**Report on Deliberation Results**

June 26, 2014
Evaluation and Licensing Division, Pharmaceutical and Food Safety 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*) |
| [Name of applicant] | Ono Pharmaceutical Co., Ltd. |
| [Date of application] | December 24, 2013 |

[Results of deliberation]
In the meeting held on June 26, 2014, the Second Committee on New Drugs concluded that 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 10 years, and the drug substance and drug product are both classified as powerful drugs and biological products.

[Conditions for approval]
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 postmarketing period, thereby taking necessary measures to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

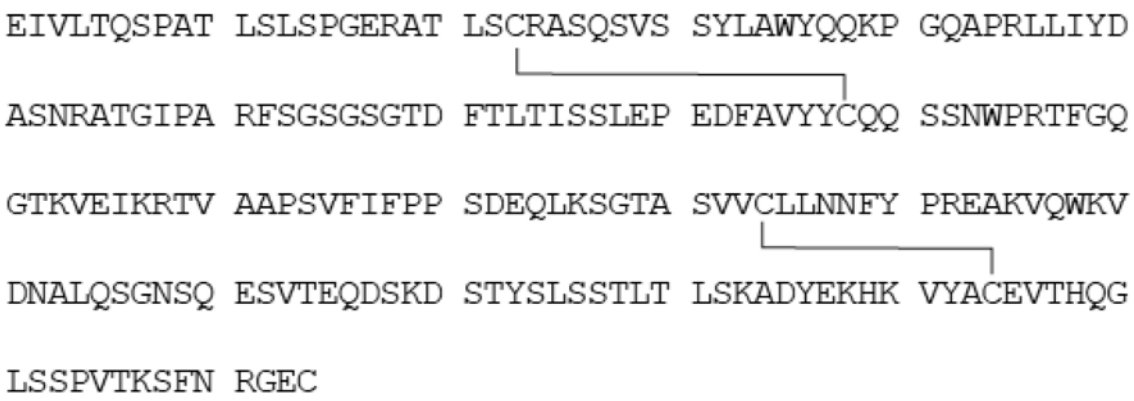
**Review Report**

June 18, 2014
Pharmaceuticals and Medical Devices Agency

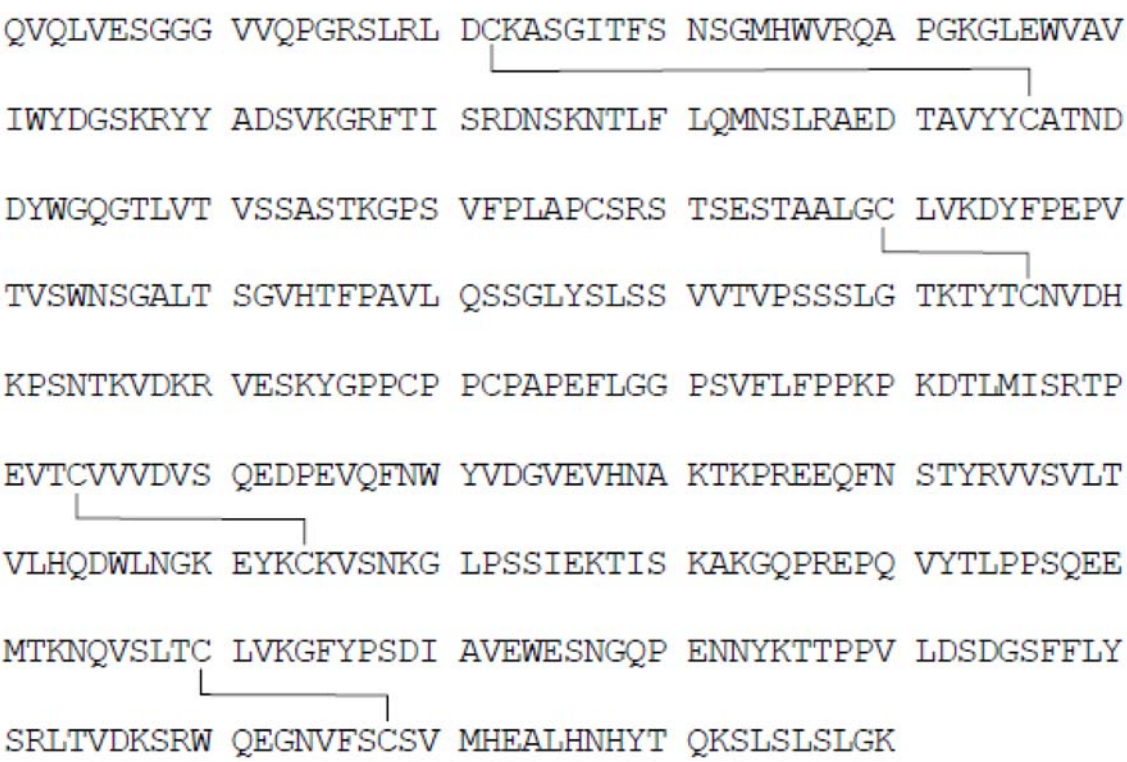
The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product that was submitted for registration are as follows.

| | |
|---|---|
| [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] | December 24, 2013 |
| [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 (1) Drug with a new active ingredient |

[Amino acid sequence]



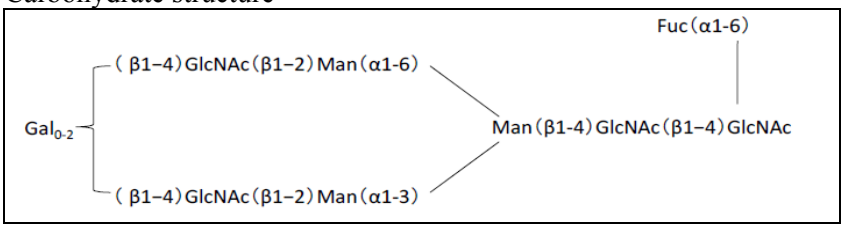

Light chain




Heavy chain

Post-translationally processed pyroglutamate residue: Heavy chain Q1
Glycosylation: Heavy chain N290
C-terminus processing: Heavy chain K440
Disulfide bond: Light chain C214–Heavy chain C127, Heavy chain C219–Heavy chain C219, Heavy chain C222–Heavy chain C222

