Report on the Deliberation Results

December 7, 2015

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

[Brand name]	Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg
[Non-proprietary name]	Nivolumab (Genetical Recombination) (JAN*)
[Applicant]	Ono Pharmaceutical Co., Ltd.
[Date of application]	July 21, 2015

[Results of deliberation]

In the meeting held on November 30, 2015, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the product is 5 years 10 months.

[Conditions for 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 to compile the safety and efficacy data of the product in the early post-marketing period, thereby taking necessary measures to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

November 18, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[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 21, 2015
[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, (6) Drug with new dosage and administration

[Items warranting special mention]
Priority Review (Notification No.0818-4 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 18, 2015)

[Reviewing office] Office of New Drug V

Review Results

November 18, 2015

[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 21, 2015

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of unresectable, advanced or recurrent non-small cell lung cancer has been demonstrated and its safety is acceptable in view of its observed benefits. Interstitial lung disease, hepatic function disorder, abnormal thyroid function, infusion reaction, skin disorder, colitis, severe diarrhoea, myasthenia gravis, myositis, neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, and encephalitis should be further investigated via post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indications and dosage and administration as shown below, with the following conditions.

[Indications]

1. Treatment of unresectable malignant melanoma
2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer

(Underline denotes addition)

[Dosage and administration]

1. Treatment of unresectable malignant melanoma
   The usual adult dosage of Nivolumab (Genetical Recombination) is 2 mg/kg body weight, administered as an intravenous infusion every 3 weeks.
2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer
   The usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks.

(Underline denotes addition)

[Conditions for 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.

Review Report (1)

October 2, 2015

I. Product Submitted for Registration

[Brand name] Opdivo Intravenous Infusion 20 mg,
Opdivo Intravenous Infusion 100 mg

[Non-proprietary name] Nivolumab (Genetical Recombination)

[Name of applicant] Ono Pharmaceutical Co., Ltd.

[Date of application] July 21, 2015

[Dosage form/Strength] Injection: Each vial of 2 mL contains 20 mg of Nivolumab (Genetical Recombination). Each vial of 10 mL contains 100 mg of Nivolumab (Genetical Recombination).

[Proposed indication]

1. Treatment of unresectable malignant melanoma
2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer

(Underline denotes addition)

[Proposed dosage and administration]

1. Treatment of unresectable malignant melanoma
   The usual adult dosage of Nivolumab (Genetical Recombination) is 2 mg/kg body weight, administered as an intravenous infusion every 3 weeks.
2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer
   The usual adult dosage of Nivolumab (Genetical Recombination) is 3 mg/kg body weight, administered as an intravenous infusion every 2 weeks.

(Underline denotes addition)

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are shown below.

The results of pharmacology studies, pharmacodynamic studies, and toxicology studies had been submitted for the initial application for approval [see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014"] and they are not included in "Non-clinical data" in this application for the new indication and dosage and administration.

1. Origin or history of discovery and usage conditions in foreign countries, etc.

1.(1) Summary of the proposed product

CD279 (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 (CD274 [programmed cell death ligand 1, PD-L1] and CD273 [programmed cell death ligand 2, 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 the 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.

1.(2) Development history, etc.

Outside Japan, as part of the clinical development programs for nivolumab, BMS conducted phase III studies involving patients with non-small cell lung cancer (NSCLC) who had received prior platinum-based chemotherapy. Study CA209017 enrolling patients with advanced or recurrent squamous (SQ) NSCLC began in October 2012, and Study CA209057 enrolling those with advanced or recurrent non-squamous (NSQ) NSCLC in November 2012. The applications for the approval of nivolumab for SQ-NSCLC were filed in the US in February 2015 and in the EU in September 2014, based on the results of the pivotal Study CA209017. Nivolumab was first approved for the indication "for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy" in the US in March 2015. Then, it was approved "for the treatment of locally advanced or recurrent squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults" in the EU in July 2015. The applications for the approval of nivolumab for NSQ-NSCLC were filed in both the US and EU in July 2015 based on the results of the pivotal Study CA209057 and they are currently under review.

As of August 2015, nivolumab has been approved in 34 countries or regions for the indication of SQ-NSCLC. It has not been approved in any countries or regions for the indication of NSQ-NSCLC.

In Japan, the applicant started phase II studies involving patients who had received prior platinum-based chemotherapy. Study ONO-4538-05 enrolling patients with advanced or recurrent SQ-NSCLC began in May 2013, and Study ONO-4538-06 enrolling those with advanced or recurrent NSQ-NSCLC in April 2013.

This partial change application for nivolumab has been filed for the additional indication and dosage and administration for the treatment of NSCLC, based on the results of the pivotal Studies CA209017 and CA209057.

2. Non-clinical data

Summary of pharmacology studies

No new study data were submitted for this partial change application for nivolumab. The applicant explained the efficacy of nivolumab in the treatment of non-small cell lung cancer (NSCLC) based primarily on the data submitted for the initial application for nivolumab.

The applicant's explanation:

Nivolumab, a human monoclonal antibody against human CD279 (programmed cell death 1, PD-1), blocks the binding of the PD-1 ligands (CD274 [programmed cell death ligand 1, PD-L1] and CD273 [programmed cell death ligand 2, PD-L2]) to the PD-1 receptor. This enhances the proliferation and activation of cancer antigen-specific T cells and their cytotoxic activity against cancer cells, resulting in the suppression of tumor growth. Therefore, nivolumab is expected to be effective against tumors irrespective of the types of cancer.

While several reports on the expression of PD-1, PD-L1, and PD-L2 in human NSCLC tissue (e.g., *Br J Cancer*. 2015;112:95-102; *Clin Lung Cancer*. 2013;14: 157-63) are available, no definitive conclusions have been reached on relationships between the expression of PD-1, PD-L1, and PD-L2 and the efficacy of nivolumab.

PMDA's view:

The applicant's explanation on the efficacy of nivolumab against NSCLC is reasonable, in light of its mechanism of action. Investigations should be further conducted on the relationship between the expression of PD-1, PD-L1, or PD-L2 and the efficacy of nivolumab because such information is important for physicians to determine eligibility of individual patients for the use of nivolumab in clinical practice. Any new findings should be communicated to healthcare professionals in an appropriate manner.

3. Clinical data

3.(i) Summary of biopharmaceutic studies and associated analytical methods

3.(i).A Summary of the submitted data

Analytical methods

3.(i).A.(1) Assay of nivolumab (genetical recombination)

Nivolumab (genetical recombination) ("nivolumab") in human serum was quantified by (a) enzyme-linked immunosorbent assay (ELISA; assay codes, [redacted], [redacted]), (b) electrochemiluminescence immunoassay (ECLIA; assay code, [redacted]) [see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014"], or (c) ECLIA using solid-phased streptavidin and biotin-labeled anti-nivolumab antibodies and ruthenium-labeled anti-nivolumab antibodies (assay code, [redacted]; lower limit of quantification, 0.2 μg/mL). The change from [redacted] to [redacted] took place with the introduction of an automated sample pretreatment system. A partial validation confirmed that the introduction of the automated system had no impact on the quantification of nivolumab.

3.(i).A.(2) Anti-nivolumab antibody assay

Anti-nivolumab antibodies in human serum were quantified by ECLIA ([redacted] and [redacted]) using solid-phase bound streptavidin, biotin-labeled nivolumab, and ruthenium-labeled nivolumab. The change from [redacted] to [redacted] took place with a change in the batch of nivolumab used as ruthenium- or biotin-labeled nivolumab. A partial validation confirmed that this change had no impact on the quantification of anti-nivolumab antibodies.

[redacted]

The applicant's explanation on the effect of nivolumab on the quantification of anti-nivolumab antibodies in samples:

The upper limit of nivolumab concentration that had no influence on the anti-nivolumab antibody assay was 800 μg/mL. The maximum nivolumab serum concentrations as measured by anti-nivolumab antibody assays were 113 and 171 μg/mL in the Japanese phase II studies, Study ONO-4538-05 and Study ONO-4538-06, respectively; 120 μg/mL in the foreign phase II study, Study CA209063; and 121 and 150 μg/mL in the foreign phase III studies, Study CA209017 and Study CA209057, respectively. These results indicated that serum nivolumab was unlikely to affect anti-nivolumab antibody assays.

3.(ii) Summary of clinical pharmacology studies

3.(ii).A Summary of the submitted data

3.(ii).A.(1) Effects on QT/QTc intervals

The foreign phase II study (Study CA209010) was conducted in patients with advanced or recurrent renal cell carcinoma, to which nivolumab was administered intravenously at 0.3 to 10 mg/kg every 3

weeks. The effect of nivolumab on QT/QTc intervals was investigated based on the pharmacokinetic (PK) data from the study.

The QT interval corrected for heat rate by the Fridericia's correction formula (QTcF) was determined. A relationship between serum nivolumab concentration and the change from baseline in QTcF (ΔQTcF) was investigated using a linear mixed effect model. The result showed no clear correlation between serum nivolumab concentrations and ΔQTcF. Within the investigated dose range, QTcF of >480 msec or ΔQTcF of >60 msec was not observed in any subjects. At the C_{max} determined in Cycles 1 and 7 (mean; 200.69 and 353.36 μg/mL, respectively) during which nivolumab was administered intravenously at 10 mg/kg every 3 weeks, the ΔQTcF (90% confidence interval [CI]) was −1.7 [–0.7, 4.1] msec and –10.3 [–23.8, 3.3] msec, respectively.

Furthermore, in the foreign phase I study (Study CA209003), the mean C_{max} after the ninth dose was 134.6 μg/mL. A steady state was assumed to be reached after the ninth dose when nivolumab was administered intravenously at 3 mg/kg every 2 weeks [see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014"]. Also, the mean C_{max} was lower than those in Cycles 1 and 7 during which nivolumab was administered intravenously at 10 mg/kg every 3 weeks. On the basis of these results, the applicant stated that nivolumab is unlikely to have any clinically significant effect on QT/QTc intervals when administered intravenously at 3 mg/kg every 2 weeks.

3.(ii).A.(2) Population pharmacokinetic (PPK) analysis

Based on the PK data (8624 sampling time points in 1044 subjects) obtained from the Japanese phase I study (Study ONO-4538-01), Japanese phase II studies (Studies ONO-4538-02, ONO-4538-05, ONO-4538-06, and ONO-4538-08), foreign phase I studies (Studies CA209001 and CA209003), foreign phase II studies (Studies CA209010 and CA209063), and the foreign phase III study (Study CA209037), a population pharmacokinetic (PPK) analysis was conducted with a nonlinear mixed effect model (NONMEM version 7.1.2). The PK of nivolumab was described based on a two-compartment model.

Candidate covariates to evaluate their effects on the clearance (CL) of nivolumab were body weight, sex, race, lactic dehydrogenase (LDH), serum albumin, age, estimated glomerular filtration rate (eGFR), Eastern Cooperative Oncology Group Performance Status (ECOG PS), C-reactive protein (CRP), total lymphocyte count, liver function and cancer types based on the US National Cancer Institute (NCI) Organ Dysfunction Group classification. Body weight, sex, and race were also candidate covariates for the volume of distribution (V_1) of the central compartment of nivolumab.

Significant covariates selected for CL were body weight, serum albumin, CRP, and total lymphocyte count. Body weight was selected as the significant covariate for V_1.

The applicant's explanation on the analysis:

- The effects of body weight, serum albumin, CRP, and total lymphocyte count on the CL of nivolumab were within the inter-subject variability of CL (coefficient of variation, 41.2%). Thus, the effects of these covariates on PK of nivolumab are negligible.

- The estimated V_1 values for subjects with body weight of 49.1 kg (5th percentile), 76.5 kg (median), and 114.1 kg (95th percentile) were 2.89, 4.06, and 5.51 L, respectively. The effect of body weight on V_1 was greater than the inter-subject variability of V_1 (coefficient of variation, 28.0%). Because the estimated V_1 (4.06 L) is equivalent to human plasma volume (*Pharm Res*. 1993;10:1093-5), nivolumab is considered to be distributed mainly in plasma. Plasma volume would increase with body weight. These findings therefore indicates that the V_1 of nivolumab increases with increasing body weight.

3.(ii).A.(3) Relationship between nivolumab exposure and efficacy/safety

3.(ii).A.(3).1) Relationship between nivolumab exposure and efficacy

In the Japanese phase II studies (Studies ONO-4538-05 and ONO-4538-06), nivolumab was intravenously administered at 3 mg/kg every 2 weeks, and a logistic regression analysis was conducted to investigate the relationship between exposure to nivolumab (AUC, C_{max}, and C_{min}) and efficacy. The results of the analysis showed no clear relationship between exposure (AUC, C_{max}, and C_{min}) and efficacy.

3.(ii).A.(3).2) Relationship between nivolumab exposure and safety

In the Japanese phase II studies (Studies ONO-4538-05 and ONO-4538-06), nivolumab was intravenously administered at 3 mg/kg every 2 weeks. A logistic regression analysis was conducted to investigate relationships between exposure to nivolumab (AUC, C_{max}, and C_{min}) and (a) Grade ≥3 adverse events for which a causal relationship to nivolumab could not be ruled out, (b) adverse events leading to drug discontinuation or death, and (c) Grade ≥3 adverse events that were considered attributable to the immunomodulatory activity of nivolumab and thus its causal relationship to nivolumab could not be ruled out. The results of the analysis showed no clear relationship between nivolumab exposure (AUC, C_{max}, and C_{min}) and the onset of adverse events classified into (a), (b), or (c).

Accordingly, the applicant explained that there is no clear evidence of a relationship between nivolumab exposure and the efficacy and safety of nivolumab within the exposure levels achieved following intravenous dosing at 3 mg/kg every 2 weeks.

3.(ii).A.(4) Effects of anti-nivolumab antibodies on the PK of nivolumab

The expression of anti-nivolumab antibodies was investigated in the Japanese phase II studies (Studies ONO-4538-05 and ONO-4538-06), foreign phase II study (Study CA209063), and the foreign phase III studies (Studies CA209017 and CA209057). In these studies, nivolumab was intravenously administered at 3 mg/kg every 2 weeks. The results of the investigation are as follows:

- The number of subjects who were anti-nivolumab antibody-positive at ≥2 consecutive sampling time points ("persistent positive") was 0 of 35 subjects (0%) in Study ONO-4538-05, 1 of 76 subjects (1.3%) in Study ONO-4538-06, 0 of 101 subjects (0%) in Study CA209063, 1 of 109 subjects (0.9%) in Study CA209017, and 0 of 251 subjects (0%) in Study CA209057.
- The number of subjects who were anti-nivolumab antibody-positive only at the final sampling time point ("only the last sample positive") was 0 of 35 subjects (0%) in Study ONO-4538-05, 2 of 76 subjects (2.6%) in Study ONO-4538-06, 6 of 101 subjects (5.9%) in Study CA209063, 4 of 109 subjects (3.7%) in Study CA209017, and 12 of 251 subjects (4.8%) in Study CA209057.
- The number of subjects who were anti-nivolumab antibody-positive other than persistent-positive or only-the-last-sample-positive subjects was 8 of 35 subjects (22.9%) in Study ONO-4538-05, 5 of 76 subjects (6.6%) in Study ONO-4538-06, 6 of 101 subjects (5.9%) in Study CA209063, 16 of 109 subjects (14.7%) in Study CA209017, and 31 of 251 subjects (12.4%) in Study CA209057.
- The number of subjects who were anti-nivolumab neutralizing antibody-positive was 1 of 35 subjects (2.9%) in Study ONO-4538-05, 0 of 76 subjects (0%) in Study ONO-4538-06, 0 of 101 subjects (0%) in Study CA209063, 3 of 109 subjects (2.8%) in Study CA209017, and 3 of 251 subjects (1.2%) in Study CA209057.

Serum concentrations of nivolumab after the first dose were investigated in the Japanese phase II studies (Studies ONO-4538-05 and ONO-4538-06), foreign phase II study (Study CA209063), and the foreign phase III studies (Studies CA209017 and CA209057) (the table below). Serum concentrations of nivolumab tended to be low in subjects who were anti-nivolumab antibody-positive at a sampling time point, as compared with subjects who were anti-nivolumab antibody negative at a sampling time point. Nevertheless, the concentration distributions of the 2 groups almost overlapped, showing no apparent difference.

