients. However, it is unclear whether PD-L1 expression status is the most appropriate predictor of OS for nivolumab, and a certain level of efficacy of nivolumab can be expected also in PD-L1 negative patients (<1% PD-L1 expression), in view of the following findings.

- Subgroup analysis by patient characteristics was performed separately for patients positive and negative for PD-L1 expression. The analysis revealed consistent differences in efficacy between the levels of several patient characteristics, regardless of PD-L1 expression status. This suggests that other patient characteristics than PD-L1 expression status may affect the efficacy of nivolumab.
- Patient characteristics affecting OS were selected by backward elimination. In PD-L1 negative patients (cutoff values, 1%, 5%, or 10%), the hazard ratio [95% CI] adjusted for the patient characteristics was as follows: 0.85 [0.52, 1.40] in patients with <1% PD-L1 expression; 0.75 [0.50, 1.13] in patients with <5% PD-L1 expression; and 0.68 [0.47, 1.00] in patients with <10% PD-L1 expression. The Kaplan-Meier curves adjusted for the selected patient characteristics showed better OS in the nivolumab group than in the IC group, from an early stage of treatment.
- Of 73 patients with <1% PD-L1 expression, 9 (12.3%) were responders, including 2 complete responders (2.7%).

Table 7. Efficacy of nivolumab by PD-L1 expression status in tumor samples

PD-L1	Treatment group	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P* value for interaction
<1%	Nivolumab	73	5.7 [4.4, 12.7]	0.88 [0.54, 1.43]	0.1668
	IC	38	5.8 [4.0, 9.8]		
≥1%	Nivolumab	88	8.7 [5.7, 9.1]	0.56 [0.37, 0.84]	
	IC	61	4.6 [3.8, 5.8]		
<5%	Nivolumab	107	7.0 [5.0, 8.8]	0.81 [0.54, 1.21]	0.1431
	IC	56	5.1 [4.0, 8.5]		
≥5%	Nivolumab	54	8.8 [4.8, NE]	0.50 [0.30, 0.83]	
	IC	43	4.6 [3.5, 6.2]		
<10%	Nivolumab	118	7.2 [5.2, 8.8]	0.73 [0.50, 1.06]	0.4339
	IC	65	4.6 [3.9, 6.3]		
≥10%	Nivolumab	43	8.7 [4.8, NE]	0.56 [0.31, 0.99]	
	IC	34	5.2 [2.6, 7.1]		

* Estimated using a Cox proportional hazards model including treatment group, PD-L1 expression status, and interaction between treatment group and PD-L1 expression status as covariates