Carbohydrate structure




Gal, D-galactose; GlcNAc, D-*N*-acetylglucosamine; Man, D-mannose; Fuc, L-fucose

Molecular formula: $C_{6362}H_{9836}N_{1712}O_{1998}S_{42}$
Molecular weight: ca. 145,000
Chemical name:
Nivolumab is a recombinant human IgG4 monoclonal antibody against human PD-1 wherein the amino acid residue at position 221 in the H chain is replaced by Pro. Nivolumab is produced by Chinese hamster ovary cells. Nivolumab is a glycoprotein (molecular weight: ca. 145,000) composed of 2 H chains (γ4 chains), each consisting of 440 amino acid residues, and 2 L chains (κ chains), each consisting of 214 amino acid residues.

[Items warranting special mention]
Orphan drug (Designation No. [25 yaku] No. 308, Notification No. 0617-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated June 17, 2013)

[Reviewing office] Office of New Drug V

**Review Results**

June 18, 2014

| | |
|---|---|
| [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] | December 24, 2013 |

[Results of review]

Based on the submitted data, it is concluded that the efficacy of Nivolumab (Genetical Recombination) in the treatment of unresectable malignant melanoma has been demonstrated and that its safety is acceptable in view of its observed benefits. Interstitial lung disease, hepatic function disorder, abnormal thyroid function, and infusion reaction need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

| | |
|---|---|
| [Indication] | Treatment of unresectable malignant melanoma |
| [Dosage and administration] | The usual adult dosage of Nivolumab (Genetical Recombination) is 2 mg/kg body weight, administered as an intravenous infusion every 3 weeks. |
| [Conditions for approval] | 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 postmarketing period, thereby taking necessary measures to ensure the proper use of the product. |

**Review Report (1)**

May 16, 2014

## 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] | December 24, 2013 |
| [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] | Malignant melanoma |
| [Proposed dosage and administration] | The usual adult dosage of Nivolumab (Genetical Recombination) is 2 mg/kg body weight administered as an intravenous infusion every 3 weeks. |

## 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 as shown below.

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

#### 1.(1) Summary of the product submitted for registration

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, natural killer T cells). PD-1 *in vivo* is thought to bind to PD-1 ligands expressed on antigen-presenting cells (CD274 [programed cell death ligand 1, PD-L1] and CD273 [programed 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 used by tumor cells to avoid attacks by antigen-specific T cells.

Nivolumab (Genetical Recombination) (hereinafter referred to as "nivolumab"), a human monoclonal antibody against human PD-1 belonging to the immunoglobulin (Ig) G4 subclass, was developed by the applicant and by Medarex in the US (currently Bristol-Myers Squibb). 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, and thus is considered to enhance the activation of cancer antigen-specific T cells and cytotoxic activation against cancer cells to inhibit tumor growth.

#### 1.(2) Development history, etc.

Outside of Japan, Medarex in the US (currently Bristol-Myers Squibb Company) initiated phase I studies, CA209001 and CA209003, in patients with advanced or recurrent solid tumors in October 2006 and October 2008, respectively.

As of April 2014, nivolumab has not been approved in any country or region.

In Japan, the applicant initiated a phase I study in patients with advanced solid tumors (ONO-4538-01) in February 2009 and a phase II study (ONO-4538-02) in patients with advanced or recurrent unresectable malignant melanoma who had a past history of chemotherapy with dacarbazine, in December 2011.

A marketing application for nivolumab was filed here in December 2013, based mostly on the results of ONO-4538-02 study.

Nivolumab was designated as an orphan drug in June 2013 with the expected indication for the treatment of malignant melanoma (Designation [25 yaku] No. 308).

## 2. Data relating to quality

### *2.A Summary of the submitted data*

#### 2.A.(1) Drug substance

#### 2.A.(1).1) Preparation and control of cell substrates

A hybridoma cell line was prepared by fusing mouse myeloma (Sp2/0) cells to spleen cells of a transgenic mouse* that had been inoculated with (a) a Chinese hamster ovary (CHO) cell line transfected with the *CD279* (programmed cell death 1, PD-1) gene and with (b) recombinant proteins in which the Fc region of human immunoglobulin (Ig) G1 had been fused to human PD-1. From this cell line, clones producing anti-PD-1 antibodies in high titers were selected and used to obtain gene fragments encoding the variable regions of the heavy and light chains of human anti-PD-1 IgG1. Gene expression constructs of Nivolumab (Genetical Recombination) (hereinafter referred to as "nivolumab") were prepared by introducing these gene fragments and gene fragments obtained from a vector containing the constant region of IgG4 into expression plasmids. These gene expression constructs were introduced into the CHO cell line. From the resulting cell line, clones highly producing anti-PD-1 antibodies were chosen. From these clones, a master cell bank (MCB) and a working cell bank (WCB) were prepared.

* A mouse whose antibody gene has been knocked out and replaced with a human antibody gene.

The MCB, WCB, EPCB, and EEPCB were characterized (by means of isozyme analysis, cytogenetic analysis, cDNA base sequence analysis, Southern blot analysis, Northern blot analysis, or gene copy number counting) to confirm genetic stability during manufacturing. The MCB, WCB, and EPCB were also subjected to impurity tests (sterility test, mycoplasma test [culture method and indicator cell culture method], an *in vitro* virus test, *in vivo* virus test, quantitative PCR mouse minute virus (MMV) test, hamster antibody production test, Xenotropic murine leukemia virus extended $S^+L^-$ focus assay, murine leukemia virus extended XC plaque assay, electron microscopy, *in vitro* bovine virus assay, *in vitro* porcine parvovirus test, reverse transcriptase activity test or co-culture test using *Mus dunni* cells). These tests did not detect adventitious viruses or non-viral adventitious agents except endogenous retroviruses and retrovirus-like particles that are commonly seen in rodent cell line.

