

Review Report

August 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	December 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/PED Notification No. 0214-7 dated February 14, 2017, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour, and Welfare)

Reviewing Office Office of New Drug V

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy and show 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 indications and dosage and administration shown below, with the following condition of approval.

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

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4. Treatment of relapsed or refractory classical Hodgkin lymphoma
5. Treatment of recurrent or distant metastatic head and neck cancer
6. Treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy

(Single underline denotes new additions. Double-underline denotes additions made as of March 24, 2017 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, recurrent or distant metastatic head and neck cancer, and unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy

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

(Single underline denotes new additions. Double-underline denotes additions made as of March 24, 2017 after submission of the present application.)

Condition of Approval

The applicant should formulate and properly implement a risk management plan.

Review Report (1)

July 14, 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

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Proposed 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 unresectable advanced or recurrent gastric cancer

(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, unresectable or metastatic renal cell carcinoma, relapsed or refractory classical Hodgkin lymphoma, and unresectable advanced or recurrent gastric cancer

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

(Underline denotes additions.)

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List of Abbreviations

AST	aspartate aminotransferase
cHL	classical Hodgkin lymphoma
CI	confidence interval
ECOG	Eastern Cooperative Oncology Group
gastric cancer	gastric cancer and gastroesophageal junction cancer
ILD	interstitial lung disease
ITT	intent-to-treat
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Gastric Cancer
NSCLC	non-small cell lung cancer
OS	overall survival
Partial change application	application for partial change approval
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PMDA	Pharmaceuticals and Medical Devices Agency
PS	performance status
RCC	renal cell carcinoma
Study 017	Study CA209017
Study 025	Study ONO-4538-03/CA209025
Study 032	Study CA209032
Study 037	Study CA209037
Study 057	Study CA209057
Study 066	Study CA209066
Study 12	Study ONO-4538-12
Study 15	Study ONO-4538-15
Study 141	Study ONO-4538-11/CA209141
Study 205	Study CA209205

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, “unresectable, advanced or recurrent non-small cell lung cancer” in December 2015, “unresectable or metastatic renal cell carcinoma” in August 2016, and “relapsed or refractory classical Hodgkin lymphoma” in December 2016. After submission of the present application, the indications were expanded to include “recurrent or distant metastatic head and neck cancer” in March 2017.

1.2 Development history, etc.

As the clinical development program of nivolumab for the treatment of gastric cancer, the applicant initiated a global phase III study in patients with unresectable advanced or recurrent gastric cancer who had received ≥ 2 chemotherapy regimens (Study ONO-4538-12 [Study 12]) in November 2014.

As of May 2017, nivolumab has not been approved in any country or region for the treatment of gastric cancer.

In Japan, patient enrollment in Study 12 started in November 2014.

The present partial change application for nivolumab has been filed for the additional indication of gastric cancer, based primarily on the results of Study 12.

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. The applicant submitted new clinical pharmacology data and discussed the differences in the pharmacokinetics of nivolumab between cancer types, etc. based on the data. PMDA concluded that the results of the applicant's discussion on the pharmacokinetics of nivolumab, submitted for the present application, are consistent with those reviewed for the initial or subsequent approvals.

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

The applicant submitted efficacy and safety evaluation data (a global phase III study) and reference data (a foreign phase I/II study) (Table 1).

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

Data type	Region	Study identifier	Phase	Subjects	N	Dosage regimen	Main endpoints
Evaluation data	Global	12	III	Patients with unresectable advanced or recurrent gastric cancer who have received ≥ 2 chemotherapy regimens	493* (a) 330 (b) 163	(a) Nivolumab 3 mg/kg intravenously administered every 2 weeks (b) Placebo intravenously administered every 2 weeks	Efficacy Safety
Reference data	Foreign	032	I/II	Gastric cancer cohort: Patients with unresectable advanced or recurrent gastric cancer	59*	Nivolumab 3 mg/kg intravenously administered every 2 weeks	Safety

* Number of patients randomized

A summary of the clinical studies is presented below. Major adverse events other than deaths reported in the studies are detailed in "7.3 Adverse events reported in clinical studies."

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 12, ongoing since November 2014 [data cutoff, August 13, 2016])

A double-blind, randomized, comparative study was conducted at 49 sites in 3 countries/regions, including Japan, to evaluate the efficacy and safety of nivolumab versus placebo in patients with unresectable advanced or recurrent gastric cancer who had received ≥ 2 chemotherapy regimens¹⁾ (target sample size, 290 to 480 subjects).

The patients received an intravenous dose of nivolumab 3 mg/kg or placebo every 2 weeks. The treatment was continued until disease progression was observed or a withdrawal criterion was met.

All 493 patients enrolled and randomized (330 in the nivolumab group and 163 in the placebo group) were included in the intention-to-treat (ITT) population and used for efficacy analyses. Of the 493 patients, 2 did not receive the study drug. The remaining 491 patients (330 in the nivolumab group and 161 in the placebo group) were included in the safety analysis population.

The primary endpoint was overall survival (OS). An interim analysis was planned to be conducted when 183 events (approximately 70% of 261 events, the original target number of events) have occurred, in order to allow early termination for futility or re-calculation of the target number of events.²⁾ The interim OS analysis was performed (data cutoff, ■■■, 20■■). Based on the analysis results, the independent data-monitoring committee recommended changing the target number of events required for the final analysis, from 261 to 328.

The final analysis of efficacy was performed (data cutoff, August 13, 2016). Shown below are the results of the final OS analysis (Table 2) and Kaplan-Meier curves of OS (Figure 1).

¹⁾ Patients with gastroesophageal junction cancer (adenocarcinoma with its center located within 5 cm proximal or distal to the anatomic gastroesophageal junction) were also eligible for the study.