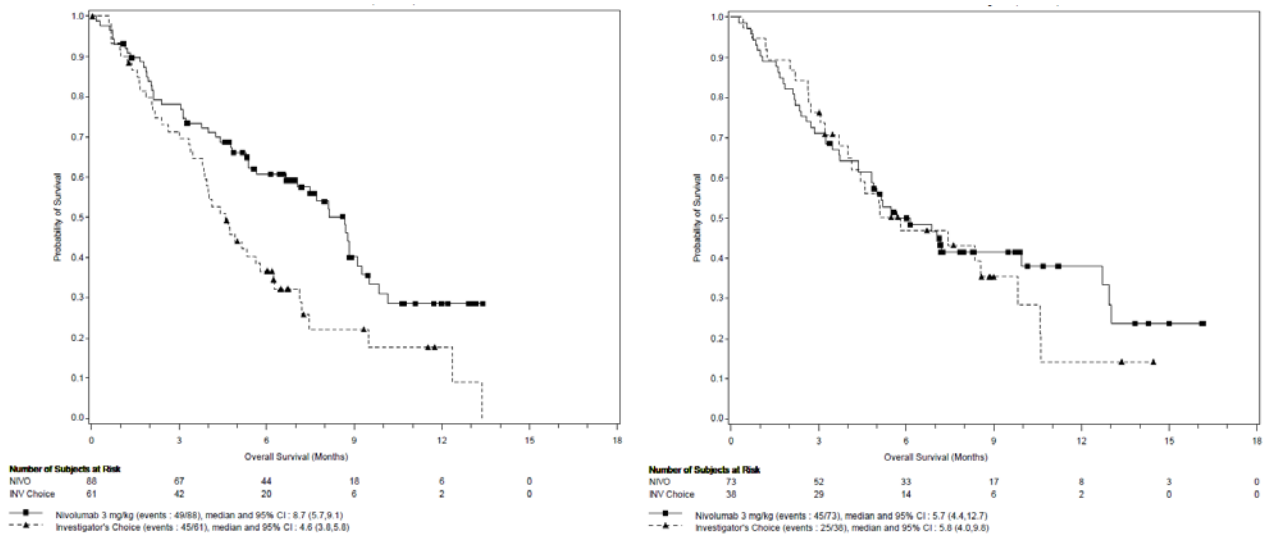

Figure 3. Kaplan-Meier curves of OS by PD-L1 expression status (left, PD-L1 expression ≥1%; right, PD-L1 expression <1%)

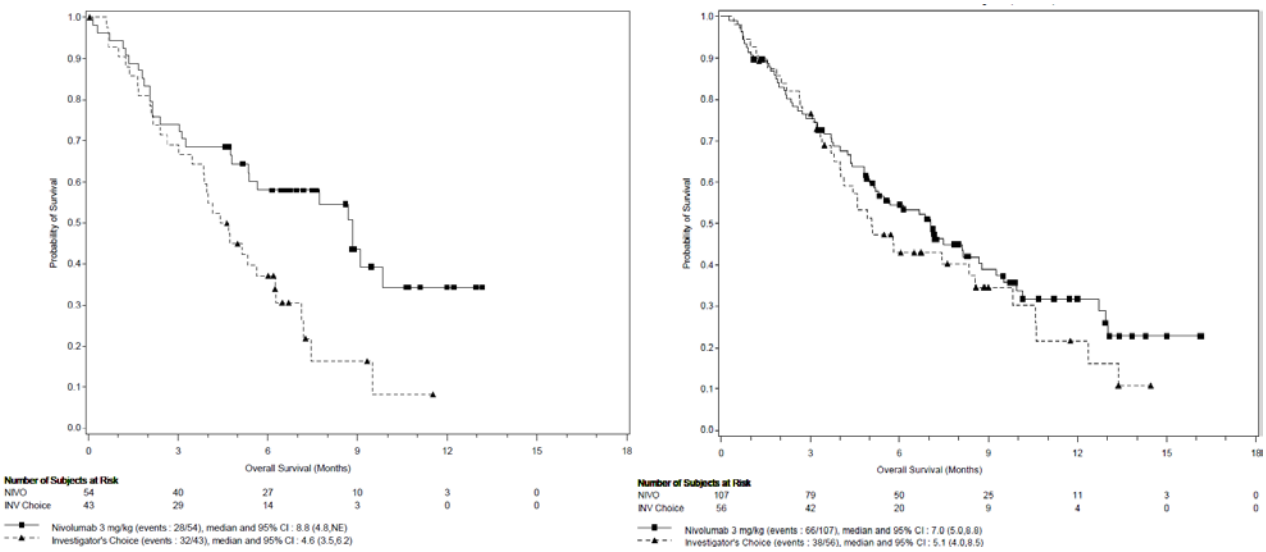

Figure 4. Kaplan-Meier curves of OS by PD-L1 expression status (left, PD-L1 expression ≥5%; right, PD-L1 expression <5%)