[redacted]

#### 2.A.(1).2) Manufacturing process

[redacted] The drug substance is stored in low-density polyethylene containers at 2°C to 8°C. The manufacturing process employs Quality by Design (QbD) techniques [see "2.A.(4) QbD"]. [redacted]

Process validation/evaluation was conducted on the drug substance manufacturing process on the production scale.

#### 2.A.(1).3) Safety evaluations of adventitious agents

The drug substance manufacturing process involves no biological materials other than the CHO cell line that are host cells.

The MCB, WCB, EPCB, and EEPCB were subjected to impurity tests [see "2.A.(1).1) Preparation and control of cell substrates"]. In the course of the process validation, [redacted] batches of culture media

following production culture were subjected to mycoplasma tests (culture method and indicator cell culture method), a quantitative PCR MMV test, and an *in vitro* virus test. These tests did not detect adventitious viruses or non-viral adventitious agents. As in-process tests, culture media following production were subjected to mycoplasma tests (culture method and indicator cell culture method), a quantitative PCR MMV test, and an *in vitro* virus test.

During the purification process, a viral clearance study was performed using model viruses. The result showed that the purification process possesses the ability to reduce viruses to some extent.

**Viral clearance study results**

| Manufacturing process | Reduction factor ($log_{10}$) | | | |
|---|---|---|---|---|
| | Amphotropic murine leukemia virus | Herpes simplex virus type 1 | Mouse minute virus | Reovirus type 3 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Virus inactivation | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Virus filtration | [redacted] | [redacted] | [redacted] | [redacted] |
| Minimum overall reduction factor | > 17.59 | > 18.15 | 13.98 | > 15.69 |

**2.A.(1).4) Manufacturing process development (comparability)**

Major changes of the manufacturing process in the drug substance development stage were as follows. (Each manufacturing process is referred to as Processes A, B, and C [the last one is the proposed process].)

- From Process A to Process B: [redacted]
- From Process B to Process C: Changes were made to matters such as chromatography procedures and virus inactivation conditions

Based on these process changes, the comparability of quality attributes was assessed to confirm the comparability of the drug substance before and after the changes.

**2.A.(1).5) Characterization**

**2.A.(1).5).(a) Structure/composition**

Primary structure

- Peptide mapping analyses were performed with trypsin and Asp-N digestion under reducing conditions using liquid chromatography-electrospray ionization mass spectrometry (LC-ESI-MS) and tandem mass spectrometry (MS/MS). The results confirmed an amino acid sequence matching the amino acid sequence derived from the cDNA sequence.
- [redacted]

Higher-order structure

- Peptide mapping with trypsin digestion under non-reducing conditions showed 2 disulfide bonds within the light chain; 4 disulfide bonds within the heavy chain; 2 disulfide bonds between the heavy chains; and 1 disulfide bond between the light chain and the heavy chain.
- Reversed-phase high performance liquid chromatography (RP-HPLC) was performed by fluorescently labeling free thiol groups. This confirmed the presence of approximately [redacted] to [redacted] mol of free thiol groups per 1 mol of nivolumab.
- [redacted]
- Differential scanning calorimetry confirmed that the melting point was [redacted] °C to [redacted] °C.
- [redacted]

[redacted]

Carbohydrate structure

- LC-ESI-MS and capillary electrophoresis with laser-induced fluorescence (CE-LIF) confirmed that ≥ [redacted]% of heavy chains had *N*-linked glycosylation of the asparagine residue at position 290. [redacted]
- The result of mass spectrometry with trypsin digestion [redacted] by LC-ESI-MS showed sialic acid-bound sugar chains accounted for [redacted]% to [redacted]% of the detected *N*-linked carbohydrate structures.

**2.A.(1).5).(b) Physicochemical properties**

Molecular weight

- The molecular weight determined by electrospray ionization—time-of-flight mass spectrometry (ESI-TOF-MS) largely agreed with the theoretically derived molecular weight.

Electrophoresis

- The result of SDS-polyacrylamide gel electrophoresis (SDS-PAGE) showed the following: under non-reducing conditions, a major band representing monomers, minor bands with molecular weights of [redacted], [redacted], [redacted], and [redacted] kDa, and bands representing aggregates; under reducing conditions, a major band representing heavy and light chains and minor bands with molecular weights of [redacted], [redacted], and [redacted] kDa.
- Capillary electrophoresis sodium dodecyl sulfate (CE-SDS) confirmed the following: under non-reducing conditions, a major peak accounted for [redacted]% to [redacted]% of the peak area; under reducing conditions, the major peaks represented heavy and light chains, with a peak representing unglycosylated heavy chains.
- [redacted]
- Isoelectric focusing (IEF) confirmed 2 major bands with pI from [redacted] to [redacted] and from [redacted] to [redacted].

Liquid chromatography

- [redacted] PD-1 binding activity, potency, PD-1 binding kinetics, and cell bioassay were measured for each peak. Each exhibited similar activities to the reference material. The applicant stated that differences in peak ratio do not affect biological activity.
- Size exclusion chromatography (SEC) coupled with a multi-angle laser light scattering detector showed major peaks representing monomers and other peaks representing dimers and multimers. Analytical ultracentrifugation sedimentation also confirmed the presence of dimers and multimers.

Other

- Absorptivity (280 nm) was confirmed to be [redacted] mL/(mg × cm).

**2.A.(1).5).(c) Biological properties**

- Enzyme-linked immunosorbent assay (ELISA) and competitive ELISA confirmed PD-1 binding activity.
- [redacted] Bioassays of cultured cells were performed to measure the potency of F(ab')2, fragments of nivolumab with a disulfide bond. The

result indicated potency comparable with the reference materials, and the applicant explained that the contribution of the Fc domain to the biological activity of nivolumab is extremely small.