²⁾ According to the methods proposed to control type I error probability for the re-estimation of the target sample size (*Stat Med.* 2011;30:3267-84, *Jpn J Biomet.* 2008;29:19-34), the criteria for futility and the criteria for sample size re-estimation were established based on the conditional power at the interim analysis.

Table 2. Final OS analysis (ITT population [data cutoff, August 13, 2016])

	Nivolumab (ONO-4538)	Placebo
N	330	163
Number of events (%)	226 (68.5)	141 (86.5)
Median [95% CI] (months)	5.26 [4.60, 6.37]	4.14 [3.42, 4.86]
Hazard ratio [95% CI]* ¹	0.63 [0.51, 0.78]	
P-value (1-sided)* ²	<0.0001	

*1, Cox regression stratified by country/region (Japan, South Korea, Taiwan), ECOG PS (0, 1), and the number of metastatic organs (≤ 1 , ≥ 2)

*2, Log-rank test stratified by country/region (Japan, South Korea, Taiwan), ECOG PS (0, 1), and the number of metastatic organs (≤ 1 , ≥ 2), with a 1-sided significance level of 0.025

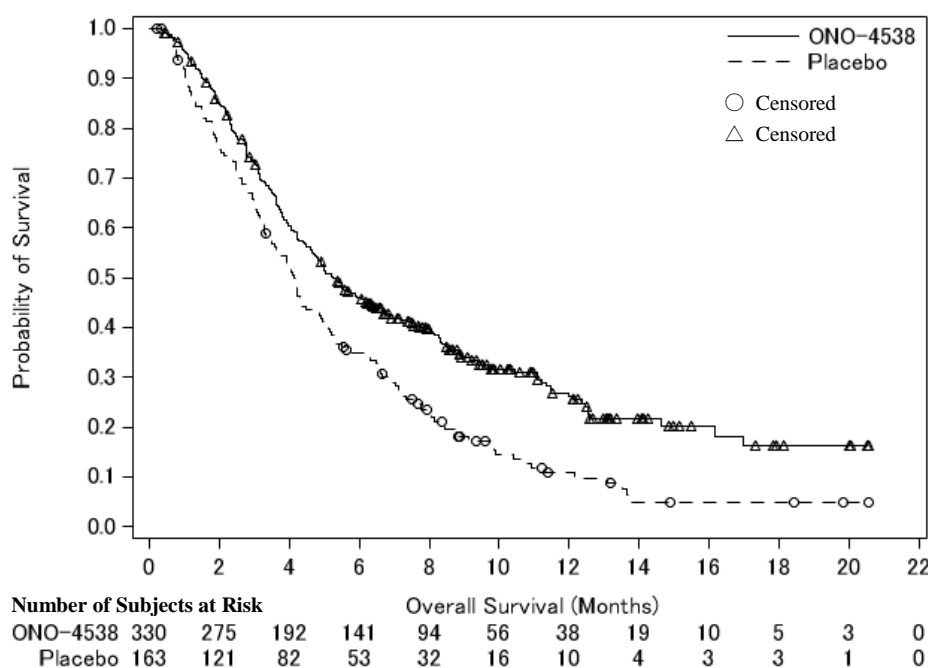


Figure 1. Kaplan-Meier curves for final OS analysis (ITT population [data cutoff, August 13, 2016])

Safety analysis revealed that 25 of 330 patients (7.6%) died in the nivolumab group and 32 of 161 patients (19.9%) died in the placebo group during the treatment period or within 28 days after the last dose. Disease progression was the most common cause of death (19 patients in the nivolumab group and 30 patients in the placebo group). Other causes in the nivolumab group were cardiac arrest, sudden death, death, pneumonia, completed suicide, and dyspnoea exertional (1 patient each), and those in the placebo group were sudden death and sepsis (1 patient each). A causal relationship to the study drug could not be ruled out for the cardiac arrest, death, pneumonia, and dyspnoea exertional (1 patient each) in the nivolumab group, and the sudden death (1 patient) in the placebo group.

7.2 Reference data

7.2.1 Foreign clinical study

7.2.1.1 Foreign phase I/II study (CTD 5.3.5.2-1, gastric cancer cohort of Study 32, ongoing since 2016 [data cutoff, 2016])

An open-label study was conducted at 18 sites outside Japan to evaluate the safety and other aspects of nivolumab in patients with unresectable advanced or recurrent gastric cancer³⁾ (target sample size, 18 to 100 subjects).

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

All 59 patients enrolled and treated with nivolumab were included in the safety analysis population.

Of the 59 patients, 9 (15.3%) died during the treatment period or within 30 days after the last dose. The deaths of the 9 patients were due to disease progression and unrelated to nivolumab.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

As a result of its review summarized below, PMDA concluded that nivolumab has demonstrated efficacy in patients with unresectable advanced or recurrent gastric cancer who have received ≥ 2 chemotherapy regimens.

7.R.1.1 Control group, efficacy endpoints, and evaluation results

The applicant's explanation about Study 12:

When Study 12 was planned, there were no established standard treatments for the target patient population; therefore, placebo was used as a control. Study 12 demonstrated the superiority of nivolumab to placebo in OS [see Section 7.1.1.1]. Shown below are the results of the final OS analysis (Table 3) and Kaplan-Meier curves of OS (Figure 2) in Japanese patients in Study 12.