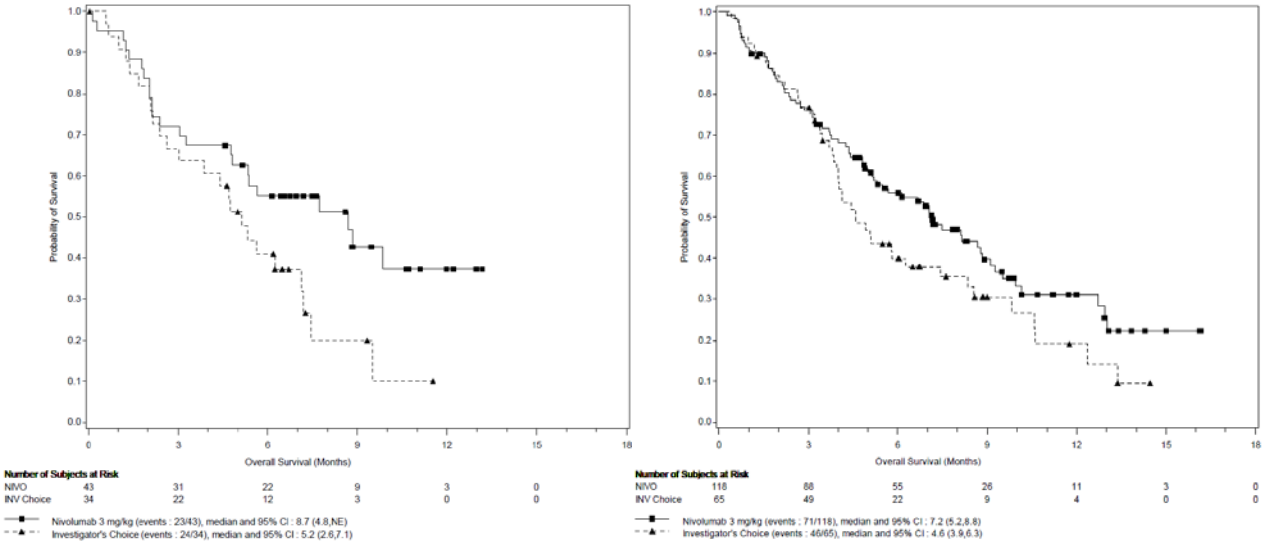

Figure 5. Kaplan-Meier curves of OS by PD-L1 expression status (left, PD-L1 expression ≥10%; right, PD-L1 expression <10%)

(b) Safety

In the nivolumab group, the incidence of adverse events (and Grade ≥3 adverse events) was as follows: 94.4% (66.2%) in patients with <1% PD-L1 expression and 97.7% (63.6%) in patients with ≥1% PD-L1 expression; 95.2% (65.7%) in patients with <5% PD-L1 expression and 98.1% (63.0%) in patients with ≥5% PD-L1 expression; 94.8% (62.9%) in patients with <10% PD-L1 expression and 100% (69.8%) in patients with ≥10% PD-L1 expression. According to these results, the safety of nivolumab had no clear relationship with PD-L1 expression status in tumor tissue samples, and did not clearly differ between PD-L1 positive and negative patients at any cutoff values in patients with recurrent or distant metastatic head and neck cancer.

The investigations in (a) and (b) above suggest that nivolumab has a certain level of efficacy in PD-L1 negative patients as well as in PD-L1 positive patients, at each cutoff value. Nivolumab therefore can be recommended for the treatment of head and neck cancer irrespective of PD-L1 expression status in tumor tissues.

Therefore, the indication of nivolumab should be "recurrent or distant metastatic head and neck cancer," without limiting the intended population by PD-L1 expression status.

PMDA's view:
The applicant's explanation is acceptable. However, Study 141 showed a higher efficacy of nivolumab in PD-L1 positive patients than in PD-L1 negative patients at each cutoff value, suggesting the likelihood that PD-L1 expression is a predictor of response to nivolumab. The results of the efficacy and safety of nivolumab by PD-L1 expression status from Study 141 is important for deciding on the initiation of treatment with nivolumab; therefore, the results should be properly provided to healthcare professionals using an information leaflet or other materials.

The applicant should continue to collect information on possible predictors of response to nivolumab, including PD-L1 expression, and appropriately provide any new findings to healthcare professionals.

7.R.3.3 Efficacy and safety of nivolumab as adjuvant chemotherapy

The applicant's explanation:
No clinical data are currently available regarding the efficacy and safety of nivolumab as adjuvant chemotherapy. The "Precautions for Indications" section of the package insert will include a precautionary statement to the effect that the efficacy and safety of nivolumab as adjuvant chemotherapy have not been established.

PMDA accepted the applicant's explanation.

7.R.4 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 statements were included in the proposed "Precautions for Dosage and Administration" section:

- 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.

As a result of the review described below, PMDA concluded that the proposed indication ("The usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight administered as an intravenous infusion every 2 weeks") is appropriate and that the following proposed precautionary statements should be included in the "Precautions for Dosage and Administration" section.

- 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.

7.R.4.1 Dosage and administration of nivolumab

The applicant's explanation on the rationale for the dosage and administration of nivolumab selected for patients with recurrent or distant metastatic head and neck cancer:

In Study 141, a dosing regimen of 3 mg/kg every 2 weeks was selected based on data including the results of the foreign phase I studies (see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg, dated June 18, 2014"). The study demonstrated the clinical usefulness of nivolumab 3 mg/kg every 2 weeks in patients with recurrent or distant metastatic head and neck cancer. The proposed dosage and administration of nivolumab is based on the dosing regimen employed in Study 141.