- The result of a PD-1 binding kinetic analysis using surface plasmon resonance (SPR) confirmed that the equilibrium dissociation constant ($K_D$) ranged from [redacted] to [redacted] × [redacted] mol/L.
- [redacted] The $K_D$ values for CD32a, CD32b/c, CD64, and FcRn were confirmed to be [redacted] to [redacted] × [redacted], [redacted] to [redacted] × [redacted], [redacted] to [redacted] × [redacted], and [redacted] to [redacted] × [redacted] mol/L, respectively.
- In the presence of human complements, nivolumab did not exhibit complement-dependent cytotoxicity (CDC) against activated CD4+ T cells expressing PD-1. In the presence of effector cells (human peripheral blood mononuclear cells), nivolumab did not exhibit antibody-dependent cell-mediated cytotoxicity (ADCC) against activated CD4+ T cells expressing PD-1.

**2.A.(1).5).(d) Product-related substances**

Product-related substances included substances with pyroglutamate formation at heavy chain N-terminus glutamine residues; heavy chain C-terminus lysine deletion variant; deamidated substances; oxidized substances; and unglycosylated substances.

**2.A.(1).5).(e) Impurity**

Process-related impurities

[redacted] Adequate removal of all process-related impurities during the manufacturing process was confirmed. Host cell protein (HCP) content is controlled by the specifications for the drug substance.

Product-related impurities

Product-related impurities were defined as low and high molecular weight species including dimers and multimers. These low and high molecular weight species are controlled by the specifications (SEC) for the drug substance.

**2.A.(1).6) Control of drug substance**

The proposed specifications for the drug substance include potency, description, identification (peptide map), pH, purity (iCIEF, SEC, CE-SDS [non-reducing and reducing conditions], HCP [ELISA]), bacterial endotoxins, microbial limits, binding activity against PD-1, competitive ELISA, and assay for protein content.

**2.A.(1).7) Stability of drug substance**

The following table lists the main stability studies performed using the drug substance:

**Summary of main stability studies of the drug substance**

| Study | Process | Number of batches | Storage conditions | Studied period | Container |
|---|---|---|---|---|---|
| Long-term | B | 3 | 5 ± 3°C | 18 months* | Low-density polyethylene containers |
| | C | 3 | | 12 months* | |
| Accelerated | C | 3 | 25 ± 2°C, 40 ± 5% RH | 6 months | |
| Heat stress | C | 1 | 40 ± 2°C, 75 ± 5% RH | 6 months | |
| Photostability | C | 1 | Overall illumination of ≥1.2 million lux × h, an integrated near ultraviolet energy of ≥200 W × h/$m^2$ | - | |

*, stability study ongoing; -, not applicable

Long-term studies showed no clear changes in quality attributes of the drug substance produced via Processes B and C throughout the test periods.

Accelerated studies confirmed IEF pattern changes with some lots after 3 and 6 months of storage. Heat stress studies showed an increase in high molecular weight species and changes in IEF and CE-SDS patterns after the first month. Additionally, the drug substance was not photostable.

Based on these results, a shelf life of 18 months has been proposed for the drug substance when stored at 2°C to 8°C in a low-density polyethylene container in a light-shielded condition. The long-term study of the drug substance will continue for [redacted] months.

**2.A.(2) Drug product**

**2.A.(2).1) Description, prescription and formulation development**

The drug product is supplied as a single 2 mL vial containing 20 mg of nivolumab or a single 10 mL vial containing 100 mg of nivolumab. The drug product contains D-mannitol, sodium citrate hydrate, sodium chloride, diethylenetriaminepentaacetic acid and polysorbate 80 as excipients. Primary packaging materials are glass vials and rubber stoppers. Secondary packaging materials are paper boxes.

**2.A.(2).2) Manufacturing process**

[redacted]

Process validation and process evaluations in the drug product manufacturing process are performed on a pilot scale.

**2.A.(2).3) Manufacturing process development**

[redacted]

**2.A.(2).4) Control of drug product**

The proposed specifications for the drug product include potency, description, identification (IEF), pH, purity (SEC and SDS-PAGE [non-reducing and reducing conditions]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, binding activity against PD-1, competitive ELISA, and assay for protein content.

**2.A.(2).5) Stability of drug product**

The following table lists the main stability studies of the drug product that were performed:

**Summary of main stability studies of the drug product**

| Study | Fill volume | Number of batches | Storage conditions | Studied period | Container |
|---|---|---|---|---|---|
| Long-term | 20 mg | 3 | 5 ± 3°C, Upright and inverted | 12 months* | Glass vial |
| | 100 mg | 3 | | 15 months* | |
| Accelerated | 20 mg | 3 | 25 ± 2°C, 60 ± 5% RH Upright and inverted | 6 months | |
| | 100 mg | 3 | | | |
| Stress (light) | 20 mg | 1 | Overall illumination of ≥1.2 million lux × h an integrated near ultraviolet energy of ≥200W × h/m$^2$ | - | Glass vial and aluminum foil-covered glass vial |
| | 100 mg | 1 | | | |

*, stability study ongoing; -, not applicable

Long-term and accelerated studies showed no significant changes in quality attributes throughout the test periods.

Stress (light) studies confirmed IEF changes of samples that were not light-shielded but showed no significant changes in quality attributes of light-shielded samples.

Based on the result, shelf lives of 12 and 15 months have been proposed for the 20 and 100 mg drug products, respectively, when stored at 2°C to 8°C in a glass vial in a light-shielded condition. The long-term stability study of the drug product will continue for [redacted] months.

**2.A.(3) Reference materials**

The primary reference material is prepared from the drug substance and stored at ≤[redacted]°C. The shelf life of the primary reference material is currently set at [redacted] years and is to be extended according to the result of stability testing carried out once a year. [redacted]

The preparation method, storage conditions, shelf life and specifications of the working reference material are the same as those of the primary reference material.

**2.A.(4) QbD**

QbD techniques are used to develop the drug substance manufacturing process. [redacted] Process control elements have been identified for each critical quality attribute (CQA).