Serum concentrations of nivolumab in subjects receiving multiple doses of nivolumab at 3 mg/kg (μg/mL)

	n	Before the second dose	n	Before the eighth dose
Anti-nivolumab antibody-positive subjects*	90	17.2±8.09	5	42.4±34.4
Anti-nivolumab antibody-negative subjects	458	19.3±8.11	235	62.5±20.9

Mean ± standard deviation
* Subjects who were anti-nivolumab antibody positive before the second or eighth dose of nivolumab

The CL of nivolumab was estimated by the final model obtained by the PPK analysis based on data from the Japanese phase I study (Study ONO-4538-01), Japanese phase II studies (Studies ONO-4538-02, ONO-4538-05, ONO-4538-06, and ONO-4538-08), foreign phase II study (Study CA209063), and the foreign phase III study (Study CA209037) [see "3.(ii).A.(2) Population pharmacokinetic (PPK) analysis"], and the values were compared between anti-nivolumab antibody-positive subjects (subjects who were anti-nivolumab antibody-positive at least once after the administration of nivolumab) and anti-nivolumab antibody-negative subjects. While CL tended to be higher in anti-nivolumab antibody-positive subjects than in anti-nivolumab antibody-negative subjects, the concentration distributions of these 2 groups almost overlapped.

Based on the above, the applicant stated that there were no marked effects of anti-nivolumab antibodies on the PK of nivolumab.

3.(ii).B Outline of the review by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanations are acceptable in terms of the effects of nivolumab on QT/QTc intervals, PPK analysis, a relationship between nivolumab exposure and efficacy/safety, and the effects of anti-nivolumab antibodies on the PK of nivolumab.

3.(iii) Summary of clinical efficacy and safety

3.(iii).A Summary of the submitted data

The results from the following 9 studies were submitted as efficacy and safety evaluation data: 1 Japanese phase I study, 2 Japanese phase II studies, 2 foreign phase I studies, 2 foreign phase II studies, and 2 foreign phase III studies. The results from the Japanese phase I study (Study ONO-4538-01) and the foreign phase I studies (Studies CA209001 and CA209003) had been submitted for the initial application for approval of nivolumab and are not included in this report [see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014"].

Summary of clinical studies on safety and efficacy

Data type	Region	Study	Phase	Subjects	n	Summary of dosage and administration	Main endpoint
Evaluation	Japanese	ONO-4538-05	II	Patients with advanced or recurrent SQ-NSCLC who had received prior platinum-based chemotherapy	35	Nivolumab 3 mg/kg administered intravenously every 2 weeks	Efficacy Safety
		ONO-4538-06	II	Patients with advanced or recurrent NSQ-NSCLC who had received prior platinum-based chemotherapy	76	Nivolumab 3 mg/kg administered intravenously at every 2 weeks	Efficacy Safety
	Foreign	CA209010	II	Patients with advanced or recurrent renal cell carcinoma who had received prior anti-angiogenic therapy	167	Nivolumab 0.3, 2, or 10 mg/kg administered intravenously every 3 weeks	Safety
		CA209063	II	Patients with advanced or recurrent SQ-NSCLC who had received prior platinum-based chemotherapy	117	Nivolumab 3 mg/kg administered intravenously every 2 weeks	Efficacy Safety
		CA209017	III	Patients with advanced or recurrent SQ-NSCLC who had received prior platinum-based chemotherapy	272 (a) 135 (b) 137	(a) Nivolumab 3 mg/kg administered intravenously every 2 weeks (b) DOC 75 mg/m^2 administered intravenously every 3 weeks	Efficacy Safety

Data type	Region	Study	Phase	Subjects	n	Summary of dosage and administration	Main endpoint
		CA209057	III	Patients with advanced or recurrent NSQ-NSCLC who had received prior platinum-based chemotherapy	582 (a) 292 (b) 290	(a) Nivolumab 3 mg/kg administered intravenously every 2 weeks (b) DOC 75 mg/m^2 administered intravenously every 3 weeks	Efficacy Safety

SQ, squamous; NSQ, non-squamous; NSCLC, non-small cell lung cancer; DOC, docetaxel hydrate

Each clinical study is summarized below.

The major adverse events other than death reported in each clinical study are detailed in "3.(iv) Adverse events observed in clinical studies," and the PK data are presented in "3.(i) Summary of biopharmaceutic studies and associated analytical procedures" and "3.(ii) Summary of clinical pharmacology studies."

Evaluation data

3.(iii).A.(1) Japanese clinical studies

3.(iii).A.(1).1) Japanese phase II study (5.3.5.2-1, Study ONO-4538-05 [ongoing from April 2013; data cut-off, [redacted], 20[redacted])

An open-label, uncontrolled study was conducted at 19 sites in Japan to investigate the efficacy and safety of nivolumab in patients with advanced or recurrent squamous (SQ) non-small cell lung cancer (NSCLC) who had received prior platinum-based chemotherapy (target sample size, 35 subjects).

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

All of the 35 treated subjects were included in the full analysis set (FAS), which was defined as the efficacy analysis population. These subjects were also included in the safety analysis population.

Response rates* assessed centrally, the primary endpoint of the study, are shown in the table below.

* The threshold response rate was determined to be 9% by referring to the response rate for monotherapy with docetaxel hydrate (DOC) in a clinical study in patients with advanced or recurrent NSCLC who had received prior chemotherapy (*J Clin Oncol*. 2004;22-1589-97).

Best overall responses and response rates (RECIST ver.1.1, central review, FAS, n = 35)

Best overall response	n (%)
Complete response (CR)	0
Partial response (PR)	9 (25.7)
Stable disease (SD)	10 (28.6)
Progressive disease (PD)	16 (45.7)
Not evaluable (NE)	0
Response (CR+ PR) (Response rate [95%CI*] [%])	9 (25.7 [14.2, 42.1])

* Wilson's normal approximation

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

3.(iii).A.(1).2) Japanese phase II study (5.3.5.2-2, Study ONO-4538-06 [ongoing from March 2013; data cut-off, [redacted], 20[redacted])

An open-label, uncontrolled study was conducted at 19 site in Japan to investigate the efficacy and safety of nivolumab in patients with advanced or recurrent non-squamous (NSQ) NSCLC who had received prior platinum-based chemotherapy (target sample size, 75 subjects).

Subjects received nivolumab intravenously at a dose of 3 mg/kg every 2 weeks. The treatment was continued until disease progression was observed or until a withdrawal criterion was met.

All of the 76 randomized and treated subjects were included in the full analysis set (FAS), which was defined as the efficacy analysis population. These subjects were also included in the safety analysis population.

Response rates* assessed centrally, the primary endpoint of the study, are shown in the table below.

* The threshold response rate was determined to be 9% by referring to the response rate for DOC monotherapy in a clinical study in patients with advanced or recurrent NSCLC who had received prior chemotherapy (*J Clin Oncol*. 2004;22-1589-97).

Best overall responses and response rates (RECIST ver.1.1, central review, FAS, n = 76)

Best overall response	n (%)
Complete response (CR)	2 (2.6)
Partial response (PR)	13 (17.1)
Stable disease (SD)	21 (27.6)
Progressive disease (PD)	38 (50.0)
Not evaluable (NE)	2 (2.6)
Response (CR + PR)	15
(Response rate [95%CI*] [%])	(19.7 [12.3, 30.0])

* Wilson's normal approximation

Death occurred in 1 of 76 subjects (1.3%) during the treatment period or within 28 days after the last dose. The cause of the death was disease progression, and its causal relationship with nivolumab was ruled out.

3.(iii).A.(2) Foreign clinical studies

3.(iii).A.(2).1) Foreign phase II study (5.3.5.4-1, Study CA209010 [ongoing from May 2011; data cut-off, [redacted], 20[redacted])

A double-blind, randomized, comparative study was conducted at 39 sites overseas to investigate the safety and other profiles of nivolumab in patients with advanced or recurrent renal cell carcinoma who had received prior chemotherapy including anti-angiogenic therapy (target sample size, 150 subjects).

Subjects received nivolumab intravenously at 0.3, 2, or 10 mg/kg every 3 weeks. The treatment was continued until disease progression or until a withdrawal criterion was met.

A total of 198 subjects were enrolled in the study. Of these, 167 subjects (59 in the 0.3 mg/kg group, 54 in the 2 mg/kg group, and 54 in the 10 mg/kg group) were treated and included in the safety analysis population.

The safety analysis revealed that the following numbers of subjects died during the treatment period or within 30 days after the last dose: 5 of 59 subjects (8.5%) in the 0.3 mg/kg group, 3 of 54 subjects (5.6%) in the 2 mg/kg group, and 2 of 54 subjects (3.7%) in the 10 mg/kg group. Other than those who died of disease progression (5 subjects in the 0.3 mg/kg group, 3 subjects in the 2 mg/kg group, and 1 subject in the 10 mg/kg group), 1 subject in the 10 mg/kg group died due to multi-organ failure. A causal relationship to nivolumab was ruled out for the event.

3.(iii).A.(2).2) Foreign phase II study (5.3.5.2-3, Study CA209063 [ongoing from November 2012; data cut-off, [redacted], 20[redacted])

An open-label, uncontrolled study was conducted at 27 sites overseas to investigate the efficacy and safety of nivolumab in patients with advanced or recurrent SQ-NSCLC who had received prior platinum-based chemotherapy (target sample size, 100 subjects).

Subjects received nivolumab intravenously at 3 mg/kg every 2 weeks until disease progression or until a withdrawal criterion was met.

A total of 140 subjects were enrolled in the study. Of these, 117 subjects were treated and included in the efficacy and the safety analysis populations.

The response rates assessed by an independent review committee (IRC), the primary endpoint in the study, are shown in the table below.

Best overall responses and response rates (RECIST ver.1.1, IRC assessments, n = 117)

Best overall assessment	n (%)
Complete response (CR)	0
Partial response (PR)	17 (14.5)
Stable disease (SD)	30 (25.6)
Progressive disease (PD)	51 (43.6)
Not evaluable (NE)	19 (16.2)
Response (CR+ PR)	17
(Response rate [95%CI*] [%])	(14.5 [8.7, 22.2])

* Clopper-Pearson method

The safety analysis revealed that 14 of 117 subjects (12.0%) died during the treatment period or within 30 days after the last dose. Nine subjects died of disease progression. Other causes of deaths were hypoxic pneumonia, aortic aneurysm rupture, morphine intoxication, septic shock, and

pneumonia/respiratory failure (1 subject each). A causal relationship to nivolumab could not be ruled out for hypoxic pneumonia (1 subject).

3.(iii).A.(2).3) Foreign phase III study (5.3.5.1-1, Study CA209017 [ongoing from October 2012; data cut-off, [redacted], 20[redacted])

An open-label, randomized, comparative study was conducted at 95 sites overseas to investigate the efficacy and safety of nivolumab versus DOC in patients with advanced or recurrent SQ-NSCLC who had received prior platinum-based chemotherapy (target sample size, 272 subjects).

Subjects received either nivolumab intravenously at 3 mg/kg every 2 weeks or DOC intravenously at 75 mg/m^2 every 3 weeks. The treatment was continued until disease progression or until a withdrawal criterion was met.

A total of 272 subjects were randomized into either treatment group (135 in the nivolumab group and 137 in the DOC group), and all of them were included in the efficacy analysis population. A total of 260 subjects (131 in the nivolumab group and 129 in the DOC group) were included in the safety analysis population, and 12 subjects (4 in the nivolumab group and 8 in the DOC group) were excluded from the analysis because they did not receive the study drug.

At the beginning of the study, overall survival (OS) and response rate were selected as the primary endpoints. For adjustment of multiplicity associated with the use of 2 primary endpoints, a two-sided significance level of 4% was used for OS, and a two-sided significance level of 1% was used for response rate. Initially, the main analysis of response rates and an interim analysis of OS were planned to be conducted after 123 events (approximately 65% of the total events necessary for the final analysis of OS [189 events]) had been observed and after ≥6 months of follow-up had been completed for all subjects. If these analyses showed statistically significantly higher response rates in the nivolumab group than in the DOC group, with OS tending to be improving in the nivolumab group, the efficacy of nivolumab would be considered to have been demonstrated, and then the study would be terminated earlier. However, while Study CA209017 was being conducted, the final analysis of Study CA209003, one of the foreign phase I studies, revealed that the response rate of subjects with SQ-NSCLC decreased to 16.7% (9 of 54 subjects), which was 50.0% (3 of 6 subjects) when Study CA209017 began. [redacted] Moreover, the interim analysis for OS-related efficacy evaluation was rescheduled for when approximately 85% of the target number of OS events (196 events) occurred. For adjustment of the probability of a type I error

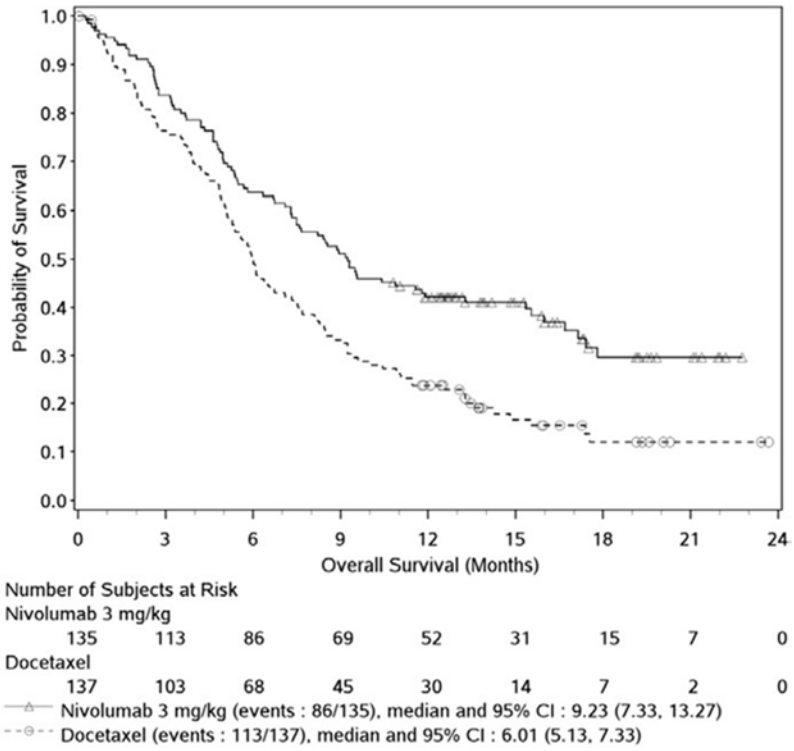
associated with the interim OS analysis, a Lan-DeMets alpha spending function of the O'Brien-Fleming type was used from the start of the study.

The results of the interim analysis of OS (the primary endpoint of the study) and their Kaplan-Meier curves are shown below.

Results of the interim OS analysis (efficacy analysis population; data cut-off [redacted], 20[redacted])

	Nivolumab	DOC
n	135	137
Number of deaths (%)	86 (63.7)	113 (82.5)
Median [95% CI] (months)	9.23 [7.33, 13.27]	6.01 [5.13, 7.33]
Hazard ratio [96.85% CI][*1]	0.59 [0.43, 0.81]	
P-value (two-sided)[*2]	0.0002	

[*1] Stratified Cox regression with region (North America, Europe, other) and prior treatment (paclitaxel, other antineoplastic drugs) as stratification factors; [*2] Stratified log-rank test with region (North America, Europe, other) and prior treatment (paclitaxel, other antineoplastic drugs) as stratification factors; significance level of 0.0315 (two-sided)



Kaplan-Meier curves for the results of the interim analysis of OS (efficacy analysis population; data cut-off, [redacted], 20[redacted])

The safety analysis revealed that 16 of 131 subjects (12.2%) died in the nivolumab group and 20 of 129 subjects (15.5%) in the DOC group during the treatment period or within 30 days after the last dose. The main cause of death was disease progression (12 subjects in the nivolumab group and 10 subjects in the DOC group). Other causes of deaths in the nivolumab group were cardio-respiratory arrest, recurrent stroke, massive haemoptysis, and unknown cause in 1 subject each; and those in the DOC group were respiratory failure, pulmonary haemorrhage, and pulmonary embolism in 2 subjects each,

and superior vena caval obstruction syndrome, interstitial lung disease, sepsis, and haemorrhagic cerebrovascular attack in 1 subject each. A causal relationship to nivolumab could not be ruled out for pulmonary haemorrhage, interstitial lung disease, and sepsis in 1 subject each in the DOC group.

3.(iii).A.(2).4) Foreign phase III study (5.3.5.1-2, Study CA209057 [ongoing from November 2012; data cut-off, [redacted], 20[redacted])

An open-label, randomized, comparative study was conducted at 112 sites overseas to investigate the efficacy and safety of nivolumab versus DOC in patients with advanced or recurrent NSQ-NSCLC who had received prior platinum-based chemotherapy (target sample size, 574 subjects).

Subjects received either nivolumab intravenously at 3 mg/kg every 2 weeks or DOC intravenously at 75 mg/m^2 every 3 weeks. The treatment was continued until disease progression or until a withdrawal criterion was met.

A total of 582 subjects were randomized into either treatment group (292 in the nivolumab group and 290 in the DOC group), and all of them were included in the efficacy analysis population. Except 27 subjects who did not receive the study drug (5 in the nivolumab group and 22 in the DOC group), 555 subjects (287 in the nivolumab group and 268 in the DOC group) were included in the safety analysis population.