PMDA accepted the applicant's explanation.

7.R.4.2 Concomitant antineoplastic drugs

The applicant's explanation:

Nivolumab has been administered only as monotherapy to patients with recurrent or distant metastatic head and neck cancer 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.5 Post-marketing investigations

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

The applicant plans to conduct post-marketing surveillance covering all patients receiving nivolumab for the treatment of recurrent or distant metastatic head and neck cancer. The purpose of the surveillance is to evaluate the safety and other aspects of nivolumab in clinical practice.

The safety profile observed in the nivolumab group of Study 141 was comparable with the safety profile found with the previously approved indications [see "7.R.2.1 Safety profile of nivolumab"].Therefore, the key survey items (events) for the post-marketing surveillance in patients with recurrent or distant metastatic head and neck cancer are the same as those for the post-marketing surveillance in patients receiving nivolumab for the previously approved indications.[3)]

The target sample size was determined as 400, focusing on ILD based on (a) the ILD events reported in patients treated with nivolumab for the previously approved indications in Japan and (b) the incidence of ILD in Study 141. Other key survey items will also be collectable in this sample size, considering the incidences of the key survey items in the overall patient population of Study 141.

The observation period is 12 months, because in Study 141, most of the events selected as the key survey items occurred within 12 months after the start of nivolumab therapy.

PMDA's view:
Only limited safety data are available in Japanese patients with recurrent or distant metastatic head and neck cancer treated with nivolumab, and no data have been available from the ongoing post-marketing surveillance for the previously approved indications. Therefore, safety information should be collected from all patients with recurrent or distant metastatic head and neck cancer treated with nivolumab in a speedy and unbiased manner for a certain period after the launch, and the collected safety information should be promptly provided to healthcare professionals.

The key survey items and target sample size proposed by the applicant are acceptable. An observation period of 6 months may be another option, considering the timing of onset of the events selected as the key survey items and other findings in Study 141.

7.2 Adverse events reported in a clinical study

Among the clinical study data submitted for safety evaluation, data on death are presented in "7.1 Evaluation data." The subsection below presents other major adverse events.

7.2.1 Global phase III study (Study 141)

Adverse events were reported in 229 of 236 patients (97.0%) in the nivolumab group and 109 of 111 patients (98.2%) in the IC group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 139 of 236 patients (58.9%) in the nivolumab group and 86 of 111 patients (77.5%) in the IC group. Table 8 shows adverse events with an incidence of ≥10% in either of the treatment groups.

3) ILD, myasthenia gravis/myocarditis/myositis/rhabdomyolysis, colitis/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, immune thrombocytopenic purpura, and cardiac disorders (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles)

Table 8. Adverse events with an incidence of ≥10% in either of the treatment groups

System Organ Class Preferred Term (MedDRA/J ver.18.1)	n (%)			
	Nivolumab N = 236		IC N = 111	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	229 (97.0)	143 (60.6)	109 (98.2)	83 (74.8)
General disorders and administration site conditions				
Fatigue	62 (26.3)	8 (3.4)	36 (32.4)	7 (6.3)
Pyrexia	30 (12.7)	1 (0.4)	16 (14.4)	3 (2.7)
Asthenia	24 (10.2)	5 (2.1)	24 (21.6)	4 (3.6)
Mucosal inflammation	8 (3.4)	0	17 (15.3)	2 (1.8)
Gastrointestinal disorders				
Nausea	45 (19.1)	1 (0.4)	34 (30.6)	1 (0.9)
Constipation	36 (15.3)	2 (0.8)	20 (18.0)	0
Diarrhoea	35 (14.8)	2 (0.8)	26 (23.4)	3 (2.7)
Dysphagia	29 (12.3)	9 (3.8)	15 (13.5)	3 (2.7)
Vomiting	27 (11.4)	1 (0.4)	14 (12.6)	0
Respiratory, thoracic and mediastinal disorders				
Cough	32 (13.6)	1 (0.4)	10 (9.0)	0
Dyspnoea	32 (13.6)	13 (5.5)	12 (10.8)	2 (1.8)
Metabolism and nutrition disorders				
Decreased appetite	44 (18.6)	3 (1.3)	22 (19.8)	4 (3.6)
Hyponatraemia	22 (9.3)	11 (4.7)	14 (12.6)	9 (8.1)
Blood and lymphatic system disorders				
Anaemia	44 (18.6)	14 (5.9)	37 (33.3)	9 (8.1)
Skin and subcutaneous tissue disorders				
Alopecia	2 (0.8)	0	14 (12.6)	3 (2.7)
Dry skin	11 (4.7)	0	12 (10.8)	0
Investigations				
Weight decreased	31 (13.1)	0	16 (14.4)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)				
Malignant neoplasm progression	43 (18.2)	43 (18.2)	25 (22.5)	25 (22.5)