Table 3. Final OS analysis in Japanese patients (data cutoff, August 13, 2016)

	Nivolumab (ONO-4538)	Placebo
N	152	74
Number of deaths (%)	107 (70.4)	63 (85.1)
Median [95% CI] (months)	5.42 [4.60, 7.39]	3.58 [2.76, 4.96]
Hazard ratio [95% CI]* ¹		0.59 [0.43, 0.81]

* Cox regression stratified by ECOG PS (0, 1) and the number of metastatic organs (≤ 1 , ≥ 2)

³⁾ Patients with gastroesophageal junction cancer (adenocarcinoma of with its center located in the distal esophagus) were also eligible for the study.

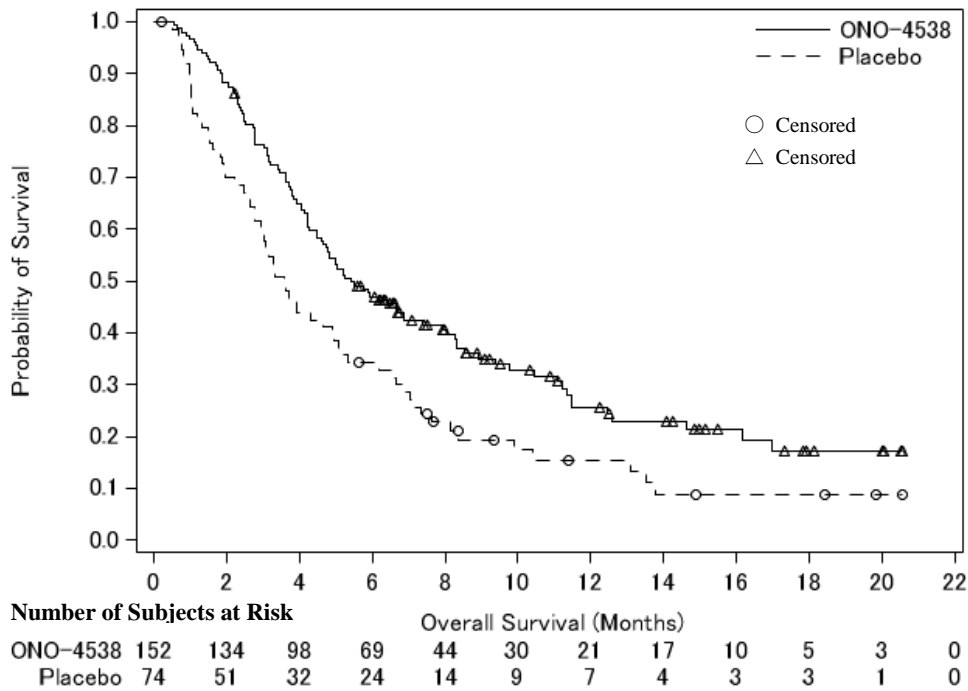


Figure 2. Kaplan-Meier curves for final OS analysis in Japanese patients (data cutoff, August 13, 2016)

PMDA concluded that the above results demonstrated the efficacy of nivolumab in the population of Study 12.

7.R.2 Safety [for adverse events, see “7.3 Adverse events reported in clinical studies”]

PMDA’s view:

Special attention should be paid to the following adverse events when administering nivolumab to patients with unresectable advanced or recurrent gastric 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 and 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 February 22, 2017,” “Package Insert for Opdivo Intravenous Infusion,” etc.). These adverse events should be carefully monitored in patients receiving nivolumab for unresectable advanced or recurrent gastric 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 gastric 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 12: Table 4 shows the safety summary of Study 12.

Table 4. Safety summary (Study 12)

	n (%)	
	Nivolumab N = 330	Placebo N = 161
All adverse events	300 (90.9)	135 (83.9)
Grade ≥ 3 adverse events	153 (46.4)	81 (50.3)
Adverse events resulting in death	35 (10.6)	25 (15.5)
Serious adverse events	131 (39.7)	75 (46.6)
Adverse events leading to drug discontinuation	23 (7.0)	12 (7.5)
Adverse events leading to drug interruption	63 (19.1)	27 (16.8)

Adverse events of any grade reported with a $\geq 5\%$ higher incidence in the nivolumab group than in the placebo group were nausea (19.7% [65 of 330 patients] in the nivolumab group, 14.3% [23 of 161 patients] in the placebo group), diarrhoea (17.6% [58 of 330 patients]; 9.3% [15 of 161 patients]), pruritus (16.1% [53 of 330 patients]; 9.3% [15 of 161 patients]), constipation (14.2% [47 of 330 patients]; 6.2% [10 of 161 patients]), rash (9.4% [31 of 330 patients]; 3.7% [6 of 161 patients]), and blood alkaline phosphatase increased (7.6% [25 of 330 patients]; 1.9% [3 of 161 patients]). The Grade ≥ 3 adverse events reported with a $\geq 2\%$ higher incidence in the nivolumab group than in the placebo group were hyponatraemia (3.3% [11 of 330 patients]; 1.2% [2 of 161 patients]). The serious adverse event with a $\geq 2\%$ higher incidence in the nivolumab group than in the placebo group was asthenia (2.7% [9 of 330 patients]; 0.6% [1 of 161 patients]). There were no adverse events leading to drug discontinuation or drug interruption with a $\geq 2\%$ higher incidence in the nivolumab group than in the placebo group.

The applicant explained the differences in the safety profile of nivolumab between patients treated for gastric cancer and those treated for the previously approved indications (malignant melanoma, non-small cell lung cancer [NSCLC], renal cell carcinoma [RCC], classical Hodgkin lymphoma [cHL], and head and neck cancer⁴).

The applicant's explanation:

The incidences of the adverse events reported in the nivolumab group of Study 12 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 malignant melanoma (Studies 066 and 037); (2) foreign phase III studies in patients with NSCLC (Studies 017 and 057); (3) a global phase III study in patients with RCC (Study 025); (4) a Japanese phase II study (Study 15) and a foreign phase II study (Study 205) in patients with cHL; and (5) a global phase III study in patients with head and neck cancer (Study 141). The results are shown in Table 5.