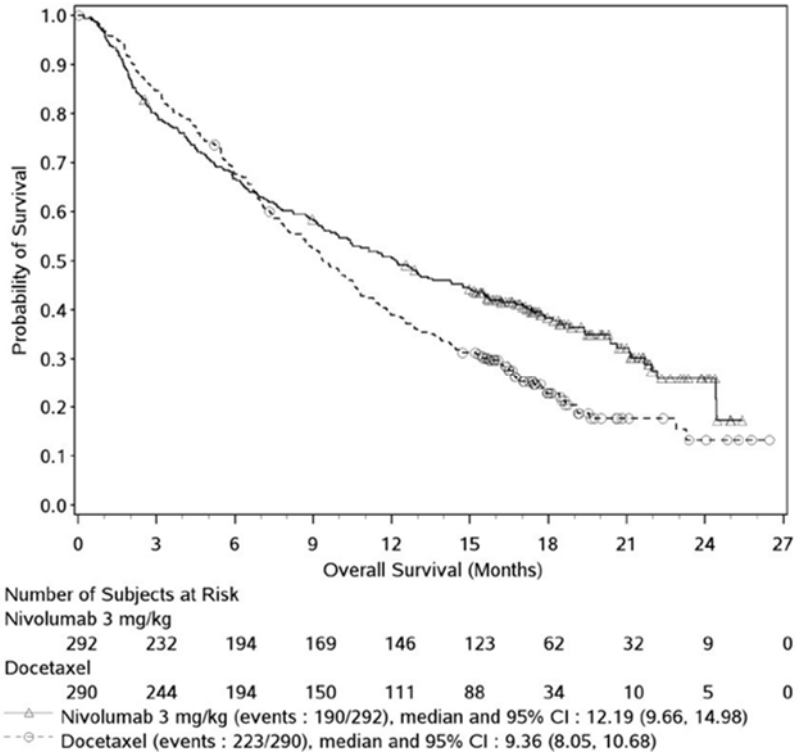
The primary endpoint of the study was OS. Initially, an interim analysis was planned to be conducted to evaluate efficacy after 262 events (approximately 65% of the target number of events [403 events]) had been observed. [redacted] For adjustment of the probability of a type I error associated with the interim analysis, a Lan-DeMets alpha spending function of the O'Brien-Fleming type was used beginning at the start of the study.

The results of the interim analysis of OS, the primary endpoint of the study, and their Kaplan-Meier curves are shown below.

Results of the interim OS analysis (efficacy analysis population; data cut-off [redacted], 20[redacted])

	Nivolumab	DOC
n	292	290
Number of deaths (%)	190 (65.1)	223 (76.9)
Median [95% CI] (months)	12.19 [9.66, 14.98]	9.36 [8.05, 10.68]
Hazard ratio [96.85% CI][*1]	0.73 [0.59, 0.89]	
p-value (two-sided)[*2]	0.0015	

[*1] Stratified Cox regression with or without prior maintenance treatment and the number of regimens of prior treatment (1, 2) as stratification factors; [*2] Stratified log-rank test with or without prior maintenance treatment and the number of regimens of prior treatment (1, 2) as stratification factors; significance level of 0.048 (two-sided).



Kaplan-Meier curves for the results of the interim OS analysis (efficacy analysis population; data cut-off, [redacted], 20[redacted])

The safety analysis revealed that 36 of 287 subjects died in the (12.5%) nivolumab group and 21 of 268 subjects (7.8%) in the DOC group during the treatment period or within 30 days after the last dose. The main cause of death was disease progression (27 subjects in the nivolumab group and 15 subjects in the DOC group). Other causes of deaths in the nivolumab group were pulmonary embolism in 2 subjects, and craniocerebral injury, dyspnoea, respiratory failure, multi-organ failure, cardiopulmonary failure, pneumonia, and unknown cause in 1 subject each. Those in the DOC group were febrile neutropenia, bilateral pneumonia, bronchitis, pneumonia, respiratory failure, and unknown cause in 1 subject each. A causal relationship to nivolumab could not be ruled out for febrile neutropenia in 1 subject in the DOC group.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Data for review

PMDA considered that Studies CA209017 and CA209057 had yielded the most important efficacy and safety data for nivolumab, and decided that the efficacy and safety of nivolumab be evaluated based primarily on data from the 2 studies. The former is a foreign phase III study conducted in patients with advanced or recurrent SQ-NSCLC, and the latter a foreign phase III study conducted in patients with advanced or recurrent NSQ-NSCLC. Patients who had received prior platinum-based chemotherapy were enrolled in either study.

The Japanese phase II studies, Studies ONO-4538-05 and ONO-4538-06, enrolled Japanese patients according to the inclusion and exclusion criteria that were similar to those used in of the foreign phase

III studies, Studies CA209017 and CA209057. The efficacy and safety of nivolumab in Japanese patients was therefore evaluated based primarily on data from Studies ONO-4538-05 and ONO-4538-06.

3.(iii).B.(2) Efficacy

Based on the review described below, PMDA concluded that the efficacy of nivolumab was demonstrated in patients with advanced or recurrent SQ-NSCLC or NSQ-NSCLC who had received prior platinum-based chemotherapy.

3.(iii).B.(2).1) Justification for choice of control group

The applicant's justification for the use of DOC as the control in Studies CA209017 and CA209057:

When the studies were designed, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer (NCCN Guidelines) recommended DOC or erlotinib hydrochloride (erlotinib) for the treatment of patients with advanced or recurrent SQ-NSCLC who have received prior platinum-based chemotherapy (eligible patients for Study CA209017) and DOC, erlotinib, or pemetrexed sodium hydrate for the treatment of those with NSQ-NSCLC (eligible patients in Study CA209057). Consequently, DOC was chosen as the control for both studies.

PMDA accepted the applicant's explanation.

3.(iii).B.(2).2) Efficacy endpoint and evaluation results

PMDA's view:

Treatment of patients with advanced or recurrent SQ-NSCLC or NSQ-NSCLC who have received prior platinum-based chemotherapy generally aims for improvement in survival. In this regard, the use of OS as the primary endpoint for Studies CA209017 and CA209057 was appropriate.

Both studies verified the superiority of nivolumab over DOC in terms of OS improvement [see "3.(iii).A.(2).3) Foreign phase III study" and "3.(iii).A.(2).4) Foreign phase III study"]. Accordingly, PMDA concluded that the efficacy of nivolumab was demonstrated in eligible patients in Studies CA209017 and CA209057.

3.(iii).B.(2).3) Efficacy of nivolumab in Japanese patients

The response rates [95% CI] centrally assessed in Studies ONO-4538-05 and ONO-4538-06 were 25.7% [14.2%, 42.1%] and 19.7% [12.3%, 30.0%], respectively. In both studies, the lower limit of 95% CI exceeded the pre-specified threshold of 9% [see "3.(iii).A.(1).1) Japanese phase II study" and "3.(iii).A.(1).2) Japanese phase II study"].

Accordingly, PMDA concluded that nivolumab shows promising efficacy in Japanese patients with advanced or recurrent SQ-NSCLC or NSQ-NSCLC who have received prior platinum-based chemotherapy.

3.(iii).B.(3) Safety [see "3.(iv) Adverse events observed in clinical studies" for non-fatal adverse events]

Based on the study results detailed in later subsections, PMDA concluded that the adverse events to which attention should be paid in patients with SQ-NSCLC or NSQ-NSCLC on nivolumab therapy are neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, and encephalitis. During the therapy, patients should be closely monitored for these adverse events, as well as for those identified in the review of nivolumab for the indication of unresectable malignant melanoma (i.e., interstitial pneumonia, hepatic function disorder, abnormal thyroid function, infusion reaction, and skin disorder) [see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014"] and those added in the package insert based on post-marketing data accumulated in Japan (i.e., colitis, severe diarrhoea, myasthenia gravis, and myositis) [see "Attachment 5 to Notification No. 0915-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 15, 2015"].

However, PMDA concluded that nivolumab is tolerable in patients, provided that physicians with adequate knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions, including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions, and drug interruption. Given the limited availability of safety data, relevant information/data should be further collected through the post-marketing surveillance [see "3.(iii).B.(6) Post-marketing investigations"].

3.(iii).B.(3).1) Safety profile of nivolumab

The applicant's explanation on the safety profile of nivolumab based on the safety data obtained from Studies ONO-4538-05, CA209017, ONO-4538-06, and CA209057:

The safety data obtained from Studies ONO-4538-05 and CA209017 in patients with SQ-NSCLC are summarized in the table below.

Safety summary (studies in patients with SQ-NSCLC)

	n (%)		
	Study ONO-4538-05 n = 35	Study CA209017	
		Nivolumab n = 131	DOC n = 129
All adverse events	33 (94.3)	127 (96.9)	125 (96.9)
Grade ≥3 adverse events	4 (11.4)	67 (51.1)	94 (72.9)
Adverse events resulting in death	0	19 (14.5)	22 (17.1)
Serious adverse events	4 (11.4)	61 (46.6)	70 (54.3)
Adverse events leading to drug discontinuation	2 (5.7)	14 (10.7)	26 (20.2)
Adverse events leading to dose reduction	NA	NA	35 (27.1)
Adverse events leading to drug interruption	9 (25.7)	36 (27.5)	33 (25.6)

NA, not applicable

In Study CA209017, adverse events of any grades reported in the nivolumab group with an incidence of ≥5% higher than that in the DOC group were dyspnoea (36.6% vs. 29.5% in the nivolumab vs. DOC groups, respectively), cough (31.3% vs. 18.6%), disease progression (14.5% vs. 8.5%), headache (13.7% vs. 7.0%), bronchitis (9.2% vs. 3.9%), pruritus (7.6% vs. 2.3%), hypercalcaemia (7.6% vs. 0%), dysphonia (6.9% vs. 0.8%) and hypothyroidism (5.3% vs. 0%). Grade ≥3 adverse events reported in the nivolumab group with an incidence of ≥2% higher than that in the DOC group were disease progression (10.7% vs. 7.0%) and hypercalcaemia (2.3% vs. 0%). The adverse event leading to drug discontinuation reported in the nivolumab group with an incidence of ≥2% higher than that in the DOC group was pneumonitis (2.3% vs. 0%). The adverse event resulting in death reported in the nivolumab group with an incidence of ≥2% higher than that in the DOC group was disease progression (10.7% vs. 6.2%).

The safety data obtained from Studies ONO-4538-06 and CA209057 in patients with NSQ-NSCLC are summarized in the table below.

Safety summary (studies in patients with NSQ-NSCLC)

	n (%)		
	Study ONO-4538-06 n = 76	Study CA209057	
		Nivolumab n = 287	DOC n = 268
All adverse events	75 (98.7)	280 (97.6)	265 (98.9)
Grade ≥3 adverse events	28 (36.8)	155 (54.0)	194 (72.4)
Adverse events resulting in death	0	46 (16.0)	23 (8.6)
Serious adverse events	22 (28.9)	134 (46.7)	111 (41.4)
Adverse events leading to drug discontinuation	16 (21.1)	48 (16.7)	58 (21.6)
Adverse events leading to dose reduction	NA	NA	69 (25.7)
Adverse events leading to drug interruption	13 (17.1)	82 (28.6)	53 (19.8)

NA, not applicable

In Study CA209057, adverse events of any grades reported in the nivolumab group with an incidence of ≥5% higher than that in the DOC group were decreased appetite (28.9% vs.21.6% in the nivolumab vs. DOC groups, respectively), constipation (23.0% vs. 16.8%), musculoskeletal pain (13.6% vs. 4.5%), back pain (12.5% vs. 6.3%), rash (12.5% vs. 4.9%), pruritus (11.5% vs. 1.9%), disease progression

(8.7% vs. 3.0%), and hypothyroidism (6.6% vs. 0%). Grade ≥3 adverse events reported in the nivolumab group with an incidence of ≥2% higher than that in the DOC group were disease progression (8.7% vs. 2.6%) and pulmonary embolism (3.8% vs. 1.5%). The adverse event leading to drug discontinuation reported in the nivolumab group with an incidence of ≥2% higher than that in the DOC group was disease progression (3.1% vs. 0.7%). The adverse event resulting in death reported in the nivolumab group with an incidence of ≥2% higher than that in the DOC group was disease progression (6.6% vs. 2.2%).

The applicant explained the difference in the safety profile of nivolumab between patients with NSCLC and those with unresectable malignant melanoma, the previously approved indication of nivolumab.

A comparison was made between adverse events reported in 529 treated patients with NSCLC in Studies ONO-4538-05, CA209017, ONO-4538-06, and CA209057 (pooled analysis for NSCLC) and those in patients with malignant melanoma in the Japanese phase II study, Study ONO-4538-02 (see the table below).

Safety summary in patients with NSCLC and those with malignant melanoma

	n (%)	
	Pooled analysis for NSCLC	Study ONO-4538-02
	n = 529	n = 35
All adverse events	515 (97.4)	35 (100)
Grade ≥3 adverse events	254 (48.0)	19 (54.3)
Adverse events resulting in death	65 (12.3)	1 (2.9)
Serious adverse events	221 (41.8)	17 (48.6)
Adverse events leading to drug discontinuation	80 (15.1)	10 (28.6)
Adverse events leading to drug interruption	140 (26.5)	6 (17.1)

In the pooled analysis for NSCLC, there were no adverse events with an incidence of ≥20% higher than that in Study ONO-4538-02. Grade ≥3 adverse events in the pooled analysis occurred at an incidence of ≥3% higher than that in Study ONO-4538-02 were disease progression (7.4% vs. 0% in the pooled analysis and Study ONO-4538-02, respectively) and pneumonia (4.0% vs. 0%). The adverse event resulting in death in the pooled analysis that occurred at an incidence of ≥3% higher than that in Study ONO-4538-02 was disease progression (6.2% vs. 0%).

Adverse events of any grades in Study ONO-4538-02 occurred at an incidence of ≥20% higher than that in the pooled analysis for NSCLC were CRP increased (37.1% vs. 1.3% in Study ONO-4538-02 vs. pooled analysis, respectively), blood lactate dehydrogenase increased (34.3% vs. 1.9%), pruritus (31.4% vs. 10.2%), malaise (28.6% vs. 4.7%), aspartate aminotransferase (AST) increased (28.6% vs. 3.8%), gamma-glutamyltransferase (GGT) increased (25.7% vs. 1.5%), tri-iodothyronine free decreased (25.7% vs. 0%), blood albumin decreased (22.9% vs. 0%), haemoglobin decreased (22.9% vs. 0.6%), haematocrit decreased (20.0% vs. 0%), protein total decreased (20.0% vs. 0%), red blood cell count

decreased (20.0% vs. 0%), and thyroxine free decreased (20.0% vs. 0%). The grade ≥3 adverse events in Study ONO-4538-02 that occurred at an incidence of ≥3% higher than that in the pooled analysis for NSCLC were anaemia (8.6% vs. 1.7%), nausea (5.7% vs. 1.7%), liver disorder (5.7% vs. 0.2%), AST increased (5.7% vs. 0.4%), blood albumin decreased (5.7% vs. 0%), blood creatine phosphokinase (CPK) increased (8.6% vs. 0.2%), GGT increased (11.4% vs. 0.4%), haematocrit decreased (8.6% vs. 0%), haemoglobin decreased (8.6% vs. 0.2%), lymphocyte count decreased (5.7% vs. 1.3%), platelet count decreased (5.7% vs. 0%), red blood cell count decreased (8.6% vs. 0%), decreased appetite (11.4% vs. 1.9%), malignant melanoma (5.7% vs. 0%), metastatic pain (5.7% vs. 0%), and cancer pain (8.6% vs. 0.2%). There were no adverse events resulting in death in Study ONO-4538-02 occurred at an incidence of ≥3% higher than that in the pooled analysis.

PMDA's view:
Although some adverse events occurred more frequently in the nivolumab group than in the DOC group in Studies CA209017 and CA209057, most of these events were grade ≤2 in severity. Therefore, PMDA concluded that nivolumab is tolerable in patients with SQ-NSCLC or NSQ-NSCLC, provided that they are followed by physicians with adequate knowledge and experience in cancer chemotherapy follow up patients by taking appropriate actions including adverse event monitoring and drug discontinuation as needed. However, the adverse events frequently reported in the nivolumab group require special attention during the therapy, and the occurrence of these events should be communicated to healthcare professionals in an appropriate manner.

3.(iii).B.(3).2) Difference in safety profiles between Japanese and non-Japanese patients
The applicant's explanation on the difference in the safety profiles of nivolumab between Japanese and non-Japanese patients with SQ-NSCLC, based on the safety data from Study ONO-4538-05 and the nivolumab group in Study CA209017:

Adverse events of any grades reported in Study ONO-4538-05 with an incidence of ≥10% higher than that in the nivolumab group in Study CA209017 were malaise (17.1% vs. 1.5% in Study ONO-4538-05 vs. the nivolumab group in Study CA209017, respectively), blood CPK increased (17.1% vs. 0%), and lymphocyte count decreased (11.4% vs. 0%). Of these, the grade ≥3 adverse event reported in Study ONO-4538-05 with an incidence of ≥5% higher than that in the nivolumab group in Study CA209017 was lymphocyte count decreased (8.6% vs. 0%).