Serious adverse events were reported in 127 of 236 patients (53.8%) in the nivolumab group and 66 of 111 patients (59.5%) in the IC group. Serious adverse events reported in the nivolumab group were malignant neoplasm progression in 43 patients (18.2%); pneumonia in 10 patients (4.2%); dyspnoea in 9 patients (3.8%); pneumonia aspiration in 8 patients (3.4%); respiratory tract infection and sepsis in 5 patients (2.1%) each; lung infection, urinary tract infection, respiratory failure, and decreased appetite in 4 patients (1.7%) each; lower respiratory tract infection, dehydration, hypercalcaemia, and pyrexia in 3 patients (1.3%) each; tumour haemorrhage, infection, haemoptysis, pleural effusion, pneumonitis, stridor, hyponatraemia, malnutrition, dysphagia, tongue haemorrhage, fatigue, cardiac failure, and back pain in 2 patients (0.8%) each; cancer pain, head and neck cancer, malignant pleural effusion, metastases to the central nervous system, neoplasm malignant, clostridium difficile colitis, localised infection, lymphangitis, neutropenic sepsis, otitis media, peritonitis, pneumonia bacterial, purulent discharge, tracheitis, wound infection, acute respiratory failure, laryngeal oedema, laryngeal stenosis, obstructive airways disorder, pharyngeal oedema, pneumothorax, pneumothorax spontaneous, respiratory distress, hyperglycaemia, hypophagia, hypophosphataemia, abdominal pain, gastric disorder, gastric haemorrhage, oesophageal stenosis, parotid gland haemorrhage, pneumoperitoneum, stomatitis, asthenia, catheter site pain, chills, disease progression, localised oedema, ulcer haemorrhage, cerebrovascular accident, complex partial seizures, encephalopathy, hydrocephalus, ischaemic stroke, speech disorder, syncope, acute myocardial infarction, atrial flutter, cardio-respiratory arrest, cardiopulmonary failure, pericarditis, infusion related reaction, post procedural haemorrhage, tracheostomy

malfunction, vascular pseudoaneurysm ruptured, wound haemorrhage, bone pain, musculoskeletal chest pain, pain in extremity, haemorrhage, hypertensive crisis, shock haemorrhagic, superior vena cava syndrome, blood alkaline phosphatase increased, blood bilirubin increased, liver function test abnormal, transaminases increased, skin mass, skin ulcer, hypophysitis, secondary adrenocortical insufficiency, secondary hypothyroidism, blindness unilateral, allergic granulomatous angiitis, and delirium in 1 patient (0.4%) each. Serious adverse events reported in the IC group were malignant neoplasm progression in 25 patients (22.5%); lung infection and pyrexia in 4 patients (3.6%) each; sepsis, lower respiratory tract infection, pleural effusion, and dysphagia in 3 patients (2.7%) each; device related infection, pneumonia aspiration, respiratory distress, abdominal pain, diarrhoea, asthenia, malaise, dizziness, and anaemia in 2 patients (1.8%) each; tumour pain, pneumonia, respiratory tract infection, clostridium difficile colitis, localised infection, neutropenic sepsis, wound infection, cellulitis, gastrointestinal infection, skin infection, upper respiratory tract infection, dyspnoea, haemoptysis, laryngeal oedema, bronchopneumopathy, hypoxia, decreased appetite, hypercalcaemia, hypernatraemia, stomatitis, colitis, gastritis, nausea, fatigue, chills, device occlusion, drug intolerance, face oedema, general physical health deterioration, mucosal inflammation, pain, syncope, headache, neuralgia, atrial flutter, atrial fibrillation, cardiac arrest, cardiovascular disorder, supraventricular tachycardia, infusion related reaction, post procedural haemorrhage, haematoma, hypotension, hypovolaemic shock, platelet count decreased, angioedema, dermatomyositis, visual acuity reduced, agoraphobia, leukopenia, tracheo-oesophageal fistula, vertigo, and acute kidney injury in 1 patient (0.9%) each. Serious adverse events for which a causal relationship to the study drug could not be ruled out were pneumonitis in 2 patients, and localised infection, pneumonia aspiration, laryngeal oedema, pharyngeal oedema, dehydration, hypercalcaemia, hyponatraemia, gastric disorder, chills, infusion related reaction, liver function test abnormal, transaminases increased, skin mass, hypophysitis, secondary adrenocortical insufficiency, secondary hypothyroidism, and allergic granulomatous angiitis in 1 patient each in the nivolumab group; and pyrexia, malaise, and anaemia in 2 patients each, and pneumonia, sepsis, lung infection, localised infection, neutropenic sepsis, gastrointestinal infection, pleural effusion, stomatitis, colitis, diarrhoea, chills, drug intolerance, mucosal inflammation, dizziness, cardiovascular disorder, infusion related reaction, platelet count decreased, leukopenia, and acute kidney injury in 1 patient each in the IC group.