⁴ Approved as of March 24, 2017, after submission of the present application

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

	n (%)					
	Gastric cancer N = 330	Malignant melanoma N = 474	NSCLC N = 418	RCC N = 406	cHL N = 260	Head and neck cancer N = 236
All adverse events	300 (90.9)	458 (96.6)	407 (97.4)	397 (97.8)	257 (98.8)	232 (98.3)
Grade ≥ 3 adverse events	153 (46.4)	231 (48.7)	222 (53.1)	230 (56.7)	92 (35.4)	153 (64.8)
Adverse events resulting in death	35 (10.6)	44 (9.3)	65 (15.6)	23 (5.7)	5 (1.9)	55 (23.3)
Serious adverse events	131 (39.7)	220 (46.4)	195 (46.7)	194 (47.8)	61 (23.5)	132 (55.9)
Adverse events leading to drug discontinuation	23 (7.0)	53 (11.2)	62 (14.8)	72 (17.7)	18 (6.9)	55 (23.3)
Adverse events leading to drug interruption	63 (19.1)	158 (33.3)	118 (28.2)	177 (43.6)	94 (36.2)	68 (28.8)

The adverse event of any grade reported with a $\geq 5\%$ higher incidence in patients with gastric cancer than in any of the other patient populations was abdominal pain (gastric cancer, 21.2%; malignant melanoma, 13.7%; NSCLC, 5.3%; RCC, 8.9%; cHL, 10.0%; head and neck cancer, 3.8%). The Grade ≥ 3 adverse event reported with a $\geq 5\%$ higher incidence in patients with gastric cancer than in any of the other patient populations was anaemia (gastric cancer, 11.5%; malignant melanoma, 3.8%; NSCLC, 2.2%; RCC, 5.9%; cHL, 2.7%; head and neck cancer, 6.4%). No serious adverse events, adverse events resulting in death, or adverse events leading to drug discontinuation or drug interruption were reported with a $\geq 5\%$ higher incidence in patients with gastric cancer than in any of the other patient populations.

The following adverse events did not occur in clinical studies of the previously approved indications, but occurred at a $\geq 1\%$ incidence in the nivolumab group of Study 12: cholangitis (any grade) (1.8% [6 of 330 patients]), urinary tract disorder (any grade) (1.2% [4 of 330 patients]), and Grade ≥ 3 cholangitis (1.2% [4 of 330 patients]). A causal relationship to nivolumab was ruled out for all events, except for urinary tract disorder in 1 patient.

The above comparisons revealed no clear differences in the incidence of clinically notable adverse events (e.g., Grade ≥ 3 adverse events, serious adverse events) between patients treated for gastric cancer and those treated for the previously approved indications, although some adverse events occurred more frequently or were newly identified in patients with gastric cancer. Thus, the safety of nivolumab does not differ between patients treated for gastric cancer and those treated for the previously approved indications.

PMDA's view:

Some adverse events occurred more frequently in the nivolumab group than in the placebo group in Study 12, but all of them were known adverse events of nivolumab. Some adverse events developed more frequently in patients with gastric cancer than in other patient populations. In Study 12, however, the incidences of these events did not differ between the nivolumab and placebo groups, suggesting possible effects of the underlying illness or other factors. All adverse events newly identified in Study 12 were classified as "Grade ≤ 2 " or "unrelated to nivolumab." Considering these findings, PMDA concluded that the use of nivolumab for patients with gastric cancer would raise no new safety concerns, and that nivolumab was tolerable also in patients with gastric 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 12.

Table 6. Safety summary (Study 12)

	n (%)	
	Japanese N = 152	Non-Japanese N = 178
All adverse events	128 (84.2)	172 (96.6)
Grade ≥ 3 adverse events	46 (30.3)	107 (60.1)
Adverse events resulting in death	3 (2.0)	32 (18.0)
Serious adverse events	34 (22.4)	97 (54.5)
Adverse events leading to drug discontinuation	8 (5.3)	15 (8.4)
Adverse events leading to drug interruption	30 (19.7)	33 (18.5)

No adverse events were reported with a $\geq 10\%$ higher incidence in Japanese patients than in non-Japanese patients. No Grade ≥ 3 adverse events, adverse events resulting in death, serious adverse events, or adverse events leading to drug discontinuation or drug interruption were reported with a $\geq 3\%$ higher incidence in Japanese patients than in non-Japanese patients.

PMDA's conclusion:

Based on the above results, PMDA concluded that there are no adverse events requiring more attention in Japanese patients than in non-Japanese patients, and that nivolumab is tolerable in Japanese patients with gastric cancer as in non-Japanese patients.

7.R.3 Clinical positioning and indication

The proposed indication of nivolumab was "treatment of unresectable advanced or recurrent gastric cancer."

The following statements were included in the proposed "Precautions for Indications" section:

- 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 described in Sections "7.R.1 Efficacy," "7.R.2 Safety," and 7.R.3.1 to 7.R.3.3, PMDA concluded that the appropriate indication is "treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy," and that the precautionary statements below should be included in the "Precautions for Indications" section.

- The efficacy and safety of nivolumab as first- or second-line treatment have not been established.
- The efficacy and safety of nivolumab in adjuvant chemotherapy have not been established.

7.R.3.1 Clinical positioning and intended population

Currently, nivolumab therapy for gastric cancer is not mentioned in the Japanese or foreign clinical practice guidelines, or standard textbooks of clinical oncology in or outside Japan.