Meanwhile, adverse events of any grades reported in the nivolumab group in Study CA209017 with an incidence of ≥10% higher than that in Study ONO-4538-05 were dyspnoea (36.6% vs. 5.7% in the nivolumab group in Study CA209017, and Study ONO-4538-05, respectively), cough (31.3% vs. 8.6%), fatigue (30.5% vs. 2.9%), anaemia (16.8% vs. 5.7%), asthenia (15.3% vs. 0%), disease progression (14.5% vs. 0%), headache (13.7% vs. 2.9%), and constipation (13.0% vs. 2.9%). Of these, the grade ≥3 adverse event reported in the nivolumab group in Study CA209017 with an incidence of ≥5% higher than that in Study ONO-4538-05 was disease progression (10.7% vs. 0%).

The applicant's explanation on the difference in the safety profile of nivolumab between Japanese and non-Japanese patients with NSQ-NSCLC, based on the safety data obtained from Study ONO-4538-06 and the nivolumab group in Study CA209057:

Adverse events of any grades reported in Study ONO-4538-06 with an incidence of ≥10% higher than that in the nivolumab group in Study CA209057 were malaise (17.1% vs. 1.4% in Study ONO-4538-06 vs. the nivolumab group in Study CA209057, respectively) and nasopharyngitis (18.4% vs. 4.5%). There were no adverse events of grade ≥3 reported in Study ONO-4538-06 with an incidence of ≥5% higher than that in the nivolumab group in Study CA209057.

Meanwhile, adverse events of any grades reported in the nivolumab group in Study CA209057 with an incidence of ≥10% higher than that in Study ONO-4538-06 were fatigue (31.7% vs. 15.8% in the nivolumab group in Study CA209057 vs. Study ONO-4538-06, respectively), cough (26.5% vs. 9.2%), constipation (23.0% vs. 9.2%), dyspnoea (22.6% vs. 2.6%), asthenia (20.6% vs. 0%), and musculoskeletal pain (13.6% vs. 2.6%). There were no grade ≥3 adverse events in the nivolumab group in Study CA209057 with an incidence of ≥5% higher than that in Study ONO-4538-06.

PMDA's view:
Because of small numbers of Japanese patients participating in Studies ONO-4538-05 and ONO-4538-06, there is a limitation in making a rigorous comparison of the incidences of adverse events between Japanese and non-Japanese patients. However, most of the adverse events reported only in Japanese patients or reported more frequently in Japanese patients than in non-Japanese patients were grade ≤2 in severity, indicating that nivolumab is tolerable in Japanese patients as well. Nevertheless, the occurrence of the adverse events observed only in Japanese patients or those occurring more frequently in Japanese patients should be communicated to healthcare professionals.

PMDA reviewed the serious adverse events reported in Studies ONO-4538-05, ONO-4538-06, CA209017, and CA209057. The details are described in subsequent sections.

3.(iii).B.(3).3) Neurological disorder

The applicant's explanation on neurological disorders observed after the administration of nivolumab:
Adverse events of neurological disorders categorized into the MedDRA System Organ Class (SOC) of "nervous system disorders" were summarized.

In Study ONO-4538-05, neurological disorders were reported in 4 of 35 subjects (11.4%). None of these was grade ≥3, serious, or fatal.

In Study CA209017, neurological disorders were reported in 45 of 131 subjects (34.4%) in the nivolumab group and 57 of 129 subjects (44.2%) in the DOC group. Grade ≥3 events were reported in

5 subjects (3.8%; cerebrovascular accident, headache, myasthenic syndrome, convulsion, spinal cord compression, and ischaemic stroke [n = 1 each] [when a subject had >1 event, each event was reported individually]) in the nivolumab group and 11 subjects (8.5%; neuropathy peripheral [n = 3], cerebrovascular accident and neurotoxicity [n = 2 each], and aphasia, dizziness, lethargy, post herpetic neuralgia, and VIIth nerve paralysis [n = 1 each] [more than 1 event experienced by a subject was reported individually]) in the DOC group. Serious events were reported in 5 subjects (3.8%; generalised tonic-clonic seizure, myasthenic syndrome, convulsion, spinal cord compression, and ischaemic stroke [n = 1 each]) in the nivolumab group and 4 subjects (3.1%; cerebrovascular accident [n = 2], and aphasia, peripheral sensory neuropathy, and VIIth nerve paralysis [n = 1 each] [more than 1 event experienced by a subject was reported individually]) in the DOC group. A causal relationship to the study drug could not be ruled out for myasthenic syndrome in the nivolumab group and the peripheral sensory neuropathy in the DOC group. No events resulted in death in the nivolumab group. In the DOC group, 1 fatal event (0.8%, cerebrovascular accident) was reported. A causal relationship between the event and DOC was ruled out.

In Study ONO-4538-06, neurological disorders were reported in 19 of 76 subjects (25.0%), and grade ≥3 events were reported in 3 subjects (3.9%; cerebral infarction, dizziness, and convulsion [n = 1 each]). Serious events were reported in 3 subjects (3.9%; cerebral infarction, dizziness, and convulsion [n = 1 each]). A causal relationship to nivolumab could not be ruled out for dizziness. No events resulted in death.

In Study CA209057, neurological disorders were reported in 100 of 287 subjects (34.8%) in the nivolumab group and 124 of 268 subjects (46.3%) in the DOC group. Grade ≥3 events were reported in 9 subjects (3.1%; headache and syncope in 2 subjects each and carotid artery stenosis, cerebrovascular accident, dizziness, hemiplegia, hydrocephalus, and neuralgia [n = 1 each] [more than 1 event experienced by a subject was reported individually]) in the nivolumab group and 7 subjects (2.6%; neuropathy peripheral [n = 3], and dizziness, loss of consciousness, somnolence, and spinal cord compression [n = 1 each]) in the DOC group. Serious events were reported in 10 subjects (3.5%; headache [n = 4], and carotid artery stenosis, cerebrovascular accident, hemiplegia, hydrocephalus, neuralgia, somnolence, and syncope [n = 1 each] [more than 1 event experienced by a subject was reported individually]) in the nivolumab group and 2 subjects (0.7%, somnolence and spinal cord compression [n = 1 each]) in the DOC group. A causal relationship to the study drug could not be ruled out for cerebrovascular accident in 1 subject in the nivolumab group. No events resulted in death in either group.

There were no fatal neurological events in any of these studies. However, in 4 foreign clinical studies that were not included in this application (Studies CA209[redacted], CA209[redacted], and CA209[redacted] in patients with malignant melanoma and Study CA209[redacted] in patients with renal cell carcinoma), subarachnoid haemorrhage, toxic encephalopathy, coma, and cerebral haemorrhage (1 subject each) resulted in death. A causal relationship to nivolumab could not be ruled out for toxic encephalopathy and coma.

Post-marketing data accumulated in Japanese patients with unresectable malignant melanoma, the approved indication, also revealed that cerebral haemorrhage in 2 patients and myasthenia gravis in 1 patient resulted in death. A causal relationship to nivolumab could not be ruled out for myasthenia gravis.

PMDA's view:
Because serious neurological disorders, including fatal events, were reported in patients on nivolumab therapy, patients should be carefully monitored for neurological disorders during the therapy. The occurrence of neurological disorders and related information should be communicated to the healthcare professionals through the package insert, etc.

3.(iii).B.(3).4) Renal disorder

The applicant's explanation on renal disorders observed after administration of nivolumab:
Adverse events of renal disorders that were categorized into the MedDRA Preferred Terms (PT) of "blood creatinine increased," "blood urea increased," "creatinine renal clearance decreased," "hypercreatininaemia," "nephritis," "nephritis allergic," "nephritis autoimmune," "renal failure," "renal failure acute," "renal tubular necrosis," "tubulointerstitial nephritis," and "urine output decreased" were summarized.

The occurrence of renal disorders reported in Studies ONO-4538-05 and CA209017 are summarized in the table below.

Occurrence of renal disorders (Studies ONO-4538-05 and CA209017)

PT (MedDRA/J ver.17.1)	n (%)					
	Study ONO-4538-05 n = 35		Study CA209017			
			Nivolumab n = 131		DOC n = 129	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Renal disorder	2 (5.7)	0	7 (5.3)	3 (2.3)	3 (2.3)	0
Blood creatinine increased	2 (5.7)	0	6 (4.6)	1 (0.8)	2 (1.6)	0
Renal failure	0	0	1 (0.8)	1 (0.8)	0	0
Tubulointerstitial nephritis	0	0	1 (0.8)	1 (0.8)	0	0
Renal failure acute	0	0	0	0	1 (0.8)	0

In Study ONO-4538-05, there were no serious or fatal events.

In Study CA209017, no serious events were reported in the DOC group, while 1 serious adverse event was reported in 1 subject (0.8%, tubulointerstitial nephritis) in the nivolumab group. A causal relationship to nivolumab could not be ruled out for tubulointerstitial nephritis. No fatal events were reported in either group.

The table below summarizes the occurrence of renal disorders reported in Studies ONO-4538-06 and CA209057.

Occurrence of renal disorders (Studies ONO-4538-06 and CA209057)

PT *	n (%)					
	Study ONO-4538-06 n = 76		Study CA209057			
			Nivolumab n = 287		DOC n = 268	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Renal disorder	5 (6.6)	1 (1.3)	16 (5.6)	0	3 (1.1)	0
Blood creatinine increased	3 (3.9)	0	11 (3.8)	0	3 (1.1)	0
Blood urea increased	2 (2.6)	0	3 (1.0)	0	0	0
Renal failure acute	1 (1.3)	1 (1.3)	2 (0.7)	0	0	0

* MedDRA/J ver.17.0 for Study ONO-4538-06, MedDRA/J ver.17.1 for Study CA209057

In Study ONO-4538-06, 1 serious event was reported in 1 subject (1.3%, renal failure acute). A causal relationship to nivolumab was ruled out for the event. No fatal events were reported.

In Study CA209057, no serious events were reported in the DOC group, while 1 serious event was reported in 1 subject (0.3%, blood creatinine increased) in the nivolumab group. A causal relationship to the study drug could not be ruled out for the serious event. No events resulted in death in either group.

PMDA's view:
Because serious renal disorders were reported in patients on nivolumab therapy, patients should be carefully monitored for these events during the therapy. The occurrence of renal disorders and related information should be communicated to healthcare professionals through the package insert, etc. in an appropriate manner. The patients should also be monitored for renal functions on a regular basis. Healthcare professionals should be advised to ensure that renal function tests are performed as frequently as those in the clinical studies, so that they can cope with abnormalities appropriately, e.g. by discontinuing nivolumab. Such requirements should be communicated appropriately to healthcare professionals through informational materials.

3.(iii).B.(3).5) Venous thrombosis and embolism

The applicant's explanation on venous thrombosis and embolism observed after the administration of nivolumab:
Venous thrombosis or embolism-related adverse events categorized into the Standardised MedDRA Queries (SMQ) of "embolic and thrombotic events, venous" were summarized.

In Study ONO-4538-05, venous thrombosis or embolism were reported in 2 of 35 subjects (5.7%). There were no grade ≥3, serious, or fatal events.

In Study CA209017, venous thrombosis or embolism was reported in 3 of 131 subjects (2.3%) in the nivolumab group and in 7 of 129 subjects (5.4%) in the DOC group. Grade ≥3 events were reported in 3 subjects (2.3%, pulmonary embolism [n = 2] and pulmonary thrombosis [n = 1]) in the nivolumab group and in 5 subjects (3.9%; pulmonary embolism [n = 3], superior vena cava syndrome and superior

vena cava occlusion [n = 1 each]) in the DOC group. Serious events were reported in 3 subjects (2.3%, pulmonary embolism [n = 2] and pulmonary thrombosis [n = 1]) in the nivolumab group and in 3 subjects (2.3%, pulmonary embolism [n = 2] and superior vena cava syndrome [n = 1]) in the DOC group. For all these serious events, a causal relationship to the study drug was ruled out. Fatal events were not reported in the nivolumab group but occurred in 3 subjects (2.3%, pulmonary embolism [n = 2] and superior vena cava syndrome [n = 1]) in the DOC group. For these fatal events, a causal relationship to the study drug was ruled out.

In Study ONO-4538-06, venous thrombosis or embolism was reported in 1 of 76 subjects (1.3%). There were no grade ≥3, serious, or fatal events.

In Study CA209057, venous thrombosis or embolism was reported in 21 of 287 subjects (7.3%) in the nivolumab group and in 11 of 268 subjects (4.1%) in the DOC group. Grade ≥3 events were reported in 12 subjects (4.2%, pulmonary embolism [n = 11] and deep vein thrombosis [n = 1]) in the nivolumab group and in 8 subjects (3.0%; pulmonary embolism [n = 4], deep vein thrombosis [n = 3], and jugular vein thrombosis [n = 1]) in the DOC group. Serious events were reported in 12 subjects (4.2%, pulmonary embolism [n = 11] and deep vein thrombosis [n = 1]) in the nivolumab group and in 6 subjects (2.2%; pulmonary embolism [n = 3], deep vein thrombosis [n = 2], and jugular vein thrombosis [n = 1]) in the DOC group. A causal relationship to the study drug could not be ruled out for pulmonary embolism in 1 subject in the nivolumab group. No events resulted in death in the DOC group. In the nivolumab group, fatal events were reported in 2 subjects (0.7%, pulmonary embolism [n = 2]), and a causal relationship to the study drug was ruled out for these events.

PMDA's view:
Venous thrombosis or embolism, including serious events, was reported in patients on nivolumab therapy. Therefore, patients should be carefully monitored for venous thrombosis or embolism during the therapy. The occurrence of the events and related information should be communicated to healthcare professionals through the package insert, etc. in an appropriate manner.

3.(iii).B.(3).6) Adrenal gland disorders

The applicant's explanation on adrenal gland disorders observed after the administration of nivolumab:
Adrenal gland-related adverse events categorized into the MedDRA PTs of "adrenal insufficiency," "adrenal suppression," "blood corticotrophin decreased," "blood corticotrophin increased," "hypothalamic pituitary adrenal axis suppression," and "secondary adrenocortical insufficiency" were summarized.

In Study ONO-4538-05, an adrenal gland disorder was reported in 1 of 35 subjects (2.9%). The event was not grade ≥3, serious, or fatal.

In Study CA209017, no adrenal gland disorder was reported.

In Study ONO-4538-06, an adrenal gland disorder was reported in 1 of 76 subjects (1.3%) but the event was not grade ≥3. A serious event was reported in 1 subject (1.3%, secondary adrenocortical insufficiency), and a causal relationship could not be ruled out for the event. No events resulted in death.

In Study CA209057, adrenal gland disorders were reported in 1 (0.3%) of 287 subjects in the nivolumab group and in 1 (0.4%) of 268 subjects in the DOC group. The event in the DOC group was not grade ≥3 and not serious, while the event in 1 subject (0.3%, adrenal insufficiency) in the nivolumab group was grade ≥3 and serious. For the serious event, a causal relationship to the study drug was ruled out. No events resulted in death in either group.

PMDA's view:
A serious adrenal gland disorder was reported in patients on nivolumab therapy. Therefore, patients should be carefully monitored for adrenal gland disorders during the therapy. Relevant data, including the occurrence of disorders, should be provided to healthcare professionals through the package insert, etc. in an appropriate manner.

3.(iii).B.(3).7) Encephalitis
The applicant's explanation on encephalitis observed after the administration of nivolumab:

Encephalitis was not reported in Study ONO-4538-05, CA209017, or ONO-4538-06.

In Study CA209057, encephalitis was not reported in the DOC group, while 1 event was reported in 1 of 287 subjects (0.3%) in the nivolumab group. The event was assessed as grade 3 and serious, and had a fatal outcome. A causal relationship to nivolumab could not be ruled out for the event.

The table below shows the characteristics of subjects on nivolumab monotherapy who experienced encephalitis in any clinical studies of nivolumab including Study CA209057.

List of subjects who experienced encephalitis

Study	Age	Sex	Primary disease	Grade	Onset (Day)	Action or treatment	Causality	Outcome
CA209[redacted]	7[redacted]	F	NSCLC	3	219	Antibiotics, etc.	Related	Death
CA209[redacted]	5[redacted]	M	MEL	4	130	Steroid, antiviral drugs, antibiotics, etc.	Related	Not resolved
CA209[redacted]	5[redacted]	M	SCLC	2	39	Steroid, immunoglobulin	Not related	Resolved
CA209[redacted]	5[redacted]	F	SCLC	4	16	Steroid, immunoglobulin	Related	Not resolved
CA209[redacted]	2[redacted]	F	HL	3	158	Antiviral drugs	Not related	Resolved

NSCLC, non-small cell lung cancer; MEL, malignant melanoma; SCLC, small cell lung cancer; HL, Hodgkin's lymphoma
M, male; F, female

PMDA's view:

Serious encephalitis, including a fatal event, were reported in patients treated with nivolumab. Therefore, patients should be carefully monitored for the onset of encephalitis during the therapy. The occurrence of encephalitis, along with advice on actions to be taken at the onset of events, should be communicated to healthcare professionals appropriately through the package insert, etc.