Adverse events leading to drug discontinuation were reported in 51 of 236 patients (21.6%) in the nivolumab group and 27 of 111 patients (24.3%) in the IC group. Adverse events leading to drug discontinuation reported in the nivolumab group were malignant neoplasm progression in 18 patients (7.6%); pneumonitis and pneumonia in 2 patients (0.8%) each; malignant pleural effusion, tumour haemorrhage, dyspnoea, pneumonia aspiration, pulmonary embolism, respiratory distress, asthenia, disease progression, fatigue, ulcer haemorrhage, infection, respiratory tract infection, amylase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, lipase increased, liver function test abnormal, transaminases increased, cardiac failure, cardio-respiratory arrest, cardiopulmonary failure, diarrhoea, nausea, oral cavity fistula, vomiting, cerebrovascular accident, ischaemic stroke, somnolence, tremor, hypotension, shock haemorrhagic, superior vena cava syndrome, hypercalcaemia, hyponatraemia, delirium, mental status changes, skin mass, skin ulcer, hypophysitis, secondary hypothyroidism, allergic granulomatous angiitis, and back pain in 1 patient (0.4%) each. Adverse events leading to drug discontinuation reported in the IC group were malignant neoplasm

progression in 6 patients (5.4%); alanine aminotransferase increased in 2 patients (1.8%); pneumonitis, bronchopneumopathy, laryngeal oedema, pleural effusion, pulmonary toxicity, face oedema, general physical health deterioration, malaise, oedema peripheral, pneumonia, lung infection, sepsis, hepatic enzyme increased, cardiac arrest, glossodynia, dermatomyositis, onycholysis, onychomadesis, rash, skin disorder, fistula, anaemia, leukopenia, neutropenia, and infusion related reaction in 1 patient (0.9%) each. Adverse events leading to drug discontinuation for which a causal relationship to the study drug could not be ruled out were pneumonitis in 2 patients, and amylase increased, lipase increased, liver function test abnormal, transaminases increased, diarrhoea, hypercalcaemia, skin mass, hypophysitis, secondary hypothyroidism, and allergic granulomatous angiitis in 1 patient each in the nivolumab group; and pneumonitis, pleural effusion, pulmonary toxicity, malaise, pneumonia, lung infection, hepatic enzyme increased, onycholysis, onychomadesis, rash, skin disorder, anaemia, leukopenia, neutropenia, and infusion related reaction in 1 patient each in the IC group.

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 5.3.5.1-1) 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 there were no obstacles to conducting its review based on the application documents submitted.