- [redacted]
- [redacted]
- [redacted]

Based on the quality attributes and process performance attributes of nivolumab, process development and characterization tests were performed to establish the control ranges of process output and input variables. Furthermore, for each process, process output variables that significantly impact the CQAs of the drug substance were identified as critical process attributes (CPAs), while process input variables that significantly impact a CPA of the process or a CQA of the drug substance were identified as critical process parameters (CPP). Based on these elements, an in-process control strategy was developed for the drug substance manufacturing process.

*, [redacted]
†, [redacted]

## *2.B Outline of the review by PMDA*

Based on the submitted data and the following review, PMDA concluded that the quality of the drug substance and product is adequately controlled.

**2.B.(1) In-process control strategy**

The applicant explained as follows:

Certain process output and input variables did not qualify as CPA or CPP because they did not impact CQAs and CPAs within the scope of process development and evaluation. Process output and input variables which are readily controlled within the established control ranges and those which are readily detected in the event of deviations were also not considered CPAs and CPPs due to low criticality, but were identified as performance attributes (PAs) and process parameters (PPs), respectively.

PMDA's considerations were as follows:

Although the ease in controlling and detecting deviations in process output and input variables may be a risk-reducing factor, the appropriateness of a CPA or CPP should be determined based on the degree of impact of the process output and input variables on CQAs and CPAs, and it is inappropriate to take into account of risk control in identifying CPAs and CPPs. Except for this point, PMDA sees no specific problems with the in-process control strategy in the manufacturing process for the drug substance developed by the applicant. In addition to the CPAs and CPPs identified by the procedure that the applicant established, PMDA instructed the applicant to specify the ranges of process output and input variables that have been confirmed for viral safety by submitting a partial change approval application. The applicant responded appropriately to the instruction, and PMDA concluded that the established in-process control strategy was acceptable.

**2.B.(2) New excipient**

The drug product contains diethylenetriaminepentaacetic acid as a new excipient. Based on the following investigations, PMDA concluded that the use of diethylenetriaminepentaacetic acid in the drug product would pose no specific problems.

**2.B.(2).1) Specifications and stability**

The specifications for diethylenetriaminepentaacetic acid differ from those for the diethylenetriaminepentaacetic acid that have been previously used. However, based on the submitted data, PMDA concluded there should be no problems with specifications and stability.

**2.B.(2).2) Safety**

Based on the submitted data, PMDA concluded the present usage of diethylenetriaminepentaacetic acid pose no safety problems.

## 3. Non-clinical data

### 3.(i) Summary of pharmacology studies

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

**3.(i).A.(1) Primary pharmacodynamics**

**3.(i).A.(1).1) Binding to PD-1 (Report MDX-1106-025-R)**

The binding of Nivolumab (Genetical Recombination) (hereinafter referred to as "nivolumab") to human CD279 (programmed cell death 1, PD-1) was investigated. The results were as follows:

- Surface plasmon resonance (SPR) found that the dissociation constant of nivolumab to a recombinant PD-1-Fc fusion protein, wherein the Fc region of human immunoglobulin (Ig) G1 was fused to the extracellular region of human PD-1, was 3.06 nmol/L.
- Flow cytometry confirmed that the 50% binding ($EC_{50}$ value) of nivolumab to the Chinese hamster ovary (CHO) cell line transfected with the human PD-1 gene (PD-1/CHO cell line) and endogenous PD-1 on activated human T cells with a $EC_{50}$ value (50% binding) of 1.66 and 0.64 nmol/L, respectively.
- Flow cytometry was performed to investigate the cross-reactivity of nivolumab using activated lymphocytes from rats, rabbits, and monkeys. This revealed that nivolumab bound only to monkey activated lymphocytes.
- SPR clarified that nivolumab binds to monkey PD-1 extracellular domain containing FLAG peptides with a dissociation constant of 3.92 nmol/L.

PD-1 is a receptor belonging to the CD28 family (a group of molecules that provide co-stimulatory signals which are involved in the control of T-cell activation). ELISA was performed to investigate the binding of nivolumab to recombinant proteins in which the Fc region of human IgG1 was fused to human CD28 species besides PD-1 (i.e., CD28, ICOS, CTLA-4, BTLA). The result showed that nivolumab does not bind to any of the recombinant proteins.

**3.(i).A.(1).2) Effects on interaction between PD-1 and PD-1 ligands (Reports MDX-1106-025-R and BDX-1106-321)**

Flow cytometry was performed to evaluate the inhibitory effects of nivolumab on the interaction between the human PD-1 receptor and human PD-1 ligands (CD274 [programmed cell death ligand 1, PD-L1] and CD273 [programmed cell death ligand 2, PD-L2]) using the PD-1/CHO cell line and biotin-labeled recombinant human PD-L1-Fc and PD-L2-Fc fusion proteins. Streptavidin labeled with R-phycoerythrin was used to detect the binding of PD-1 to biotin-labeled recombinant PD-L1-Fc and PD-L2-Fc fusion proteins. The result showed that nivolumab inhibited the binding of PD-1 to PD-L1 and PD-L2 in a concentration-dependent manner with 50% inhibitory concentration ($IC_{50}$) values of 1.04 and 0.97 nmol/L, respectively.

Western blotting and mass spectrometry were performed to investigate nivolumab epitopes. The results suggest that nivolumab binds to the extracellular domain of PD-1 (PD-1 ligand binding site).

**3.(i).A.(1).3 Effect on immunoreactivity (Reports MDX-1106-026-R, MDX-1106-042-R, [redacted]00006)**

***In vitro***:

- The effect of nivolumab on alloantigen-induced T-cell activation was investigated based on mixed lymphocyte reactions using human CD4+ T cells and human monocytic dendritic cells from different donors. T-cell proliferation was measured based on $^{3}$H-labeled thymidine uptake. The results confirmed that nivolumab (0.0005-50 μg/mL) facilitates T-cell proliferation in a concentration-dependent manner. Furthermore, ELISA was performed to measure interferon (IFN)-γ production. The result showed that nivolumab (0.0005-50 μg/mL) elevated IFN-γ production in a concentration-dependent manner.
- The effect of nivolumab on antigen-specific T cell reactivity was investigated by re-stimulating peripheral blood mononuclear cells (PBMC) of cytomegalovirus (CMV)-infected patients with CMV antigens (CMV-infected cell extract) and measuring IFN-γ production by PBMC after 4 days of incubation. The result confirmed that nivolumab (0.0001-30 μg/mL) increased IFN-γ production in a concentration-dependent manner.