3.(iii).B.(3).8) Other

According to the applicant, foreign clinical study data that were not submitted for this application indicate risks of skin disorders and haemophagocytic lymphohistiocytosis associated with the use of nivolumab. The applicant's explanation on the occurrence of these events is as follows:

(a) Serious skin disorders

The table below shows the characteristics of subjects who experienced toxic epidermal necrolysis (TEN), a serious skin disorder, in foreign clinical studies.

List of subjects who experienced TEN

Study	Age	Sex	Primary disease	Grade	Onset (Day)	Action or treatment	Causality	Outcome
CA209[redacted]	5[redacted]	M	FL	5	12	Steroid, immunoglobulin, antibiotics, antimycotics, etc.	Related	Death
CA209[redacted]	7[redacted]	M	NSCLC	5	71	Steroid, immunoglobulin, antibiotics, antimycotics, cyclophosphamide, immunosuppressant, etc.	Related	Death
CA209[redacted]	6[redacted]	F	MEL	Unknown	116	Steroid, immunosuppressant	Related	Not resolved
CA209[redacted]	7[redacted]	M	MEL	4	106	Steroid, antibiotics, etc.	Related	Resolved

FL, follicular lymphoma; NSCLC, non-small cell lung cancer; MEL, malignant melanoma
M, male; F, female

(b) Haemophagocytic lymphohistiocytosis

The table below shows the characteristics of subjects who experienced haemophagocytic lymphohistiocytosis in foreign clinical studies.

List of subjects who experienced haemophagocytic lymphohistiocytosis

Study	Age	Sex	Primary disease	Grade	Onset (Day)	Action or treatment	Seriousness	Causality	Outcome
CA209[redacted]	6[redacted]*	M	Gastric cancer	Unknown	56	Steroid, antibiotics	Serious	Related	Resolved
CA209[redacted]	7[redacted]	M	MEL	3	556	Unknown	Serious	Not related	Death

MEL, malignant melanoma; * combination therapy with nivolumab and ipilimumab
M, male; F, female

PMDA's view:

(a) TEN was observed in patients on nivolumab therapy, and some were fatal. Patients on nivolumab therapy should be therefore carefully monitored for TEN during the therapy. Relevant information on

TEN, including the occurrence of the event, should be provided to healthcare professionals through the package insert, etc. in an appropriate manner.

(b) A causal relationship between haemophagocytic lymphohistiocytosis and nivolumab is not clear at present. Generally, haemophagocytic lymphohistiocytosis is likely to become serious. Relevant information should be further collected, and any new findings on the event should be communicated to healthcare professionals in an appropriate manner.

3.(iii).B.(4) Clinical positioning and indication

The proposed indication of nivolumab was "unresectable, advanced or recurrent non-small cell lung cancer." The following statements were included in the "Precautions for Indication" 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.
- In order to determine the eligibility of patients for nivolumab therapy, the "Clinical Studies" section should be read thoroughly and carefully for a good understanding of the efficacy and safety of nivolumab. Alternative therapeutic options should also be carefully considered before initiating the therapy.

Based on the discussions in "3.(iii).B.(2) Efficacy," "3.(iii).B.(3) Safety," and the following subsections, PMDA concluded that the "Precautions for Indication" section should contain the above precautionary advice defined by the applicant and that the indication of nivolumab should be "unresectable, advanced or recurrent non-small cell lung cancer" as proposed by the applicant.

3.(iii).B.(4).1) Clinical positioning of nivolumab

Japanese and foreign clinical practice guidelines and major oncology publications contains the following statements on nivolumab for the treatment of unresectable, advanced or recurrent NSCLC. Currently, there is no statement on nivolumab in The Evidence-based Clinical Practice Guidelines for Lung Cancer 2014 edited by the Japan Lung Cancer Society (Kanehara & Co., Ltd.; 2014) or in New Clinical Oncology for Cancer Medication Specialists, 4th Edition (Nankodo; 2015).

Clinical practice guidelines

- NCCN Guidelines (v.7, 2015)
  - Based on the results of Study CA209017, nivolumab is recommended for the treatment of patients with unresectable, advanced or recurrent SQ-NSCLC with performance status (PS) 0 to 2 who have received prior platinum-based chemotherapy.
  - Based on the results of Study CA209057, nivolumab is recommended for the treatment of patients with unresectable, advanced or recurrent NSQ-NSCLC with PS 0 to 2 who have received prior platinum-based chemotherapy. Because there is no available information indicating a relationship between the efficacy of nivolumab and the expression of PD-L1, testing for PD-L1 expression is not recommended prior to treatment with nivolumab.

- The US National Cancer Institute's Physician Data Query (NCI PDQ) (version updated on September 3, 2015)
  - Based on the results of Studies CA209017 and CA209057, nivolumab is recommended for the treatment of patients with unresectable, advanced or recurrent NSCLC who have received prior platinum-based chemotherapy. However, patients should be carefully monitored for the onset of immune-related adverse events during treatment.

Oncology publications

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (Lippincott Williams & Wilkins 2015, PA, USA)
  - Because the efficacy of nivolumab was also demonstrated in patients with NSCLC in the foreign phase I study (Study CA209003), foreign phase II and III studies in patients with SQ-NSCLC and a foreign phase III study in patients with NSQ-NSCLC are currently underway.

PMDA's view:

Based on the results of Studies CA209017 and CA209057, nivolumab is expected to be a new therapeutic option for patients with unresectable, advanced or recurrent NSCLC who have received prior platinum-based chemotherapy, eligible patients for these studies.

3.(iii).B.(4).2) Intended population

Based on the results of Studies CA209017 and CA209057, the applicant considers that the intended population of nivolumab should be patients with unresectable, advanced or recurrent NSCLC who have received prior platinum-based chemotherapy, eligible patients for these studies.

Nivolumab is a human anti-PD-1 antibody drug. PMDA asked the applicant to explain the efficacy and safety of nivolumab and the intended population of nivolumab therapy in relation to the expression levels of PD-L1, a ligand for PD-1.

The applicant's response:

In Studies CA209017 and CA209057, the expression of PD-L1[*] in formalin-fixed paraffin-embedded tumor tissue samples was examined using rabbit anti-human PD-L1 antibody (clone 28-8) to collect data. A relationship between the data (cut-off values; 1%, 5%, and 10%) and the efficacy and safety of nivolumab were investigated. The results are summarized below. Factors other than PD-L1 are being analyzed, and the results are expected to be obtained in the [redacted] quarter of 20[redacted] or later.

[*] At the central assessment organization, the presence of ≥100 evaluable tumor cells in the tumor tissue sample was confirmed. Then, the proportion of cells with stained cell membranes (hereinafter PD-L1-positive cells) relative to evaluable tumor cells was calculated.

(a) Efficacy

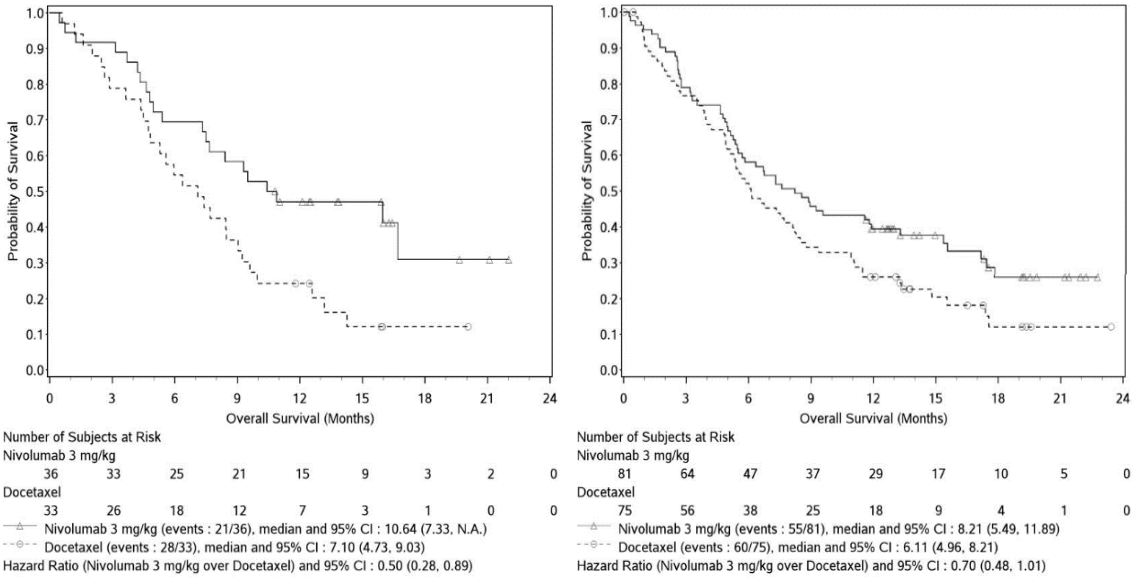
In Study CA209017, the percentage of PD-L1 positive tumors was determined in tumor samples from PD-L1 quantifiable subjects with SQ-NSCLC (nivolumab group, 117 of 135 subjects [86.7%]; DOC

group, 108 of 137 subjects [78.8%]) to identify their PD-L1 expression status. The table and figure below show the OS in these patients by PD-L1 expression status (cut-off value, 10% only). The OS in the nivolumab group improved regardless of the PD-L1 expression status as compared with that in the DOC group.

Efficacy by PD-L1 expression status in the tumor cell sample (Study CA209017)

PD-L1	Treatment group	n	OS		
			Median [95% CI] (months)	Hazard ratio * [95% CI]	*P*-value for interaction
<1%	Nivolumab	54	8.71 [5.68, 15.54]	0.58 [0.37, 0.91]	0.5556
	DOC	52	5.91 [4.96, 7.69]		
≥1%	Nivolumab	63	9.30 [5.45, 15.97]	0.70 [0.46, 1.06]	
	DOC	56	7.24 [4.86, 8.77]		
<5%	Nivolumab	75	8.54 [5.49, 13.27]	0.69 [0.47, 1.02]	0.4747
	DOC	69	6.14 [5.13, 8.28]		
≥5%	Nivolumab	42	9.95 [5.82, 17.15]	0.55 [0.33, 0.92]	
	DOC	39	6.37 [4.50, 9.03]		
<10%	Nivolumab	81	8.21 [5.49, 11.89]	0.70 [0.48, 1.00]	0.4062
	DOC	75	6.11 [4.96, 8.21]		
≥10%	Nivolumab	36	10.64 [7.33, NE]	0.52 [0.30, 0.92]	
	DOC	33	7.10 [4.73, 9.03]		

NE, not estimated;
* Estimated using a Cox proportional hazard model with covariates of treatment group, PD-L1 expression status, and interaction between treatment group and PD-L1 expression status



Kaplan-Meier curves of OS by PD-L1 expression status in Study CA209017 based on the interim analysis (Data cut-off, [redacted], 20[redacted]; left, subjects with PD-L1 of ≥10%; right, subjects with PD-L1 of <10%)

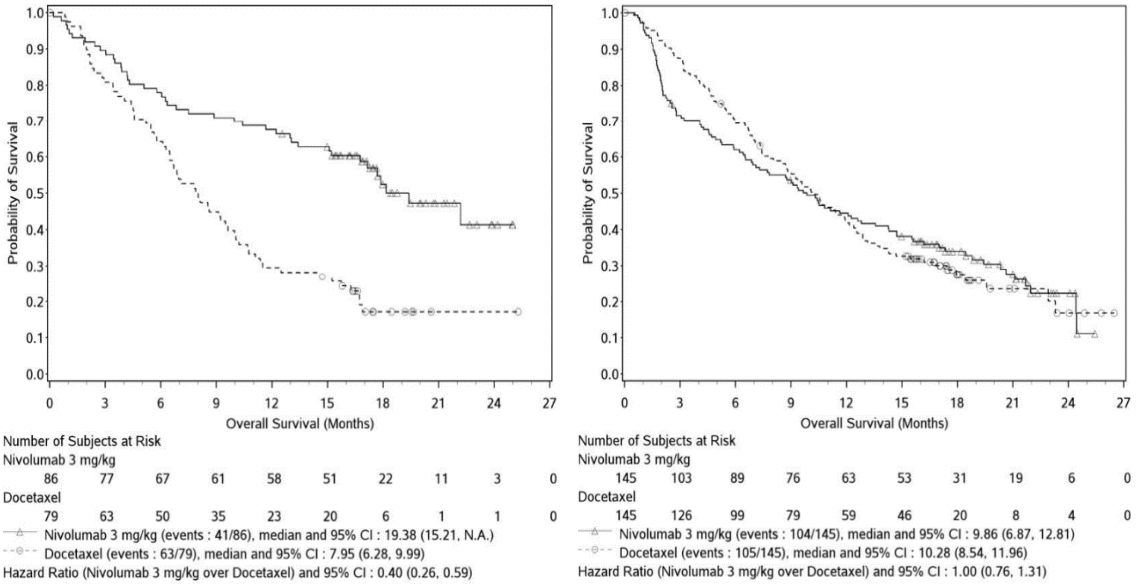
In Study CA209057, the percentage of PD-L1-positive tumors was determined in tumor samples from PD-L1 quantifiable subjects with NSQ-NSCLC. PD-L1 expression status was identified for 231 of 292 subjects (79.1%) in the nivolumab group and 224 of 290 subjects (77.2%) in the DOC group. The table and figure below show the OS in these patients by PD-L1 expression status (cut-off value, 10% only). While OS improved in PD-L1-positive subjects in the nivolumab group regardless of cut-off value (1%,

5%, or 10%) as compared with the DOC group, OS in PD-L1-negative subjects in the nivolumab group was similar to that in the DOC group regardless of cut-off value (1%, 5%, or 10%). The pre-specified threshold for interaction tests that may be a predictive factor for clinically significant efficacy was $P \leq 0.2$. The table below also shows the *P*-value results for interaction.

Efficacy by PD-L1 expression status in tumor samples (Study CA209057)

PD-L1	Treatment group	n	OS		
			Median [95% CI] (months)	Hazard ratio * [95% CI]	*P*-value for interaction
<1%	Nivolumab	108	10.41 [7.29, 14.26]	0.90 [0.66, 1.24]	0.0646
	DOC	101	10.09 [7.36, 11.93]		
≥1%	Nivolumab	123	17.15 [12.09, 20.63]	0.59 [0.43, 0.81]	
	DOC	123	9.00 [7.10, 10.55]		
<5%	Nivolumab	136	9.66 [6.87, 12.62]	1.01 [0.76, 1.33]	0.0004
	DOC	138	10.09 [8.05, 11.93]		
≥5%	Nivolumab	95	18.17 [15.21, NE]	0.43 [0.30, 0.63]	
	DOC	86	8.11 [6.47, 10.05]		
<10%	Nivolumab	145	9.86 [6.87, 12.81]	1.00 [0.76, 1.31]	0.0002
	DOC	145	10.28 [8.54, 11.96]		
≥10%	Nivolumab	86	19.38 [15.21, NE]	0.40 [0.27, 0.59]	
	DOC	79	7.95 [6.28, 9.99]		

NE, not estimated;
* Estimated using a Cox proportional hazard model with covariates of treatment group, PD-L1 expression status, and interaction between treatment group and PD-L1 expression status.



Kaplan-Meier curves for OS by PD-L1 expression status in Study CA209057 based on the interim analysis (Data cut-off, [redacted], 20[redacted]; left, subjects with PD-L1 of ≥10%; right, subjects with PD-L1 of <10%)

(b) Safety

In Study CA209017, the incidence of adverse events was 98.1% in the subgroup of subjects with the percentage of PD-L1-positive cell (PD-L1 positivity) of <1% and that was 98.3% in the subgroup of subjects with PD-L1 positivity of ≥1%. The incidence of grade ≥3 adverse events was 53.7% and 50.8% in the subgroups of subjects with PD-L1 positivity of <1% and ≥1%, respectively. In the subgroups of

subjects withPD-L1 positivity of <5% and ≥5%, the incidence of adverse events was 97.3% and 100%, respectively; and the incidence of grade ≥3 adverse events was 50.7% and 55.0%, respectively. In the subgroups of subjects with PD-L1 positivity of <10% and ≥10%, the incidence of adverse events was 97.5% and 100%, respectively; and the incidence of grade ≥3 adverse events was 51.9% and 52.9%, respectively. The results showed no clear difference between the status of PD-L1 expression in the tumor tissue samples and the safety of nivolumab in subjects with SQ-NSCLC.