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

Nivolumab can be positioned as a therapeutic option for the population of Study 12, that is, patients with unresectable advanced or recurrent gastric cancer who have received ≥ 2 chemotherapy regimens. Study 12 enrolled patients with gastric cancer or gastroesophageal junction cancer. However, the 2 diseases need not be distinguished from each other in the "Indication" section, for the following reasons.

- A meta-analysis of clinical studies showed no differences in the efficacy of chemotherapy between gastric cancer and gastroesophageal junction cancer (*Ann Oncol.* 2009;20:885-91).
- The National Comprehensive Cancer Network Clinical Practice Guidelines (NCCN guidelines) (ver. 1. 2017) describe that gastric cancer and gastroesophageal junction cancer should be treated with the same chemotherapy regimens.

Nivolumab therapy is acceptable also to patients with 1 prior chemotherapy regimen, who were ineligible for Study 12, for the following reasons:

- In Study 032, nivolumab therapy was effective in 1 of 10 patients with gastric cancer who had received 1 prior chemotherapy regimen.
- The standard first-line treatment of gastric cancer is the combination therapy with a fluorinated pyrimidine and a platinum agent. Some patients, however, experience neuropathy associated with the therapy and, as a result, become intolerant of taxanes, the standard second-line treatment. Nivolumab is expected to provide a therapeutic option to such patients.

In consideration of the above-mentioned facts, the proposed indication was determined to be "treatment of unresectable advanced or recurrent gastric cancer." The characteristics of the patients enrolled in Study 12 are described in the "Clinical Studies" section of the package insert, and the following statements are included in the "Precautions for Indications" section.

- The efficacy and safety of nivolumab in chemotherapy-naïve patients 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.

PMDA's conclusion:

Nivolumab therapy cannot be recommended to patients with gastric cancer previously treated with only 1 chemotherapy regimen, because no clinical study results have shown the clinical usefulness of nivolumab in the population. The use of nivolumab should be limited to the population of Study 12, that is, patients with gastric cancer requiring third line or subsequent treatment. Therefore, the indication of nivolumab should be "treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy" to clearly state that the intended patient population of nivolumab is patients with gastric cancer that is

progressing after cancer chemotherapy, at least in the “Indications” section. The following statement should be included in the “Precautions for Indications” section.

- The efficacy and safety of nivolumab as first- or second-line treatment have not been established.

Another proposed statement, “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.” is not necessary, because it does not include information to be particularly specified or cautioned.

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 12, the PD-L1 expression levels in tumor samples were determined by the PD-L1 IHC 28-8 pharmDx “Dako” assay (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 tissues could be evaluated in 130 of 330 patients (39.4%) in the nivolumab group and 62 of 163 patients (38.0%) in the placebo group. Table 7 and Figure 3 show the OS in these patients by PD-L1 expression status (cutoff value, 1%) (data cutoff, August 13, 2016). In both subgroups with <1% PD-L1 expression and ≥1% PD-L1 expression, patients receiving nivolumab showed a prolonged OS as compared with those receiving placebo. Nivolumab is thus effective regardless of PD-L1 expression status.

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

PD-L1	Treatment group	N	OS		P value for interaction
			Median [95% CI] (months)	Hazard ratio* [95% CI]	
< 1%	Nivolumab	114	6.05 [4.83, 8.54]	0.72 [0.49, 1.05]	0.5784
	Placebo	52	4.19 [3.02, 6.93]		
≥ 1%	Nivolumab	16	5.22 [2.79, 9.36]	0.51 [0.21, 1.25]	
	Placebo	10	3.83 [0.79, 4.96]		

* Non-stratified Cox regression

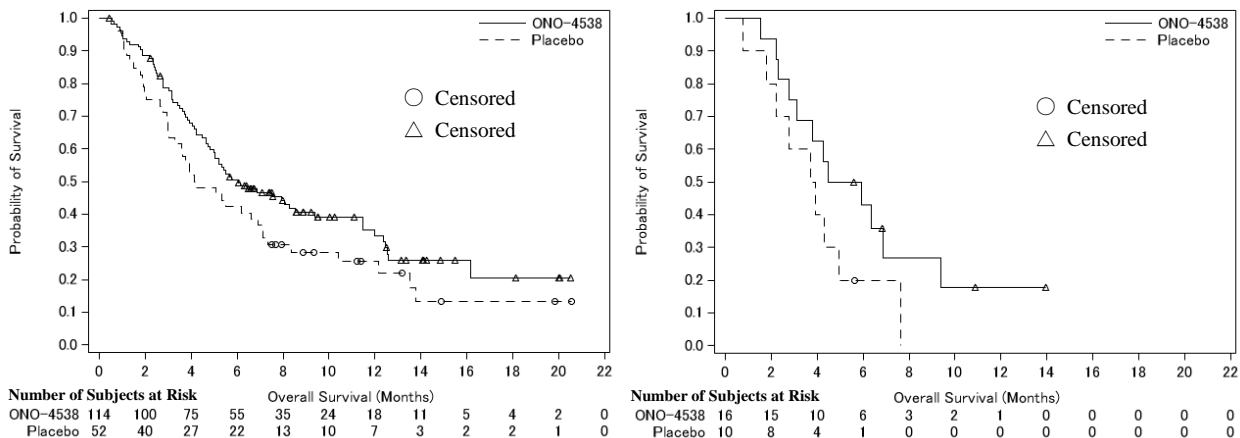


Figure 3. Kaplan-Meier curves of OS by PD-L1 expression status (left, PD-L1 expression <1%; right, PD-L1 expression ≥1%)

(b) Safety

In the subgroup with <1% PD-L1 expression, the incidences of adverse events were 93.0% (any grade) and 39.5% (Grade ≥3) in patients receiving nivolumab and 84.3% (any grade) and 47.1% (Grade ≥3) in patients receiving placebo. In the subgroup with ≥1% PD-L1 expression, the incidences of adverse events were 75.0% (any grade) and 31.3% (Grade ≥3) in patients receiving nivolumab and 90.0% (any grade) and 60.0% (Grade ≥3) in patients receiving placebo.