***In vivo*:**

Cynomolgus monkeys (n = 3/sex/group) were inoculated with 3 kinds of antigens (the hepatitis B virus surface antigen vaccine [HBsAg], the human malignant melanoma SKMel cell line, and 2,4-dinitrophenyl-Ficoll [DNP-Ficoll]) every 4 weeks (Days 1*, 29, and 57 [Only HBsAg and the SKMel cell line on Day 57]). The effects of nivolumab (10 mg/kg administered intravenously on Days 1*, 29, and 57 for a total of 3 times) on the immunoresponse to each antigen were investigated. As compared with the control (physiological saline) group, intensified delayed-type hypersensitivity reaction to HBsAg and increased antibody titers for the SKMel cell line were observed in the nivolumab group. However, the immunoresponse to DNP-Ficoll was not enhanced.

* Day 1 marked the first day of nivolumab administration.

**3.(i).A.(1).4 Activity against malignant tumors (Reports MDX-1106-028-R, MDX-1106-200-R, MDX-1106-023-R, E[redacted]QA052, MDX-1106-022-R, MDX-1106-006-R, MDX-1106-034-R, MDX-1106-036-R, MDX-1106-035-R, MDX-1106-021-R, MDX-1106-020-R, E[redacted]CT017 [reference data])**

The homology in the amino acid sequence of nivolumab epitopes between human PD-1 and mouse PD-1 was 66% and that between human PD-1 and rat PD-1 was 73%. Because nivolumab did not cross-react with rat PD-1, nivolumab was assumed not to cross-react with mouse PD-1. Therefore, the effects of anti-PD-1 antibody on tumor growth inhibition was investigated using 4H2, a chimeric antibody wherein the variable region of rat anti-mouse PD-1 antibody was bound to the constant region of mouse IgG1k. Additionally, the $EC_{50}$ value of 4H2 against the CHO cell line transfected with the mouse PD-1 gene was 2.91 nmol/L. The $IC_{50}$ values of 4H2 against the binding of mouse PD-1 to mouse PD-L1 and mouse PD-L2 were 3.59 and 4.91 nmol/L, respectively. These figures were comparable with nivolumab [see "3.(i).A.(1).1) Binding to PD-1" and "3.(i).A.(1).2) Effect on interaction between PD-1 and PD-1 ligands"].

**Malignant melanoma:**

The effects of 4H2 on tumor growth inhibition was investigated in mice that had been grafted subcutaneously with mouse malignant melanoma B16F10 cells. At 8 days after grafting, when the volume of the grafted tumor was approximately 67 $mm^3$, 10 mg/kg of 4H2 was administered intraperitoneally to investigate its effect on tumor growth (10 mice per group). The result showed that 4H2 failed to inhibit tumor growth as compared with 10 mg/kg of phosphate buffered saline or mouse IgG1.

As reference data, mouse malignant melanoma Clone M-3 cells were grafted into mice and it demonstrated that 4H2 did not inhibit tumor growth in these mice.

**Malignant tumors other than malignant melanoma:**

In mice grafted subcutaneously with mouse colon cancer [redacted] cells, 3, 10, and 30 mg/kg of 4H2 were shown to inhibit tumor growth as compared with the control, a mixture of mouse IgG1 and rat IgG1 (10 mg/kg each), and significantly extended survival ($P < 0.05$, log-rank test). With 3, 10, or 30 mg/kg

of 4H2, complete tumor regression was seen in 2, 1, and 1 out of the 10 mice, respectively, but tumor growth was not inhibited at all within 20 days after grafting in 6, 4, and 2 out of the 10 mice, respectively.

[redacted] Additionally, for comparison, 10 mg/kg of mouse IgG (20 mg/kg on Day 0*) was used. [redacted]

* Day 0 was the date on which the tumor tissue was grafted.

Mice grafted with mouse fibrosarcoma [redacted] cells received 1, 3, 10, or 30 mg/kg of 4H2. As compared with the control (30 mg/kg of phosphate buffered saline or mouse IgG1), tumor growth was inhibited at all doses of 4H2, and the survival of mice grafted with fibrosarcoma were significantly extended at ≥3 mg/kg of 4H2 ($P < 0.05$, log-rank test). Complete tumor disappearance was confirmed in 5 of the 40 mice. In 4 of the 5 mice in which SA1/N cells were grafted after the tumor disappearance following the administration of 4H2, no tumor formation was observed during the 42 days of observation. The applicant explained that the results suggest the immunoresponse to tumors persists even after the end of the administration of 4H2.

In mice grafted with mouse plasmacytoma [redacted] cells, complete tumor disappearance was achieved at 10 mg/kg of 4H2 in 2 of the 8 mice. However, no clear inhibition was seen as compared with the control (10 mg/kg of phosphate buffered saline or mouse IgG1).

In mice grafted with mouse kidney cancer [redacted] cells, mouse breast cancer [redacted] cells, and mouse colon cancer [redacted] cells, no tumor growth inhibition was seen at 10 mg/kg of 4H2 as compared with the control (phosphate buffered saline or 10 or 20 mg/kg of mouse IgG1).

**3.(i).A.(2) Secondary pharmacodynamics (Reports MDX-1106-025-R, BDX-1106-320, MDX-1106-201-R)**

- The antibody-dependent cell-mediated cytotoxicity (ADCC) of nivolumab (0.003-50 μg/mL) against activated human CD4+ T cells was investigated using activated human CD4+ T cells as target cells and human PBMC as effector cells. ADCC was not observed.
- The complement-dependent cytotoxicity (CDC) of nivolumab (0.00064-50 μg/mL) against activated human CD4+ T cells was investigated using human complements. CDC was not observed.
- Nivolumab (10 or 100 μg/mL) was added to human PBMC to investigate antigen-independent lymphocyte activation. The production of various cytokines (IFN-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-2, 4, 6, 10) was measured 4, 6, and 24 hours later by flow cytometry. The result showed that nivolumab did not enhance the production of these cytokines.