In Study CA209057, in the subgroups of subjects with PD-L1 positivity of <1% and ≥1%, the incidence of adverse events was 97.2% and 97.5%, respectively; and the incidence of grade ≥3 adverse events was 49.1% and 53.7%, respectively. In the subgroup of subjects with the PD-L1 positivity of <5% and ≥5%, the incidence of adverse events was 97.0% and 97.8%, respectively; and that of grade ≥3 adverse events was 50.0% and 53.8%, respectively. In the subgroup of subjects with PD-L1 positivity of <10% and ≥10%, the incidence of adverse events was 97.2% and 97.6%, respectively; and that of grade ≥3 adverse events was 51.0% and 52.4%, respectively. The results showed no clear difference between the status of PD-L1 expression in the tumor tissue samples and the safety of nivolumab in subjects with NSQ-NSCLC.

The results of the investigations in above (a) and (b) showed similar OS of PD-L1-negative subjects with NSQ-NSCLC in both the nivolumab and DOC groups. The observed interaction between PD-L1-positive subjects and PD-L1-negative subjects indicates the possibility that PD-L1 expression is a predictive factor for the effect of nivolumab. However, given that the incidence of grade ≥3 adverse events was lower in the nivolumab group than in the DOC group [see "3.(iii).B.(3) Safety"] demonstrating a good safety profile, nivolumab is recommended for the treatment of both SQ-NSCLC and NSQ-NSCLC irrespective of PD-L1 expression in tumor tissue samples.

PMDA's view:

The results of OS by PD-L1 expression status in Study CA209057 were of an exploratory subgroup analysis. The applicant explains that nivolumab is recommended for the treatment of patients with advanced or recurrent SQ-NSCLC or NSQ-NSCLC who have received prior platinum-based chemotherapy irrespective of PD-L1 expression in tumor tissue samples, and this is acceptable at this point. The package insert, while noting that eligible patients for Studies CA209017 and CA209057 had a history of prior platinum-based chemotherapy in the "Clinical Studies" section, should define the indication as "unresectable, advanced or recurrent non-small cell lung cancer" as proposed by the applicant along with the following precautionary advice.

- The efficacy and safety of nivolumab in chemotherapy-naïve patients have not been established.
- In order to determine the eligibility of patients for nivolumab therapy, the "Clinical Studies" section should be read thoroughly and carefully for a good understanding of the efficacy and safety of nivolumab. Alternative therapeutic options should also be carefully considered before initiating the therapy.

However, the observed interaction between PD-L1-positive patients and PD-L1-negative patients suggests the possibility that PD-L1 expression is a predictive factor for the effect of nivolumab. Data on predictive factors for the effect of nivolumab including PD-L1 expression should be further collected, and any new findings should be provided to healthcare professionals in an appropriate manner. Besides PD-L1, there may be other factors useful for determining the use of nivolumab. Investigations on such factors should be conducted, and the results thereof should be communicated to healthcare professionals once available.

3.(iii).B.(4).3) Efficacy and safety of nivolumab in adjuvant chemotherapy

There are no clinical study data that support the efficacy and safety of nivolumab in adjuvant chemotherapy. The applicant considers that nivolumab is not recommended for adjuvant chemotherapy at this point, and mentioned that this advice would included in the "Precautions for Indication" section.

PMDA accepted the applicant's explanation.

3.(iii).B.(5) Dosage and administration

The proposed dosage and administration of nivolumab was "the usual adult dosage of nivolumab (genetical recombination) is 3 mg/kg body weight administered as an intravenous infusion every 2 weeks." The following precautionary advice was 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 to 1.2 μm) should be used for infusion.
- The efficacy and safety of nivolumab in combination with other antineoplastic drugs have not been established.

Based on the discussions in the following subsections, PMDA concluded that the dosage and administration of nivolumab should be "the usual adult dosage of nivolumab (genetical recombination) is 3 mg/kg body weight administered as an intravenous infusion every 2 weeks" as proposed by the applicant. PMDA also concluded that the following precautionary advice should be added in to the "Precautions for Dosage and Administration" section for the treatment of NSCLC:

- 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.

3.(iii).B.(5).1) Dosage and administration of nivolumab

The applicant's justification for the dosing regimen of nivolumab selected for patients with unresectable, advanced or recurrent NSCLC:

The efficacy and safety of nivolumab were demonstrated in Studies ONO-4538-05, ONO-4538-06, CA209017, and CA209057 conducted with the dosing regimen determined based on the clinical study results shown below. Therefore, the dosing regimen of nivolumab employed in these 4 studies has been proposed in this application. The "Precautions for Dosage and Administration" section should advise that the nivolumab solution be intravenously infused over at least 1 hour based on the infusion procedure used in the 4 studies.

- In the foreign phase I study in patients with advanced or recurrent NSCLC (Study CA209003), the response rate was higher in patients treated with nivolumab at 3 or 10 mg/kg every 2 weeks than in those treated with nivolumab at 1 mg/kg every 2 weeks.
- In Study CA209003, the incidences of serious (grade 3 or 4) adverse events and adverse events leading to drug discontinuation were higher in patients treated with nivolumab at 10 mg/kg every 2 weeks than in those treated with nivolumab at 0.1 to 3 mg/kg every 2 weeks. The results indicated that nivolumab should not be administered at 10 mg/kg every 2 weeks for a safety reason.

PMDA accepted the applicant's explanation.

3.(iii).B.(5).2) Pore size of in-line filter

The use of an in-line filter with a pore size of 0.2 or 0.22 μm was recommended for infusion of nivolumab in patients with unresectable malignant melanoma (the approved indication). However, the pore size was changed to 0.2 to 1.2 μm for this application.

The applicant's justification for the change in the in-line filter pore size:

Nivolumab may form aggregates when dissolving into the solution, thereby potentially enhancing immune responses. In order to remove aggregates, in-line filters with a pore size of 0.2 or 0.22 μm were used at the beginning of Studies ONO-4538-05, ONO-4538-06, CA209063, CA209017, and CA209057. Later, the pore size was changed to 0.2 to 1.2 μm because an increase in the options for in-line filter pore size was expected to enhance convenience for the medical institutions.

The pore size was changed after all subjects had been enrolled in the studies. Therefore, a relationship between the safety of nivolumab and the in-line filter pore size was not evaluated.

PMDA's view:

Given that there are no clinical study data supporting the safety of nivolumab administered using in-line filters with pore sizes of >0.22 μm, the change in the pore-size of in-line filter to 0.2 to 1.2 μm is not appropriate.

3.(iii).B.(5).3) Combination therapy with other antineoplastic drugs

There are no data on the efficacy and safety of nivolumab administered to patients with NSCLC in combination with other antineoplastic drugs. The applicant mentioned that a precautionary statement on this matter would be included in the "Precautions for Dosage and Administration" section.

PMDA accepted the applicant's explanation.

3.(iii).B.(6) Post-marketing investigations

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

Post-marketing surveillance (the survey) will be conducted to investigate the safety of nivolumab in all NSCLC patients treated with nivolumab.

Priority investigation items of the survey were determined in light of potential adverse events particularly attributable to the pharmacological action of nivolumab or those reported frequently in the clinical studies, which are namely interstitial lung disease, hepatic function disorder, abnormal thyroid function, colitis, and infusion reaction.

The survey aims to gather data from the target number of 1000 patients. Interstitial lung disease is of particular concern in patients with NSCLC, because it may worsen the patient condition, leading to decreased respiratory function. Based on the incidence of interstitial lung disease in the Japanese phase II studies (Studies ONO-4538-05 and ONO-4538-06), the applicant chose the sample size of 1000 patients that was considered adequate for the detection of the lung disease. This target sample size will allow exploring risk factors in clinical or laboratory findings on baseline pulmonary function.

In Studies ONO-4538-05, ONO-4538-06, CA209063, CA209017, and CA209057, approximately 90% of the adverse events included in the priority investigation items were observed within 12 months after the start of treatment, and no new adverse events were reported after 12 months of treatment. Accordingly, the follow-up period is planned to be 12 months.

PMDA's view:

The availability of safety data from Japanese patients with NSCLC who received nivolumab is limited. Post-marketing data should be collected from all patients on nivolumab therapy in a prompt and unbiased manner for a specific period, and new safety findings should be communicated to healthcare professionals immediately.

Severe diarrhoea, myasthenia gravis and myositis, neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, encephalitis, and severe skin disorder should be added in to the priority investigation items proposed by the applicant, because these events require special attention during nivolumab therapy.

The target number of patients and the follow-up period should be reconsidered based on the incidences and time to onset of the adverse events that are to be added in to the priority investigation items.

3.(iv) Adverse events reported in clinical studies

Fatal events included in safety data from clinical studies submitted by the applicant are described in "3.(iii) Summary of clinical efficacy and safety." The subsections below explain major adverse events other than deaths. The results of the Japanese phase I study (Study ONO-4538-01) and the foreign phase I studies (Studies CA209001 and CA209003) were submitted and evaluated for the initial application for nivolumab [see "Review Report for Opdivo Intravenous Infusion 20 mg, Opdivo Intravenous Infusion 100 mg dated June 18, 2014"]. Those data were therefore not included in this report.

3.(iv).(1) Japanese phase II study (Study ONO-4538-05)

Adverse events were reported in 33 (94.3%) of 35 subjects and drug-related adverse events were reported in 24 (68.6%) of 35 subjects. The table below shows adverse events with an incidence of ≥10%.

Adverse events with an incidence of ≥10%

System Organ Class Preferred Term (MedDRA/J ver.17.1)	n (%) n = 35	
	All Grades	Grade ≥3
All adverse events	33 (94.3)	4 (11.4)
Gastrointestinal disorders		
Diarrhoea	5 (14.3)	0
Nausea	4 (11.4)	0
General disorders and administration site conditions		
Malaise	6 (17.1)	0
Pyrexia	9 (25.7)	0
Investigations		
Blood creatine phosphokinase increased	6 (17.1)	0
Lymphocyte count decreased	4 (11.4)	3 (8.6)
Metabolism and nutrition disorders		
Decreased appetite	8 (22.9)	0
Skin and subcutaneous tissue disorders		
Rash	5 (14.3)	0

The following serious adverse events were reported in 4 of 35 subjects (11.4%): atrial fibrillation, diarrhoea, malignant pleural effusion, interstitial lung disease, and pneumonitis (2.9%, n = 1 each). For atrial fibrillation, interstitial lung disease, and pneumonitis (n = 1 each), a causal relationship to the study drug could not be ruled out.

The following adverse events led to drug discontinuation in 2 of 35 subjects (5.7%): secondary adrenocortical insufficiency and interstitial lung disease in (2.9%, n = 1 each). For both events, a causal relationship to the study drug could not be ruled out.

3.(iv).(2) Japanese phase II study (Study ONO-4538-06)

Adverse events were reported in 75 of 76 subjects (98.7%) and adverse events for which causal relationship to the study drug were reported in 64 of 76 subjects (84.2%). The table below shows adverse events with an incidence of ≥10%.

Adverse events with an incidence of ≥10%

System Organ Class Preferred Term (MedDRA/J ver.17.0)	n (%) n = 76	
	All Grades	Grade ≥3
All adverse events	75 (98.7)	28 (36.8)
Gastrointestinal disorders		
Diarrhoea	9 (11.8)	0
Nausea	13 (17.1)	1 (1.3)
Vomiting	8 (10.5)	1 (1.3)
General disorders and administration site conditions		
Fatigue	12 (15.8)	1 (1.3)
Malaise	13 (17.1)	0
Pyrexia	16 (21.1)	1 (1.3)
Infections and infestations		
Nasopharyngitis	14 (18.4)	0
Metabolism and nutrition disorders		
Decreased appetite	17 (22.4)	4 (5.3)
Skin and subcutaneous tissue disorders		
Pruritus	9 (11.8)	1 (1.3)
Rash	14 (18.4)	0

The following serious adverse events were reported in 22 of 76 subjects (28.9%): interstitial lung disease and pleural effusion (3.9%, n = 3 each); decreased appetite and lung disorder (2.6%, n = 2 each); and cardiac tamponade, secondary adrenocortical insufficiency, colitis, pyrexia, liver disorder, bronchitis, subdural haematoma, prostate cancer, cerebral infarction, convulsion, dizziness, renal failure acute, and pneumothorax (1.3%, n = 1 each). A causal relationship to the study drug could not be ruled out for interstitial lung disease (n = 3); lung disorder and pleural effusion (n = 2 each); and secondary adrenocortical insufficiency, colitis, liver disorder, bronchitis, subdural haematoma, decreased appetite, and dizziness (n = 1 each).

The following adverse events led to drug discontinuation in 16 of 76 subjects (21.1%): interstitial lung disease (5.3%, n = 4); pleural effusion (3.9%, n = 3); ascites and lung disorder (2.6%, n = 2 each); and cardiac tamponade, secondary adrenocortical insufficiency, thyroiditis chronic, colitis, vomiting, fatigue, generalised oedema, and myalgia (1.3%, n = 1 each). A causal relationship to the study drug could not be ruled out for interstitial lung disease (n = 4); lung disorder and, pleural effusion (n = 2 each); and secondary adrenocortical insufficiency, thyroiditis chronic, ascites, colitis, fatigue, and myalgia (n = 1 each).

3.(iv).(3) Foreign phase II study (Study CA209010)

Adverse events were reported in 58 of 59 subjects (98.3%) in the 0.3 mg/kg group, 54 of 54 subjects (100%) in the 2 mg/kg group, and 53 of 54 subjects (98.1%) in the 10 mg/kg group. Adverse events for which a causal relationship to the study drug were reported in 44 of 59 subjects (74.6%) in the 0.3 mg/kg group, 36 of 54 subjects (66.7%) in the 2 mg/kg group, and 42 of 54 subjects (77.8%) in the 10 mg/kg group. The table below shows adverse events with an incidence of ≥20% in any group.

Adverse events with an incidence of ≥20% in any group

System Organ Class Preferred Term (MedDRA/J ver.16.0)	n (%)					
	0.3mg/kg n = 59		2mg/kg n = 54		10mg/kg n = 54	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	58 (98.3)	30 (50.8)	54 (100)	36 (66.7)	53 (98.1)	25 (46.3)
Gastrointestinal disorders						
Nausea	16 (27.1)	2 (3.4)	15 (27.8)	2 (3.7)	12 (22.2)	0
Constipation	12 (20.3)	1 (1.7)	17 (31.5)	0	9 (16.7)	0
Vomiting	11 (18.6)	0	7 (13.0)	0	11 (20.4)	0
Diarrhoea	6 (10.2)	0	9 (16.7)	0	12 (22.2)	0
General disorders and administration site conditions						
Fatigue	24 (40.7)	4 (6.8)	23 (42.6)	2 (3.7)	28 (51.9)	1 (1.9)
Metabolism and nutrition disorders						
Decreased appetite	5 (8.5)	0	13 (24.1)	0	10 (18.5)	0
Musculoskeletal and connective tissue disorders						
Back pain	10 (16.9)	1 (1.7)	14 (25.9)	2 (3.7)	17 (31.5)	0
Arthralgia	6 (10.2)	0	15 (27.8)	1 (1.9)	14 (25.9)	1 (1.9)
Pain in extremity	5 (8.5)	0	14 (25.9)	1 (1.9)	3 (5.6)	0
Respiratory, thoracic and mediastinal disorders						
Cough	17 (28.8)	1 (1.7)	16 (29.6)	0	9 (16.7)	0
Dyspnoea	16 (27.1)	5 (8.5)	8 (14.8)	2 (3.7)	12 (22.2)	3 (5.6)
Skin and subcutaneous tissue disorders						
Rash	6 (10.2)	0	5 (9.3)	0	12 (22.2)	0

Serious adverse events were reported in 27 of 59 subjects (45.8%) in the 0.3 mg/kg group, 33 of 54 subjects (61.1%) in the 2 mg/kg group, and 22 of 54 subjects (40.7%) in the 10 mg/kg group. The serious adverse events reported in at least 2 subjects in the 0.3 mg/kg group were hypercalcaemia, malignant neoplasm progression, and anaemia (5.1%, n = 3 each); and pain, pulmonary embolism, constipation, nausea, convulsion, spinal cord compression, and renal cell carcinoma (3.4%, n = 2 each). Those in the 2 mg/kg group were spinal cord compression (7.4%, n = 4); malignant neoplasm progression (5.6%, n = 3); and oedema peripheral, haemoptysis, pleural effusion, pancreatitis, hyperglycaemia, dehydration, paraesthesia, pneumonia, anaemia, hypotension, and renal failure acute (3.7%, n = 2 each). Those in the 10 mg/kg group were dyspnoea (5.6%, n = 3) and pulmonary embolism, abdominal pain, malignant neoplasm progression, and metastases to central nervous system (3.7%, n = 2 each). A causal relationship to the study drug could not be ruled out for pancreatitis, hyperglycaemia, and anaemia (n = 1 each) in the 2 mg/kg group and dyspnoea (n = 1) in the 10 mg/kg group.