Although the results should be carefully interpreted because of the small number of patients with <1% PD-L1 expression, the incidence of adverse events did not tend to increase with nivolumab as compared with placebo in either subgroup (<1% or ≥1% PD-L1 expression). This indicates that nivolumab is tolerable regardless of PD-L1 expression status.

The investigations in (a) and (b) above suggest that nivolumab is expected to be effective and tolerable, regardless of PD-L1 expression status, in patients with gastric cancer.

PMDA’s conclusion:

The applicant’s explanation is acceptable. However, 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 study 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 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 its review described in Sections “7.R.1 Efficacy,” “7.R.2 Safety,” and 7.R.4.1, PMDA concluded that the proposed dosage and administration are acceptable and that the proposed precautionary statements should be included in the “Precautions for Dosage and Administration” section.

7.R.4.1 Dosage and administration of nivolumab

The applicant’s rationale for the dosage and administration of nivolumab selected for patients with unresectable advanced or recurrent gastric cancer:

In Study 12, a dosing regimen of 3 mg/kg every 2 weeks was selected based on data including 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 study demonstrated the clinical usefulness of nivolumab 3 mg/kg every 2 weeks in patients with unresectable advanced or recurrent gastric cancer. The dosage and administration, and the “Precautions for Dosage and Administration” section were proposed based on the dosing regimen employed in Study 12.

PMDA accepted the applicant’s explanation.

7.R.5 Post-marketing investigations

The applicant’s explanation on the proposed post-marketing surveillance plan:

The applicant plans to conduct post-marketing surveillance covering patients receiving nivolumab for the treatment of unresectable advanced or recurrent gastric 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 12 was comparable with the safety profile found with the previously approved indications [see Section 7.R.2.1]. In addition, a certain amount of post-marketing safety information has been collected from patients treated for the previously approved indications. In view of these facts, the post-marketing surveillance in patients with gastric cancer was designed to collect information about all adverse events occurring in clinical practice without selecting particular safety specifications.

The proposed target sample size is 500. This number was selected based on the comparability of the safety profile between the post-marketing surveillance and Study 12. Most of the adverse events occurring in Study 12 can be collected with this sample size.

The proposed observation period is 12 months, for the following reasons: (a) Most adverse events occurred within 12 months after the start of treatment in Study 12. (b) In Study 12, the first episodes of most adverse events developed within 3 months of treatment, but some events occurred for the first time after 9 months of treatment. (c) No adverse events tended to occur more frequently with longer duration of treatment.

PMDA's view:

Since the launch of nivolumab in Japan, various adverse drug reactions that may be attributed to excessive immunological reactions associated with the activation of T cells (the mode of action of nivolumab) have been reported. Alerts against some of the reactions have been issued through the package insert or other materials. The final analysis results of the ongoing post-marketing surveillance of the previously approved indications have not yet been obtained. Therefore, post-marketing surveillance should be conducted in patients with unresectable advanced or recurrent gastric cancer, to evaluate the safety and other aspects of nivolumab and collect information from the population.

PMDA accepts (a) the proposed strategy of collecting information on all adverse events occurring in clinical practice without setting particular safety specifications and (b) the proposed target sample size. An observation period of 6 months may be another option, considering the occurrence of adverse events in Study 12.

7.3 Adverse events reported in clinical studies

Among the clinical study data submitted for safety evaluation, data on death are presented in “7.1 Evaluation data” and “7.2 Reference data.” Other major adverse events are presented in the following.

7.3.1 Global phase III study (Study 12)

Adverse events were reported in 300 of 330 patients (90.9%) in the nivolumab group and 135 of 161 patients (83.9%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 141 of 330 patients (42.7%) in the nivolumab group and 43 of 161 patients (26.7%) in the placebo group. Table 8 shows adverse events occurring at a $\geq 10\%$ incidence in either treatment group.

Table 8. Adverse events occurring at a $\geq 10\%$ incidence in either treatment group

System Organ Class Preferred Term (MedDRA/J ver.19.0)	n (%)			
	Nivolumab N = 330		Placebo N = 161	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
All adverse events	300 (90.9)	153 (46.4)	135 (83.9)	81 (50.3)
Blood and lymphatic system disorders				
Anaemia	43 (13.0)	38 (11.5)	23 (14.3)	19 (11.8)
Gastrointestinal disorders				
Abdominal pain	70 (21.2)	14 (4.2)	39 (24.2)	6 (3.7)
Constipation	47 (14.2)	1 (0.3)	10 (6.2)	0
Diarrhoea	58 (17.6)	4 (1.2)	15 (9.3)	1 (0.6)
Nausea	65 (19.7)	1 (0.3)	23 (14.3)	2 (1.2)
Vomiting	45 (13.6)	4 (1.2)	18 (11.2)	3 (1.9)
General disorders and administration site conditions				
Fatigue	32 (9.7)	3 (0.9)	28 (17.4)	5 (3.1)
Pyrexia	34 (10.3)	3 (0.9)	19 (11.8)	1 (0.6)
Investigations				
AST increased	33 (10.0)	12 (3.6)	11 (6.8)	4 (2.5)
Metabolism and nutrition disorders				
Decreased appetite	65 (19.7)	9 (2.7)	44 (27.3)	8 (5.0)
Skin and subcutaneous tissue disorders				
Pruritus	53 (16.1)	0	15 (9.3)	0