**3.(i).A.(3) Safety pharmacology**

**3.(i).A.(3).1) Effects on the central nervous system (Reports [redacted]00026, [redacted]00025, [redacted]552003)**

The effects of nivolumab on the clinical signs of cynomolgus monkeys were investigated in a 4-week repeated-dose toxicity study (n = 5/sex/group) and a 13-week repeated-dose toxicity study (n = 6/sex/group) [see "3.(iii).A.(2) Repeated-dose toxicity"]. No effects of nivolumab were observed.

Furthermore, 10 or 50 mg/kg of nivolumab was administered intravenously once to cynomolgus monkeys (n = 3/sex/group) to investigate its effects on body temperature. No effects of nivolumab were observed.

**3.(i).A.(3).2 Effects on the cardiovascular system (Reports [redacted]00026, [redacted]552003)**
The effects of nivolumab on heart rate and ECG parameters (PR interval, QRS duration, QT interval, QTcF) were investigated in a 13-week repeated-dose toxicity study of cynomolgus monkeys (n = 6/sex/group) [see "3.(iii).A.(2) Repeated-dose toxicity"]. No effects of nivolumab were observed.

Furthermore, 10 or 50 mg/kg of nivolumab was administered intravenously once to cynomolgus monkeys (n = 3/sex/group). No effects of nivolumab on blood pressure, heart rate, or ECG parameters (RR interval, QT interval, QTcF) were observed.

**3.(i).A.(3).3 Effects on the respiratory system (Reports [redacted]00025, [redacted]552003)**
The effects of nivolumab on respiratory rate and hemoglobin oxygen saturation were investigated in a 4-week repeated-dose toxicity study in cynomolgus monkeys (n = 5/sex/group) and a 13-week repeated-dose toxicity study of cynomolgus monkeys (n = 6/sex/group) [see "3.(iii).A.(2) Repeated-dose toxicity"]. No effects of nivolumab were seen.

## *3.(i).B Outline of the review by PMDA*
Based on the submitted data, the following review, and the mechanism of action of nivolumab, PMDA concluded that the applicant's explanation of the efficacy of nivolumab against human malignant melanoma is acceptable.

**Efficacy of nivolumab**
The applicant explained about the mechanism of action of nivolumab as follows:
Nivolumab is a human monoclonal antibody of the IgG4 subclass against human PD-1, which binds to the extracellular domain of PD-1 (PD-1 ligand binding site), thereby blocking the interaction between PD-1 and the PD-1 ligands. This enhances the activation of cancer antigen-specific T cells and the cytotoxic effect on cancer cells, resulting in the suppressing tumor growth.

Since the administration of 4H2 (another anti-PD-1 antibody) did not suppress the growth of 2 kinds of mouse malignant melanoma cell lines (B16F10 and Clone M-3), PMDA asked the applicant to explain the efficacy of nivolumab against malignant melanomas, based on its mechanism of action mentioned above. The applicant responded as follows:

In studies of mice grafted with tumor cell lines, the expression levels of PD-1 and PD-L1 in B16F10-derived tumor tissue (the growth of which was not inhibited by 4H2) was lower than those in [redacted]-derived tumor tissue (the growth of which was inhibited by 4H2). Therefore, the lack of tumor growth suppression may be attributable to the fact that immunological escape mediated by PD-1 and PD-L1 does not occur.

At this point in time, no data is available to show the efficacy of the anti-PD-1 antibody against mouse malignant melanoma cell lines. However, reports indicate that the expression of PD-L1 is induced and that immunological escape mediated by PD-1 and PD-L1 occurs in the tumor tissue of patients with malignant melanomas (*Sci Transl Med*. 2012;4:127ra37). Based on these findings and the mechanism of action of nivolumab, the applicant explained that nivolumab is expected to be effective against human malignant melanoma.

PMDA's considerations were as follows:
The applicant's explanation that nivolumab is expected to be effective against human malignant melanomas is understandable, considering its mechanism of action. The following points, however, suggest that not only the expression of PD-1 and PD-L1 but also any other factors may affect the efficacy of nivolumab. The search for such factors is important in terms of the selection of eligible patients for the use of nivolumab in clinical settings and thus should be continued so as to provide new information to the medical community.
- Clinical studies of nivolumab have confirmed efficacy in patients with malignant melanomas that lack PD-L1 expression.
- In studies using [redacted], [redacted], and [redacted] cell lines, the administration of 4H2 eliminated tumors in some mice but failed to inhibit tumor growth in others.

## 3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetics (PK) of nivolumab in animals was investigated using cynomolgus monkeys.

#### 3.(ii).A.(1) Analytical procedures

##### 3.(ii).A.(1).1) Nivolumab assay

Nivolumab in monkey serum was quantified by (a) ELISA using solid-phased PD-1-Fc fusion protein and alkaline phosphatase (ALP)-labeled mouse anti-human IgG4 antibodies and (b) electrochemical luminescence immunoassay (ECLIA) using solid-phased streptavidin and biotin-labeled anti-nivolumab antibodies and ruthenium-labeled anti-nivolumab antibodies.

##### 3.(ii).A.(1).2) Anti-nivolumab antibody assay

Anti-nivolumab antibodies in monkey serum were detected by (a) ELISA using nivolumab bound to the solid phase, biotin-labeled nivolumab and ALP-labeled streptavidin and (b) ECLIA using streptavidin bound to the solid phase, biotin-labeled nivolumab, and ruthenium-labeled nivolumab.