Adverse events led to drug discontinuation in 3 of 59 subjects (5.1%) in the 0.3 mg/kg group, 11 of 54 subjects (20.4%) in the 2 mg/kg group, and 7 of 54 subjects (13.0%) in the 10 mg/kg group. The adverse

events leading to drug discontinuation were in the 0.3 mg/kg group were dyspnoea, pleural effusion, central nervous system lesion, and pericarditis (1.7%, n = 1 each). Those in the 2 mg/kg group were spinal cord compression (3.7%, n = 2); and fatigue, pneumonitis, cough, wheezing, nausea, pancreatitis, enterocolitis, small intestine ulcer, back pain, paraesthesia, rash, AST increased, hypothyroidism, and adrenal insufficiency (1.9%, n = 1 each). Those in the 10 mg/kg group were multi-organ failure, dyspnoea, pleural effusion, pulmonary embolism, pneumonitis, haemorrhage intracranial, balance disorder, blood ALP increased, AST increased, and ALT increased (1.9%, n = 1 each). A causal relationship to the study drug could not be ruled out for pericarditis (n = 1) in the 0.3 mg/kg group; pneumonitis, cough, wheezing, pancreatitis, enterocolitis, rash, AST increased, hypothyroidism, and adrenal insufficiency (n = 1 each) in the 2 mg/kg group; and pleural effusion, pneumonitis, haemorrhage intracranial, balance disorder, blood ALP increased, AST increased, and ALT increased (n = 1 each) in the 10 mg/kg group.

3.(iv).(4) Foreign phase II study (Study CA209063)

Adverse events were reported in 117 of 117 subjects (100%), and adverse events for which causal relationship to the study drug could not be ruled out were reported in 87 of 117 subjects (74.4%). The adverse events with an incidence of ≥20% are shown in the table below.

Adverse events with an incidence of ≥20%

System Organ Class Preferred Term (MedDRA/J ver.17.0)	n (%) n = 117	
	All Grades	Grade ≥3
All adverse events	117 (100)	75 (64.1)
Gastrointestinal disorders		
Constipation	28 (23.9)	0
Nausea	34 (29.1)	2 (1.7)
General disorders and administration site conditions		
Fatigue	58 (49.6)	8 (6.8)
Metabolism and nutrition disorders		
Decreased appetite	41 (35.0)	3 (2.6)
Respiratory, thoracic and mediastinal disorders		
Cough	37 (31.6)	2 (1.7)
Dyspnoea	44 (37.6)	10 (8.5)

Serious adverse events were reported in 68 of 117 subjects (58.1%). Serious adverse events reported in at least 2 subjects were malignant neoplasm progression (6.8%, n = 8), dyspnoea and pneumonia (6.0%, n = 7 each); pneumonitis and hypercalcaemia (4.3%, n = 5 each); chronic obstructive pulmonary disease (3.4%, n = 4); haemoptysis and pain (2.6%, n = 3); and pleural effusion, pulmonary haemorrhage, abdominal pain, hypotension, superior vena cava syndrome, musculoskeletal chest pain, and confusional state (1.7%, n = 2 each). For pneumonitis (n = 5) and pneumonia (n = 1), a causal relationship to the study drug could not be ruled out.

Adverse events led to drug discontinuation in 37 of 117 subjects (31.6%). The following adverse events leading to drug discontinuation were reported in at least 2 subjects: pneumonitis (4.3%, n = 5); malignant

neoplasm progression (3.4%, n = 4); and dyspnoea, fatigue, and pneumonia (1.7%, n = 2 each). For pneumonitis (n = 5) and fatigue (n = 2), a causal relationship to the study drug could not be ruled out.

3.(iv).(5) Foreign phase III study (Study CA209017)

Adverse events were reported in 127 of 131 subjects (96.9%) in the nivolumab group and 125 of 129 subjects (96.9%) in the DOC group. Adverse events for which causal relationship to the study drug could not be ruled out were reported in 76 of 131 subjects (58.0%) in the nivolumab group and 111 of 129 subjects (86.0%) in the DOC group. The table below shows adverse events with an incidence of ≥20% in either group.

Adverse events with an incidence of ≥20% in either group

System Organ Class Preferred Term (MedDRA/J ver.17.1)	n (%)			
	Nivolumab n = 131		DOC n = 129	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	127 (96.9)	67 (51.1)	125 (96.9)	94 (72.9)
Blood and lymphatic system disorders				
Anaemia	22 (16.8)	4 (3.1)	37 (28.7)	4 (3.1)
Neutropenia	2 (1.5)	1 (0.8)	43 (33.3)	38 (29.5)
Gastrointestinal disorders				
Diarrhoea	20 (15.3)	2 (1.5)	33 (25.6)	4 (3.1)
Nausea	20 (15.3)	3 (2.3)	32 (24.8)	3 (2.3)
General disorders and administration site conditions				
Asthenia	20 (15.3)	0	27 (20.9)	9 (7.0)
Fatigue	40 (30.5)	3 (2.3)	51 (39.5)	11 (8.5)
Metabolism and nutrition disorders				
Decreased appetite	32 (24.4)	1 (0.8)	35 (27.1)	2 (1.6)
Respiratory, thoracic and mediastinal disorders				
Cough	41 (31.3)	2 (1.5)	24 (18.6)	0
Dyspnoea	48 (36.6)	7 (5.3)	38 (29.5)	8 (6.2)
Skin and subcutaneous tissue disorders				
Alopecia	1 (0.8)	1 (0.8)	29 (22.5)	1 (0.8)

Serious adverse events were reported in 61 of 131 subjects (46.6%) in the nivolumab group and 70 of 129 subjects (54.3%) in the DOC group. The serious adverse events reported in at least 2 subjects in the nivolumab group were malignant neoplasm progression (13.7%, n = 18); pneumonia (5.3%, n = 7); pyrexia (3.8%, n = 5); hypercalcaemia (3.1%, n = 4); and upper respiratory tract infection, chronic obstructive pulmonary disease, dyspnoea, pneumonitis, pulmonary embolism, respiratory failure, dehydration, anaemia, and dysphagia (1.5%, n = 2 each). Those in the DOC group were febrile neutropenia (10.1%, n = 13); pneumonia (7.8%, n = 10); malignant neoplasm progression (7.0%, n = 9); neutropenia (3.1%, n = 4); lung infection, pulmonary haemorrhage, dehydration, and atrial fibrillation (2.3%, n = 3 each); and infection, sepsis, dyspnoea, pulmonary embolism, respiratory failure, haemoptysis, asthenia, and cerebrovascular accident (1.6%, n = 2 each). A causal relationship to the study drug could not be ruled out for pyrexia (n = 2), upper respiratory tract infection, chronic obstructive pulmonary disease, and pneumonitis (n = 1 each) in the nivolumab group, and febrile

neutropenia (n = 13), neutropenia (n = 4), dehydration (n = 2), pneumonia, infection, lung infection, sepsis, and pulmonary haemorrhage (n = 1 each) in the DOC group.

Adverse events led to drug discontinuation in 14 of 131 subjects (10.7%) in the nivolumab group and 26 of 129 subjects (20.2%) in the DOC group. The adverse events leading to drug discontinuation reported in at least 2 subjects in the nivolumab group were malignant neoplasm progression (3.1%, n = 4); pneumonitis and pneumonia (2.3%, n = 3 each); and respiratory failure (1.5%, n = 2). Those in the DOC group were neuropathy peripheral (3.1%, n = 4); respiratory failure, malignant neoplasm progression, asthenia, and fatigue (1.6%, n = 2 each). A causal relationship to the study drug could not be ruled out for pneumonitis (n = 2) in the nivolumab group and neuropathy peripheral (n = 4), fatigue (n = 2), and asthenia (n = 1) in the DOC group.

3.(iv).(6) Foreign phase III study (Study CA209057)

Adverse events were reported in 280 of 287 subjects (97.6%) in the nivolumab group and 265 of 268 subjects (98.9%) in the DOC group. Adverse events for which causal relationship to the study drug could not be ruled out were reported in 199 of 287 subjects (69.3%) in the nivolumab group and 236 of 268 subjects (88.1%) in the DOC group. The table below shows adverse events with an incidence of ≥20% in either group.

Adverse events with an incidence of ≥20% in either group

System Organ Class Preferred Term (MedDRA/J ver.17.1)	n (%)			
	Nivolumab n = 287		DOC n = 268	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	280 (97.6)	155 (54.0)	265 (98.9)	194 (72.4)
Blood and lymphatic system disorders				
Anaemia	34 (11.8)	5 (1.7)	68 (25.4)	13 (4.9)
Neutropenia	2 (0.7)	1 (0.3)	87 (32.5)	75 (28.0)
Gastrointestinal disorders				
Constipation	66 (23.0)	2 (0.7)	45 (16.8)	2 (0.7)
Diarrhoea	45 (15.7)	3 (1.0)	73 (27.2)	3 (1.1)
Nausea	63 (22.0)	5 (1.7)	80 (29.9)	2 (0.7)
General disorders and administration site conditions				
Asthenia	59 (20.6)	10 (3.5)	62 (23.1)	11 (4.1)
Fatigue	91 (31.7)	9 (3.1)	102 (38.1)	18 (6.7)
Metabolism and nutrition disorders				
Decreased appetite	83 (28.9)	5 (1.7)	58 (21.6)	4 (1.5)
Respiratory, thoracic and mediastinal disorders				
Cough	76 (26.5)	1 (0.3)	62 (23.1)	0
Dyspnoea	65 (22.6)	15 (5.2)	63 (23.5)	10 (3.7)
Skin and subcutaneous tissue disorders				
Alopecia	4 (1.4)	0	70 (26.1)	0

Serious adverse events were reported in 134 of 287 subjects (46.7%) in the nivolumab group and 111 of 268 subjects (41.4%) in the DOC group. The serious adverse events reported in at least 3 subjects in the nivolumab group were malignant neoplasm progression (8.0%, n = 23), pneumonia (4.2%, n = 12), pulmonary embolism (3.8%, n = 11), dyspnoea (3.1%, n = 9), pleural effusion (2.8%, n = 8), respiratory failure (2.1%, n = 6), pain (1.7%, n = 5), pneumonitis, general physical health deterioration, pyrexia, nausea, and headache (1.4%, n = 4 each), metastases to the central nervous system, bronchitis, asthenia, and diarrhoea (1.0%, n = 3 each). Those in the DOC group were febrile neutropenia (9.0%, n = 24); pneumonia (4.9%, n = 13); neutropenia (3.0%, n = 8); malignant neoplasm progression (2.6%, n = 7); dyspnoea (1.9%, n = 5); respiratory failure, pyrexia, anaemia, and dehydration (1.5%, n = 4 each); and pulmonary embolism, pleural effusion, haemoptysis, bronchitis, respiratory tract infection, pain, general physical health deterioration, asthenia, back pain, pericardial effusion, and mental status changes (1.1%, n = 3 each). A causal relationship to the study drug could not be ruled out for pneumonitis (n = 4), nausea (n = 2), pulmonary embolism, dyspnoea, and diarrhoea (n = 1 each) in the nivolumab group, febrile neutropenia (n = 2), neutropenia (n = 8), pneumonia (n = 5), pyrexia, asthenia, anaemia, dehydration (n = 3 each), bronchitis and respiratory tract infection (n = 2 each) in the DOC group.

Adverse events led to drug discontinuation in 48 of 287 subjects (16.7%) in the nivolumab group and 58 of 268 subjects (21.6%) in the DOC group. The adverse events leading to drug discontinuation reported in at least 3 subjects in the nivolumab group were malignant neoplasm progression, (3.1%, n = 9), respiratory failure (1.4%, n = 4), and dyspnoea, pneumonitis, and pulmonary embolism (1.0%, n = 3 each). Those in the DOC group were fatigue (3.4%, n = 9); asthenia, oedema peripheral, pneumonia, and neuropathy peripheral (1.9%, n = 5 each); and general physical health deterioration (1.1%, n = 3).

A causal relationship to the study drug could not be ruled out for pneumonitis (n = 3) dyspnoea, and pulmonary embolism (n = 1 each) in the nivolumab group, fatigue (n = 9), oedema peripheral, neuropathy peripheral (n = 5 each), asthenia (n = 4), and pneumonia (n = 1) in the DOC group.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

The inspections are underway. The results and PMDA's conclusion will be reported in Review Report (2).

2. PMDA's conclusion on the results of GCP on-site inspection

The inspections are underway. The results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, PMDA has concluded that the efficacy of nivolumab (Opdivo) in the treatment of unresectable, advanced or recurrent non-small cell lung cancer has been demonstrated and that its safety is acceptable in view of its observed benefits. Nivolumab offers a new option for the treatment of unresectable, advanced or recurrent non-small cell lung cancer, and is therefore considered of clinical significance. The indication, dosage and administration, post-marketing issues, etc. are to be further discussed in the Expert Discussion.

This application may be approved if Opdivo is not considered to have any particular problems based on the comments from the Expert Discussion.

Review Report (2)

November 17, 2015

I. Product Submitted for Registration

[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 21, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for registration, 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) Efficacy

On the basis of the review shown in "II.3.(iii).B.(2) Efficacy" in Review Report (1), PMDA concluded that these results demonstrated the efficacy of nivolumab (genetical recombination) ("nivolumab") in eligible patients for Studies CA209017 and CA209057. This conclusion was drawn from the following results: the overall survival (OS), the primary endpoint, improved in the nivolumab group as compared to the docetaxel hydrate (DOC) group as the control, in the foreign phase III study in patients with squamous (SQ) non-small cell lung cancer (NSCLC) who had received prior platinum-based chemotherapy (Study CA209017) and the foreign phase III study in patients with non-squamous (NSQ) NSCLC who had received prior platinum-based chemotherapy (Study CA209057).

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

(2) Safety

On the basis of the review shown in "II.3.(iii).B.(3) Safety" in the Review Report (1), PMDA concluded that the following adverse events should be closely monitored when nivolumab is administered to patients with NSCLC:

(a) Adverse events that were identified in the data previously submitted in the application for the indication of unresectable malignant melanoma and that are considered typically associated with the use of nivolumab (i.e., interstitial pneumonia, hepatic function disorder, abnormal thyroid function, infusion reaction, and skin disorder)

(b) Adverse events added in the package insert for precautions based on post-marketing data accumulated in Japan (i.e., colitis, severe diarrhoea, myasthenia gravis, and myositis)

(c) Neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, and encephalitis

PMDA also concluded that nivolumab is tolerable in patients, provided that physicians with adequate knowledge and experience in cancer chemotherapy follow up the patients by taking appropriate actions including adverse event monitoring, differential diagnosis and management of potential immune-mediated adverse reactions. At the Expert Discussion, the expert advisors supported the above conclusion by PMDA, and made the following comment:

- Immune-mediated adverse reactions are rare with conventional antineoplastic drugs, and even expert physicians in cancer chemotherapy may not be used to handling immune-mediated adverse reactions associated with nivolumab therapy. Healthcare professionals should be provided with specific information on immune-mediated adverse reactions including measures to be taken for such adverse reactions.

PMDA's view:
Based on the comment from the Expert Discussion, PMDA concluded that specific measures for addressing immune-mediated adverse reactions associated with nivolumab therapy should be communicated to healthcare professionals through information materials, etc.

PMDA instructed the applicant to address this matter appropriately, and the applicant agreed to the instruction.

(3) Clinical positioning and indication

Based on the review in "II.3.(iii).B.(4) Clinical positioning and indication" in the Review Report (1), PMDA concluded that (i) the "Clinical Studies" section of the package insert should state that Studies CA209017 and CA209057 enrolled patients who had received prior platinum-based chemotherapy, that (ii) as proposed by the applicant, nivolumab should be indicated for the treatment of "unresectable, advanced or recurrent non-small cell lung cancer" along with the following precautionary advice in the "Precautions for Indication" section:

Precautions for Indication

- Eligible patients must be selected based on a careful review of the contents of the Clinical Studies section, a thorough understanding of the efficacy and safety of Opdivo, and a thorough evaluation of the use of therapies other than the product.
- 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.

At the Expert Discussion, the expert advisors supported the conclusion by PMDA, and made the following comment:

- A subgroup analysis based on CD274 (programmed cell death-ligand 1, PD-L1) expression status identified using the tumor tissue samples from subjects in Study CA209057 revealed that the hazard ratio [95% confidence interval] for OS in the subgroup of subjects with low PD-L1 positivity (<10%) was 1.00 [0.76, 1.31] [see "II.3.(iii).B.(4).2) Intended population"]. Although it would be difficult to limit the intended population of nivolumab based on the results of the subgroup analysis, the results are important data for determining whether to use nivolumab. Therefore, the correlation between PD-L1 expression status and the efficacy and safety of nivolumab should be closely investigated, and information including the safety data from the individual subgroups in Studies CA209017 and CA209057 should be communicated to healthcare professionals.