Serious adverse events were reported in 131 of 330 patients (39.7%) in the nivolumab group and 75 of 161 patients (46.6%) in the placebo group. The serious adverse events reported in ≥ 3 patients in the nivolumab group were malignant neoplasm progression in 24 patients (7.3%); asthenia in 9 patients (2.7%); ileus in 7 patients (2.1%); abdominal pain, cholangitis, and pneumonia in 6 patients (1.8%) each; blood bilirubin increased and decreased appetite in 4 patients (1.2%) each; and anaemia, vomiting, pyrexia, jaundice cholestatic, back pain, dyspnoea, and ILD in 3 patients (0.9%) each. The serious adverse events reported in ≥ 3 patients in the placebo group were malignant neoplasm progression in 13 patients (8.1%); abdominal pain in 6 patients (3.7%); pneumonia and pleural effusion in 5 patients (3.1%) each; ileus in 4 patients (2.5%); and decreased appetite, fatigue, hydronephrosis, and sepsis in 3 patients (1.9%) each. A causal relationship to the study drug could not be ruled out for the following serious adverse events: ILD in 3 patients, pyrexia and pneumonia in 2 patients each, and asthenia, abdominal pain, vomiting, blood bilirubin increased, decreased appetite, and dyspnoea in 1 patient each in the nivolumab group; and pneumonia and fatigue in 1 patient each in the placebo group.

Adverse events leading to drug discontinuation were reported in 23 of 330 patients (7.0%) in the nivolumab group and 12 of 161 patients (7.5%) in the placebo group. The following adverse events led to drug discontinuation in ≥ 3 patients in either group: the nivolumab group, malignant neoplasm progression in 8 patients (2.4%), and blood bilirubin increased and ILD in 3 patients (0.9%) each; the placebo group, malignant neoplasm progression in 3 patients (1.9%). A causal relationship to the study drug could not be ruled out for the ILD in 3 patients in the nivolumab group.

7.3.2 Foreign phase I/II study (Study 032)

Adverse events were reported in 58 of 59 patients (98.3%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 41 of 59 patients (69.5%). Table 9 shows the adverse events with an incidence of $\geq 20\%$.

Table 9. Adverse events with a $\geq 20\%$ incidence

System Organ Class Preferred Term (MedDRA/J ver.18.1)	n (%) N = 59	
	All Grades	Grade ≥ 3
All adverse events	58 (98.3)	34 (57.6)
Blood and lymphatic system disorders		
Anaemia	17 (28.8)	5 (8.5)
Gastrointestinal disorders		
Abdominal pain	18 (30.5)	2 (3.4)
Constipation	16 (27.1)	0
Diarrhoea	16 (27.1)	3 (5.1)
Nausea	21 (35.6)	1 (1.7)
Vomiting	19 (32.3)	2 (3.4)
General disorders and administration site conditions		
Fatigue	32 (54.2)	5 (8.5)
Pyrexia	15 (25.4)	0
Metabolism and nutrition disorders		
Decreased appetite	21 (35.6)	3 (5.1)
Skin and subcutaneous tissue disorders		
Pruritus	12 (20.3)	0

Serious adverse events were reported in 31 of 59 patients (52.5%). The serious adverse events reported in ≥ 3 patients were malignant neoplasm progression in 10 patients (16.9%), dyspnoea in 5 patients (8.5%), and abdominal pain, pleural effusion, and anaemia in 3 patients (5.1%) each. A causal relationship to the study drug was ruled out for all events.

Adverse events leading to drug discontinuation were reported in 7 of 59 patients (11.9%); however, no adverse events led to drug discontinuation in ≥ 3 patients.

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

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

The 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 the 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 advanced or recurrent gastric cancer that has progressed after cancer chemotherapy and show

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 unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy. PMDA also considers that the indication 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)

August 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	December 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

PMDA's conclusion:

As a result of its 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 unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy. This conclusion is based on the results of a global phase III study (Study ONO-4538-12 [Study 12]), which demonstrated the superiority of nivolumab to placebo in overall survival (the primary endpoint) in patients with unresectable advanced or recurrent gastric cancer (including adenocarcinoma with its center located within 5 cm proximal and distal to the anatomic gastroesophageal junction) who had received ≥ 2 chemotherapy regimens.

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

1.2 Safety

PMDA's conclusion:

As a result of its 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 unresectable advanced or recurrent gastric cancer who have received prior cancer chemotherapy; these events were identified as requiring attention at the regulatory reviews for the previously approved indications: interstitial pneumonia (ILD), hepatic function disorder, abnormal thyroid function, infusion reaction, skin

disorder, colitis and 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.

Attention should be paid to the occurrence of the above adverse events; however, nivolumab is tolerable in patients with unresectable advanced or recurrent gastric cancer who have received prior cancer chemotherapy, 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.

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

1.3 Clinical positioning and indication

PMDA's conclusion:

As a result of its review described in "7.R.3 Clinical positioning and indication" of the Review Report (1), PMDA concluded that the indication of nivolumab should be "treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy," and that the following statements should be included in the "Precautions for Indications" section.

Precautions for Indications

- The efficacy and safety of nivolumab as first- or second-line treatment have not been established.
- The efficacy and safety of nivolumab as adjuvant chemotherapy have not been established.