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 recurrent or distant metastatic head and neck cancer and acceptable safety in view of the benefits indicated by the data submitted. Nivolumab is clinically meaningful because it offers a therapeutic option for patients with recurrent or distant metastatic head and neck cancer. 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)

February 22, 2017

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	July 27, 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.1 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of nivolumab (genetical recombination) ("nivolumab") has been demonstrated in the treatment of patients with recurrent or distant metastatic primary squamous cell carcinoma of the head and neck (oral cavity, oropharynx/hypopharynx, and larynx) that has progressed or recurred within 6 months after platinum-based chemotherapy.[4)] This conclusion is based on the following finding: In a global phase III study (Study ONO-4538-11/CA209141 [Study 141]), overall survival (the primary endpoint) was significantly longer with nivolumab than with the investigator's choice of therapy (control treatment) in patients with recurrent or distant metastatic primary squamous cell carcinoma of the head and neck (oral cavity, oropharynx/hypopharynx, and larynx) that had progressed or recurred within 6 months after platinum-based chemotherapy.

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

1.2 Safety

As a result of the review described in "7.R.2 Safety" of the Review Report (1), PMDA concluded that the following adverse events should be closely monitored when nivolumab is administered to patients with recurrent or distant metastatic head and neck cancer; these events were identified as requiring attention at the regulatory reviews for the previously approved indications[5)]: interstitial pneumonia (ILD), hepatic function

4) Including curative-intent or adjuvant chemoradiotherapy

5) Unresectable malignant melanoma, unresectable, advanced or recurrent non-small-cell lung cancer (NSCLC), unresectable or metastatic renal cell carcinoma (RCC), and relapsed or refractory classical Hodgkin lymphoma (cHL)

disorder, abnormal thyroid function, infusion reaction, skin disorder, colitis/severe diarrhoea, myasthenia gravis/myocarditis/rhabdomyolysis/myositis, neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, encephalitis, type 1 diabetes mellitus, immune thrombocytopenic purpura, and cardiac disorder.

PMDA concluded that nivolumab is tolerable 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 the PMDA's conclusion and offered the following comments.

- ILD (including fatal ILD) occurred in patients with non-small cell lung cancer (NSCLC) who received an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) after nivolumab therapy (PSEHB/SD Notification No. 0722-3, dated July 22, 2016). Cetuximab (genetical recombination) ("cetuximab") has been approved for the treatment of head and neck cancer. Cetuximab is not an EGFR-TKI, but an antibody drug targeting EGFR, the same molecule. The necessity of issuing a warning about the occurrence of ILD in patients receiving cetuximab after nivolumab therapy should be considered.
- Treatment of head and neck cancer may include radiation to the lung. The necessity of issuing a warning about the occurrence of ILD in patients receiving nivolumab after radiation therapy should be considered.

PMDA asked the applicant to explain the incidence of ILD in (a) patients receiving cetuximab after nivolumab therapy and (b) patients receiving nivolumab after radiation to the lung in Study 141.

The applicant's explanation:

(a) In Study 141, 23 patients received cetuximab after nivolumab therapy, and none experienced ILD. In other clinical studies of nivolumab and post-marketing settings in and outside Japan, 2 patients received cetuximab after nivolumab therapy, and neither experienced ILD.

(b) In Study 141, the incidence of ILD was 2.1% (3 of 146 patients) in patients with prior radiation to the lung and 4.4% (4 of 90 patients) in those without prior radiation to the lung; the incidence of Grade ≥3 ILD was 0% in patients with prior radiation to the lung and 3.3% (3 of 90 patients) in those without prior radiation to the lung.

PMDA's conclusion:

No warnings for patients (a) or (b) are necessary, because Study 141 or other data have revealed no specific clinical problems concerning patients (a) or (b), and because no definite conclusion has been reached on whether treatment with EGFR-TKIs following nivolumab therapy increases the risk of ILD.

Special attention should continue to be paid to ILD in patients receiving nivolumab. New data obtained from patients with head and neck cancer should be properly provided to healthcare professionals.

1.3 Clinical positioning and indication

As a result of the review described in "7.R.3 Clinical positioning and indication" of the Review Report (1), PMDA concluded that the proposed indication "recurrent or distant metastatic head and neck cancer" is appropriate, provided that the detailed characteristics of the patients enrolled in Study 141 are described in the "Clinical Studies" section of the package insert and that the following statements are included in the "Precautions for Indications" section.

Precautions for Indications

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

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

PMDA instructed the applicant to include the indication and statements for "Precautions for Indications" in the package insert, and to modify the precautionary statements concerning adjuvant chemotherapy and unresectable or metastatic RCC in the "Precautions for Indications." The applicant agreed.