PMDA asked the applicant to explain the safety data analyzed based on PD-L1 expression status in Studies CA209017 and CA209057.

The following is the applicant's response:
The summary of the safety of nivolumab by PD-L1 expression status (cut-off value, 10%) and the adverse events resulting in death in Study CA209017 are respectively shown in the tables below.

Summary of safety according to PD-L1 expression status in the tumor tissue sample (cut-off value of 10%) (Study CA209017)

	n (%)			
	PD-L1			
	≥10%		<10%	
	Nivolumab n = 34	DOC n = 31	Nivolumab n = 79	DOC n = 69
All adverse events	34 (100)	29 (93.5)	77 (97.5)	68 (98.6)
Grade ≥3 adverse events	18 (52.9)	21 (67.7)	41 (51.9)	52 (75.4)
Adverse events resulting in death	5 (14.7)	2 (6.5)	9 (11.4)	13 (18.8)
Serious adverse events	16 (47.1)	16 (51.6)	36 (45.6)	36 (52.2)
Adverse events leading to drug discontinuation	4 (11.8)	5 (16.1)	9 (11.4)	17 (24.6)
Adverse events leading to drug interruption	12 (35.3)	8 (25.8)	20 (25.3)	19 (27.5)

Adverse events resulting in death by PD-L1 expression status in the tumor tissue sample (cut-off value of 10%) (Study CA209017)

System Organ Class Preferred Term (MedDRA/J ver.17.1)	n (%)			
	PD-L1 ≥10%		PD-L1 <10%	
	Nivolumab n = 34	DOC n = 31	Nivolumab n = 79	DOC n = 69
All adverse events	5 (14.7)	2 (6.5)	9 (11.4)	13 (18.8)
Cardiac disorders				
Cardio-respiratory arrest	0	0	1 (1.3)	0
General disorders and administration site conditions				
Sudden death	1 (2.9)	0	0	0
General physical health deterioration	1 (2.9)	0	0	0
Infections and infestations				
Sepsis	0	1 (3.2)	0	0
Metabolism and nutrition disorders				
Dehydration	0	0	0	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Malignant neoplasm progression	2 (5.9)	1 (3.2)	8 (10.1)	5 (7.2)
Metastases to central nervous system	0	0	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders				
Haemoptysis	0	0	0	1 (1.4)
Interstitial lung disease	0	0	0	1 (1.4)
Pulmonary haemorrhage	0	0	0	2 (2.9)
Respiratory failure	1 (2.9)	0	0	2 (2.9)

The summary of the safety of nivolumab by PD-L1 expression status (cut-off value, 10%) and the adverse events resulting in death in Study CA209057 study are respectively shown in the tables below.

Summary of safety according to PD-L1 expression status in the tumor tissue sample (cut-off value of 10%) (Study CA209057)

	n (%)			
	PD-L1			
	≥10%		<10%	
	Nivolumab n = 84	DOC n = 72	Nivolumab n = 143	DOC n = 135
All adverse events	82 (97.6)	71 (98.6)	139 (97.2)	133 (98.5)
Grade ≥3 adverse events	44 (52.4)	57 (79.2)	73 (51.0)	95 (70.4)
Adverse events resulting in death	9 (10.7)	10 (13.9)	31 (21.7)	7 (5.2)
Serious adverse events	38 (45.2)	39 (54.2)	68 (47.6)	47 (34.8)
Adverse events leading to drug discontinuation	11 (13.1)	16 (22.2)	27 (18.9)	30 (22.2)
Adverse events leading to drug interruption	29 (34.5)	11 (15.3)	36 (25.2)	30 (22.2)

Adverse events resulting in death by PD-L1 expression status in the tumor tissue sample (cut-off value of 10%) (Study CA209057)

System Organ Class Preferred Term (MedDRA/J ver.17.1)	n (%)			
	PD-L1 ≥10%		PD-L1<10%	
	Nivolumab n = 84	DOC n = 72	Nivolumab n = 143	DOC n = 135
All adverse events	9 (10.7)	10 (13.9)	31 (21.7)	7 (5.2)
Blood and lymphatic system disorders				
Anaemia	0	0	0	1 (0.7)
Febrile neutropenia	0	1 (1.4)	0	0
Cardiac disorders				
Cardiopulmonary failure	1 (1.2)	0	0	0
General disorders and administration site conditions				
Multi-organ failure	1 (1.2)	0	0	0
Pain	0	0	1 (0.7)	1 (0.7)
Sudden death	0	1 (1.4)	1 (0.7)	0
General physical health deterioration	0	1 (1.4)	2 (1.4)	0
Infections and infestations				
Bronchitis	0	0	0	1 (0.7)
Infection	1 (1.2)	0	0	0
Pneumonia	2 (2.4)	2 (2.8)	1 (0.7)	0
Injury, poisoning and procedural complications				
Head injury	1 (1.2)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Metastases to bone	0	1 (1.4)	0	0
Malignant neoplasm progression	0	2 (2.8)	18 (12.6)	3 (2.2)
Lung neoplasm malignant	1 (1.2)	0	0	0
Neoplasm progression	0	0	1 (0.7)	0
Non-small cell lung cancer	0	0	1 (0.7)	1 (0.7)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	2 (2.4)	1 (1.4)	2 (1.4)	0
Dyspnoea at rest	0	0	1 (0.7)	0
Hypoxaemia	0	0	1 (0.7)	0
Pulmonary embolism	0	0	1 (0.7)	0
Respiratory failure	1 (1.2)	1 (1.4)	3 (2.1)	2 (1.5)

PMDA asked the applicant to explain factors that may have affected the efficacy of nivolumab other than PD-L1 expression status in Study CA209057.

The applicant's response:

The table below shows OS influenced by factors other than PD-L1 expression status in Study CA209057.

Efficacy influenced by factors other than PD-L1 expression status in the tumor tissue sample (Study CA209057)

Factor		Treatment group	n	OS	
				Median [95% CI] (months)	Hazard ratio* [95% CI]
Prior maintenance treatment	Yes	Nivolumab	122	12.35 [10.32, 18.79]	0.80 [0.58, 1.10]
		DOC	111	10.51 [9.23, 14.23]	
	No	Nivolumab	170	12.19 [6.93, 14.72]	0.73 [0.57, 0.93]
		DOC	179	8.71 [7.00, 10.58]	
Number of prior regimens	1	Nivolumab	256	12.75 [9.99, 16.20]	0.69 [0.56, 0.85]
		DOC	259	9.30 [8.02, 10.68]	
	2	Nivolumab	35	8.21 [2.79, 15.54]	1.34 [0.73, 2.43]
		DOC	31	10.09 [5.88, NE]	
	Other	Nivolumab	1	14.72 [NE, NE]	NE [NE, NE]
		DOC	0	NE [NE, NE]	
Region	North America	Nivolumab	105	16.76 [10.81, 20.63]	0.52 [0.37, 0.72]
		DOC	110	8.02 [6.70, 10.09]	
	Europe	Nivolumab	135	10.32 [6.51, 15.54]	0.81 [0.61, 1.07]
		DOC	134	9.30 [7.46, 10.81]	
	Other	Nivolumab	52	11.14 [6.21, 14.26]	1.49 [0.91, 2.45]
		DOC	46	14.46 [10.28, NE]	
History of smoking habit	Yes	Nivolumab	231	12.09 [9.33, 15.21]	0.70 [0.56, 0.86]
		DOC	227	9.33 [7.95, 10.74]	
	No	Nivolumab	58	12.85 [7.59, 20.37]	1.02 [0.64, 1.61]
		DOC	60	9.95 [6.77, NE]	
	Unknown	Nivolumab	3	11.99 [7.23, NE]	NE [NE, NE]
		DOC	3	3.29 [2.83, NE]	
Epidermal growth factor receptor (EGFR) gene mutation	Yes	Nivolumab	44	9.20 [5.19, 13.11]	1.18 [0.69, 2.00]
		DOC	38	11.53 [5.75, 17.81]	
	No	Nivolumab	168	13.57 [10.41, 18.43]	0.66 [0.51, 0.86]
		DOC	172	9.26 [7.72, 10.74]	
	Unknown	Nivolumab	80	11.29 [7.72, 15.74]	0.74 [0.51, 1.06]
		DOC	80	9.33 [7.20, 11.96]	
Metastases to central nervous system	Yes	Nivolumab	34	7.61 [4.47, 11.14]	1.04 [0.62, 1.76]
		DOC	34	7.33 [4.40, 10.55]	
	No	Nivolumab	258	13.11 [10.32, 17.15]	0.71 [0.58, 0.88]
		DOC	256	9.95 [8.54, 11.10]	

NE, not estimated;
* Estimated using a Cox proportional hazard model including treatment group as a covariate.

PMDA's view:

In response to the opinions of the Expert Discussion, the relationship between the PD-L1 expression status and the efficacy and safety of nivolumab was closely investigated. (a) In Study CA209017, the PD-L1 expression status did not significantly affect the safety or efficacy results. (b) In Study CA209057, the hazard ratios for OS in the subgroups of subjects with factors other than PD-L1 expression status were >1. These results, (a) and (b), indicate limitations to the investigation of a relationship between the PD-L1 expression status and the efficacy and safety of nivolumab based on currently available data. However, information on the efficacy and safety of nivolumab according to PD-L1 expression status (i.e., data obtained in Studies CA209017 and CA209057) is important for decision making on the use of nivolumab, and therefore should be communicated to healthcare professionals through informational materials.

PMDA instructed the applicant to specify the indication of nivolumab and precautions for indication as discussed above and to ensure that information on the efficacy and safety of nivolumab and PD-L1 expression is provided to healthcare professionals through informational materials. The applicant agreed to the instructions.

(4) Dosage and administration

Based on the review in "II.3.(iii).B.(5) Dosage and administration" in the Review Report (1), PMDA concluded that the dosage and administration statement should be "the usual adult dosage of nivolumab (genetical recombination) is 3 mg/kg body weight administered as an intravenous infusion every 2 weeks," along with the following precautionary advice in the "Precautions for Dosage and Administration" section:

Precautions for Dosage and Administration

- Preparation method for 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 above conclusion by PMDA.

PMDA instructed the applicant to modify the "Dosage and Administration" and the "Precautions for Dosage and Administration" sections as above. The applicant agreed to the instruction.

(5) Risk management plan (draft)

The applicant plans to conduct a 12-month, all-case, post-marketing surveillance (the survey) with a target number of 1,000 patients with unresectable, advanced or recurrent NSCLC receiving nivolumab to investigate the safety of nivolumab in clinical use. The priority investigation items were determined in light of potential adverse events particularly attributable to the pharmacological action of nivolumab or those reported frequently in the clinical studies, which are namely interstitial lung disease, hepatic function disorder, abnormal thyroid function, colitis, and infusion reaction.

Based on the review in "II.3.(iii).B.(6) Post-marketing investigations" in the Review Report (1), PMDA concluded that the safety of nivolumab should be investigated through post-marketing surveillance covering all patients receiving nivolumab in clinical practice. PMDA also pointed out the following about the survey plan:

- The priority investigation items should include severe diarrhoea, myasthenia gravis and myositis, neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, encephalitis, and severe skin disorder, in addition to those proposed by the applicant. These events require special attention during nivolumab therapy.
- The target number of patients and the follow-up period should be reconsidered based on the incidences and time to onset of the adverse events that are additionally included in the priority investigation items.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

PMDA instructed the applicant to reconsider the survey plan according to the above advice.

The applicant's response:
- Adverse events that require special attention during nivolumab therapy, namely severe diarrhoea, myasthenia gravis and myositis, neurological disorder, renal disorder, venous thrombosis and embolism, adrenal disorder, encephalitis, and severe skin disorder, will be added in to the priority investigation items.
- The follow-up period will be 12 months in light of the incidences and time to onset of the above-mentioned adverse events that are to be added in to the priority investigation items.
- The survey aims to gather data from the target number of 1000 patients. Interstitial lung disease is of particular concern in patients with NSCLC because it may worsen the patient condition, leading to decreased respiratory function. Based on the incidence of interstitial lung disease in the Japanese phase II studies (Studies ONO-4538-05 and ONO-4538-06), the applicant chose the sample size of 1000 patients that was considered adequate for the detection of the lung disease. This target sample size also allows to investigate the occurrence of other events included in the priority investigation items.

PMDA accepted the applicant's response.

Based on the above discussions, PMDA concluded that the proposed risk management plan should include the safety and efficacy specifications shown in the table below and that additional pharmacovigilance activities and risk minimization activities should be implemented.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Interstitial lung disease • Myasthenia gravis and myositis • Colitis and severe diarrhoea • 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-mediated adverse reactions • Embryonic/fetal toxicity	Not applicable
Efficacy specification		
• Efficacy in patients with unresectable malignant melanoma in clinical practice • Efficacy in patients with unresectable, advanced or recurrent NSCLC in clinical practice		

Additional pharmacovigilance and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey in patients with unresectable malignant melanoma (all-case surveillance) • Use-results survey in patients with unresectable, advanced or recurrent NSCLC (all-case surveillance) Planned number of patients, 1,000 Duration of follow-up, 12 months • 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)	• Provision of data from early post-marketing phase vigilance • Preparation and provision of materials for healthcare professionals • Preparation and provision of materials for patients

Underlines indicate those activities to be carried out when the new indication is added

Outline of use-results survey plan (draft)

Objective	Investigation on the safety of nivolumab in routine clinical use
Survey method	All-case surveillance using the central registration system
Target patient population	Patients with unresectable, advanced or recurrent NSCLC
Duration	12 months
Planned number of patients	1000 patients
Main items to be investigated	Priority investigation items; interstitial lung disease, myasthenia gravis, myositis, colitis, severe diarrhoea, hepatic function disorder, abnormal thyroid function, neurological disorder, renal disorder, adrenal disorder, encephalitis, severe skin disorder, venous thrombosis and embolism, and infusion reaction Other major investigation items; patient characteristics (e.g., ECOG Performance Status, smoking history, timing of diagnosis, disease stage classification, prior treatments), use status of nivolumab, concomitant drugs, laboratory data, antitumor effect, patient outcome, adverse events, and other relevant items

III. Results of Compliance Assessment Concerning the Data Submitted in the Application and Conclusion by PMDA

1. PMDA's conclusion regarding the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted 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 for the data submitted in the application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion regarding the results of GCP on-site inspection

A GCP on-site inspection was conducted 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 for the data submitted in the application (5.3.5.2-1, 5.3.5.2-2). The clinical studies were generally performed in accordance with GCP, and PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents. However, the following issue was noted at the sponsor site, and it was notified to the applicant (i.e., the sponsor):

Finding requiring corrective actions

Sponsor

- Some information on unexpected serious adverse drug reactions was not properly communicated to the investigators and the heads of the study sites.

IV. Overall Evaluation

Based on the above review, PMDA has concluded that the product may be approved with the following conditions after the indications and the dosage and administration are modified as shown below; provided that necessary precautionary advice and information on the proper use of nivolumab are communicated through the package insert appropriately after the market launch; and that nivolumab is used by or under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy and at medical institutions capable of emergency response. This application has been submitted for approval of an additional indication for which nivolumab is not designated as an orphan drug, while nivolumab with a new active ingredient was granted an orphan designation for the approved indication. Therefore, PMDA has concluded that the re-examination period for nivolumab for the additional indication is 5 years and 10 months.

[Indications]

1. Treatment of unresectable malignant melanoma
2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer

(Underline denotes addition)

[Dosage and administration]

1. Treatment of unresectable malignant melanoma

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

2. Treatment of unresectable, advanced or recurrent non-small cell lung cancer

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

(Underline denotes addition)

[Conditions for 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] (Unchanged)

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

[Contraindications] (Unchanged)

Patients with a history of hypersensitivity to the ingredients of Opdivo

[Precautions for Indications] (Underline denotes addition)

(1) The efficacy and safety of Opdivo in chemotherapy-naïve patients have not been established.

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

(3) Eligible patients with unresectable malignant melanoma must be selected based on a careful review of the contents of the Clinical Studies section, a thorough understanding of the efficacy and safety of Opdivo, and a thorough evaluation of the use of therapies other than Opdivo.

(4) Eligible patients with unresectable, advanced or recurrent non-small cell lung cancer must be selected based on a careful review of the contents of the Clinical Studies section and a thorough understanding of the efficacy and safety of Opdivo.

[Precautions for Dosage and Administration] (Underline denotes addition)

(1) Preparation method for injection solution and the duration of infusion

1) Prior to injection, the required volume of the solution should be withdrawn from a vial(s) to achieve a single dose of 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.

2) Opdivo should be intravenously infused over at least 1 hour.

(2) An in-line filter (pore size, 0.2 or 0.22 μm) should be used for the administration of the product.

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