Discussion at the Expert Discussion:

Some expert advisors supported the PMDA's conclusion, for example, because the intended patient population of nivolumab is better clarified by the description, "progressing after cancer chemotherapy," in the "Indications" section, while others made the following comments:

- Ramucirumab (genetical recombination) that has been approved for gastric cancer is indicated for "unresectable advanced/recurrent gastric cancer," and its package insert (the "Precautions for Indications" section) includes a precautionary statement to the effect that the efficacy and safety of ramucirumab as first-line chemotherapy have not been established. In this situation, "treatment of unresectable advanced or recurrent gastric cancer" is appropriate as the indication of nivolumab, as long as the "Precautions for Indications" section includes a precautionary statement to the effect that the efficacy and safety of nivolumab as first- or second-line treatment have not been established.

PMDA's conclusion:

At the Expert Discussion, some expert advisors objected to the PMDA's conclusion about the indication of nivolumab, while others supported the conclusion.

A global phase II/III study is currently ongoing to evaluate the efficacy and safety of nivolumab in chemotherapy-naïve patients with unresectable gastric cancer (Study ONO-4538-37). Nivolumab therapy should be introduced into clinical practice as the treatment of chemotherapy-naïve patients with unresectable gastric cancer, based on PMDA’s review, the results of Study ONO-4538-37, and other findings.

Based on the above review, PMDA has concluded that the appropriate indication of nivolumab is “treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy,” based on the PMDA’s discussion presented in “7.R.3 Clinical positioning and indication” of the Review Report (1).

PMDA instructed the applicant to include the indication and the statements for “Precautions for Indications” in the package insert. The applicant agreed.

1.4 Dosage and administration

PMDA’s conclusion as a result of its 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 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.

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

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 patients with unresectable advanced or recurrent gastric cancer who receive nivolumab, to evaluate the safety and other aspects of nivolumab in clinical practice. The target sample size is 500 patients. The proposed observation period is 12 months.

PMDA's conclusion as a result of its review described in "7.R.5 Post-marketing investigations" of the Review Report (1):

The applicant should conduct post-marketing surveillance covering patients with unresectable advanced or recurrent gastric cancer who receive nivolumab in clinical practice, to evaluate the safety and other aspects of nivolumab and collect further information.

PMDA's conclusion regarding the plan for the post-marketing surveillance:

- PMDA accepts (a) the proposed strategy of collecting information on all adverse events occurring in clinical practice without setting particular safety specifications and (b) the proposed target sample size.
- An observation period of 6 months may be another option, considering the occurrence of adverse events in Study 12.

These conclusions were supported by the expert advisors at the Expert Discussion.

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 occurrence of adverse events in Study 12.

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 10, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 11.

Table 10. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
<ul style="list-style-type: none"> • ILD • Myasthenia gravis, myocarditis, myositis, 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 	<ul style="list-style-type: none"> • Excessive immune response • Embryonic/fetal toxicity • Cardiac disorder (e.g., atrial fibrillation, bradycardia, ventricular extrasystoles) • Haemolytic anaemia 	<ul style="list-style-type: none"> • None
Efficacy specification (relating to the present partial change application)		
<ul style="list-style-type: none"> • <u>Efficacy in the treatment of patients with unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy in clinical practice</u> 		

Table 11. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
<ul style="list-style-type: none"> • Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Specified use-results survey in patients with unresectable, advanced or recurrent NSCLC (all-case surveillance) • Specified use-results survey in patients with unresectable or metastatic RCC (all-case surveillance) • Specified use-results survey in patients with relapsed or refractory cHL (all-case surveillance) • Use-results survey in patients with recurrent or distant metastatic head and neck cancer (all-case surveillance) • <u>Use-results survey in patients with unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy</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) • <u>Post-marketing clinical study in patients with unresectable advanced or recurrent gastric cancer who have received ≥ 2 chemotherapy regimens (extension study of Study 12)</u> 	<ul style="list-style-type: none"> • <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 12. Outline of use-results survey (draft)

Objective	To evaluate the safety etc. of nivolumab in clinical practice after the market launch
Survey method	Central registration system
Population	Patients with unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy
Observation period	6 months
Planned sample size	500 patients
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. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA has concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-1.1) 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. The clinical studies were generally performed in accordance with GCP. PMDA thus 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

- Protocol deviation (The study site did not comply with requirements for reporting of serious adverse events.)

3. 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 condition 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. Double-underline denotes additions made as of March 24, 2017 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

6. Treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy

Dosage and Administration (Single underline denotes new additions. Double-underline denotes additions made as of March 24, 2017 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, recurrent or distant metastatic head and neck cancer, and unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy

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

Condition of Approval

The applicant should formulate and properly implement a risk management plan.

Warnings (No change)

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

Contraindication (No change)

Patients with a history of hypersensitivity to the ingredients of Opdivo

Precautions for Indications (Single underline denotes new additions. Crossed-out words are deleted. Double underline denotes additions made as of March 24, 2017 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.
- (2) The efficacy and safety of Opdivo have not been established in chemotherapy-naïve patients with unresectable or metastatic renal cell carcinoma or patients with unresectable or metastatic renal cell carcinoma who have received cytokine therapy as the only prior treatment.
- (3) The efficacy and safety of Opdivo have not been established in platinum-based chemotherapy-naïve patients with recurrent or distant metastatic head and neck cancer.
- (4) The efficacy and safety of Opdivo have not been established in first- or second-line treatment of unresectable advanced or recurrent gastric cancer that has progressed after cancer chemotherapy.
- (45) The efficacy and safety of Opdivo in adjuvant chemotherapy have not been established.
- (56) When Opdivo is used in the treatment of malignant melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, or head and neck cancer, eligible patients must be selected based on a careful review of the content of the “Clinical Studies” section and a thorough understanding of the efficacy and safety of Opdivo.

Precautions for Dosage and Administration (Single underline denotes new additions. Crossed-out words are deleted. Double-underline denotes additions made as of March 24, 2017 after submission of the present application.)

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