1.4 Dosage and administration

PMDA's conclusion as a result of the review described in "7.R.4 Dosage and administration" of the Review Report (1):

The dosage and administration of nivolumab should be as follows: "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 statements should be included 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 recurrent or distant metastatic head and neck cancer who receive nivolumab, to evaluate the safety of nivolumab in clinical practice. The target sample size is 400 patients. The proposed observation period is 12 months.

In view of the discussions presented in "7.R.5 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 speedy and unbiased manner for a certain period of time after the market launch, and should promptly provide the collected information to healthcare professionals. PMDA also reached the following conclusions regarding the plan for the post-marketing surveillance:

- The key survey items and target sample size for the post-marketing surveillance proposed by the applicant are acceptable.
- An observation period of 6 months may be another option, considering the timing of onset of the events selected as the key survey items and other findings in Study 141.

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

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

The applicant's response:
The observation period for the post-marketing surveillance is changed to 6 months, considering the timing of onset of the events selected as the key survey items and other findings in Study 141.

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 9, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 10.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Myasthenia gravis, myocarditis, myositis, and rhabdomyolysis • 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 • Immune thrombocytopenic purpura	• Excessive immune response • Embryonic/fetal toxicity • Cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles) • Haemolytic anaemia	• None
Efficacy specification (relating to the present partial change application)		
• Efficacy in the treatment of patients with recurrent or distant metastatic head and neck cancer in clinical practice		

Table 10. 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) • <u>Use-results survey in patients with recurrent or distant metastatic head and neck cancer (all-case surveillance)</u> • Post-marketing clinical study in patients with unresectable malignant melanoma (extension study of Study ONO-4538-02) • Post-marketing clinical study in patients with unresectable, advanced or recurrent SQ-NSCLC (extension study of Study ONO-4538-05) • Post-marketing clinical study in patients with unresectable, advanced or recurrent NSQ-NSCLC (extension study of Study ONO-4538-06) • Post-marketing clinical study in patients with chemotherapy-naïve, unresectable malignant melanoma (extension study of Study ONO-4538-08) • Post-marketing clinical study involving 2 dosing regimens in patients with unresectable malignant melanoma (extension study of Study ONO-4538-31) • Post-marketing clinical study in patients with advanced or metastatic clear cell RCC and prior chemotherapy (extension study of Study ONO-4538-03/CA209025) • Post-marketing clinical study in patients with relapsed or refractory cHL (extension study of Study ONO-4538-15)	• Provision of data from the early postmarketing phase vigilance (unresectable or metastatic RCC) • <u>Preparation and provision of materials for healthcare professionals</u> • <u>Preparation and provision of materials for patients</u>

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

Table 11. 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 recurrent or distant metastatic head and neck cancer
Observation period	6 months
Planned sample size	400 patients
Main survey items	Key survey items: ILD, myasthenia gravis/myocarditis/myositis/rhabdomyolysis, colitis/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, immune thrombocytopenic purpura, and cardiac disorders (e.g., atrial fibrillation, bradycardia, and ventricular extrasystoles) Other main survey items: patient characteristics (e.g., performance status, 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 re-examination period for the present application is the remainder of the ongoing re-examination period for the initial approval of nivolumab (until October 16, 2021).

Indications (Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 or December 2, 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

5. Treatment of recurrent or distant metastatic head and neck cancer

Dosage and Administration (Single underline denotes new additions and double-underline denotes additions made as of August 26, 2016 or December 2, 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, relapsed or refractory classical Hodgkin lymphoma, and recurrent or distant metastatic head and neck cancer

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

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. Double underline denotes additions made as of August 26, 2016 or December 2, 2016 after submission of the present application. Crossed-out words are deleted.)

(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 have not been established in chemotherapy-naïve patients with unresectable or metastatic renal cell carcinoma or patients with unresectable or metastatic renal cell carcinoma who have received cytokine therapy as the only prior treatment.

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

(~~2~~4) The efficacy and safety of Opdivo in adjuvant chemotherapy have not been established ~~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.~~

(~~3~~5) 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 August 26, 2016 or December 2, 2016 after submission of the present application. Crossed-out words are deleted.)

(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, or head and neck cancer.
2) Opdivo should be intravenously infused over at least 1 hour.

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

(4) The efficacy and safety of Opdivo in combination with other antineoplastic drugs (including cytokines) have not been established.