#### 3.(ii).A.(2) Absorption

##### 3.(ii).A.(2).1) Single-dose administration

Serum concentrations of nivolumab were measured in male and female cynomolgus monkeys following a single dose of 1 or 10 mg/kg of nivolumab [see the following table]. In male monkeys, the $C_{max}$ and $AUC_{inf}$ of nivolumab were generally dose proportional. No clear sex differences were seen in $C_{max}$ or $AUC_{inf}$ with a single dose of 1 mg/kg. The $V_{ss}$ value was comparable with the monkey plasma volume (0.0448 L/kg) (*Pharm Res*. 1993;10:1093-5) and, the applicant explained this suggests that nivolumab is mostly distributed in the circulating blood. The applicant also explained the reason why $t_{1/2}$ was longer in the male 10 mg/kg group as compared with the 1 mg/kg group was the large inter-subject variability in the male 10 mg/kg group.

Anti-nivolumab antibodies were detected in serum on Day 27 in 2 males and 3 females in the 1 mg/kg group and in 2 males in the 10 mg/kg group, but no clear differences were found in PK parameters of nivolumab between anti-nivolumab antibody-positive and -negative monkeys.

**PK parameters of nivolumab (single intravenous dosing to male and female cynomolgus monkeys)**

| Dose (mg/kg) | Sex | $C_{max}$ (μg/mL) | $AUC_t$* (μg × h/mL) | $AUC_{inf}$ (μg × h/mL) | $t_{1/2}$ (h) | CL (mL/h/kg) | $V_{ss}$ (L/kg) |
|---|---|---|---|---|---|---|---|
| 1 | Male | 34.3 ± 2.20 | 4010 ± 645 | 4470 ± 423 | 124 ± 20.3 | 0.224 ± 0.0207 | 0.0460 ± 0.00538 |
| | Female | 30.6 ± 1.71 | 3570 ± 573 | 4050 ± 616 | 139 ± 12.7 | 0.250 ± 0.0390 | 0.0519 ± 0.00160 |
| 10 | Male | 346 ± 21.6 | 47,100 ± 12,400 | 64,200 ± 27,400 | 261 ± 226 | 0.172 ± 0.0589 | 0.0598 ± 0.0158 |

Mean ± SD; n = 3; *, $AUC_{384h}$ for the 1 mg/kg group and $AUC_{648h}$ for the 10 mg/kg group

##### 3.(ii).A.(2).2) Repeated-dose administration

Male and female cynomolgus monkeys received 1, 10, or 50 mg/kg of nivolumab intravenously once a week for 4 weeks. Serum concentrations of nivolumab were measured following the first and fourth doses [see the following table]. No clear sex differences in PK parameters of nivolumab were seen after the first dose. Within the investigated dose range, serum concentrations of nivolumab 15 minutes after administration ($C_{15min}$) and $AUC_{168h}$ generally exhibited dose proportionality. After the fourth dose, the $C_{15min}$ and $AUC_t$ of nivolumab generally exhibited dose proportionality within the investigated dose range in males. However, in females, $C_{15min}$ and $AUC_t$ increased more than dose-proportionally for the 1 and 10 mg/kg groups and were dose-proportional between 10 and 50 mg/kg.

Anti-nivolumab antibodies were detected in the serum of 1 male and 3 females in the 1 mg/kg group, 1 male in the 10 mg/kg group, and 1 male in the 50 mg/kg group. The $C_{15min}$ and $AUC_t$ of nivolumab in all monkeys (anti-nivolumab antibody-positive and -negative monkeys) were lower than those in anti-nivolumab antibody-negative monkeys alone.

With repeated dosing, the PK of nivolumab was nonlinear only in female monkeys. Anti-nivolumab antibodies were detected in 1 male in the 1 mg/kg group but in 3 females in the 1 mg/kg group.

According to the applicant, the serum concentration of nivolumab was low in female monkeys in the 1 mg/kg group because anti-nivolumab antibodies were detected in many monkeys.

**PK parameters of nivolumab following initial dose**
**(Four-week repeated dosing in male and female cynomolgus monkeys)**

| Dose (mg/kg) | Sex | $C_{15min}$ (μg/mL) | $AUC_{168h}$ (μg × h/mL) | $t_{1/2}$ (h) | CL (mL/h/kg) | $V_{ss}$ (L/kg) |
|---|---|---|---|---|---|---|
| 1 | Male | 22.0 ± 4.34 | 1740 ± 411 | 148 ± 35.4 | 0.323 ± 0.0917 | 0.0679 ± 0.0183 |
| | Female | 23.1 ± 3.37 | 2040 ± 370 | 146 ± 25.5 | 0.266 ± 0.0663 | 0.0562 ± 0.00882 |
| 10 | Male | 288 ± 40.1 | 23,800 ± 1650 | 267 ± 104 | 0.161 ± 0.0525 | 0.0558 ± 0.00273 |
| | Female | 255 ± 40.3 | 21,600 ± 2950 | 223 ± 37.5 | 0.187 ± 0.0317 | 0.0600 ± 0.00645 |
| 50 | Male | 1120 ± 133 | 91,700 ± 9070 | 238 ± 94.5 | 0.222 ± 0.0621 | 0.0707 ± 0.00862 |
| | Female | 1200 ± 131 | 109,000 ± 14,200 | 260 ± 133 | 0.188 ± 0.0818 | 0.0597 ± 0.00811 |

Mean ± SD; n = 5

**PK parameters of nivolumab following the fourth dose**
**(Four-week repeated dosing in male and female cynomolgus monkeys)**

| Dose (mg/kg) | Sex | All cases | | | Anti-nivolumab antibody-negative cases | | |
|---|---|---|---|---|---|---|---|
| | | n | $C_{15min}$ (μg/mL) | $AUC_t$ (μg × h/mL) | n | $C_{15min}$ (μg/mL) | $AUC_t$ (μg × h/mL) |
| 1 | Male | 5 | 27.9 ± 13.9 | 3060 ± 2240 | 4 | 33.5 ± 6.66 | 3820 ± 1680 |
| | Female | 4 | 21.4 ± 11.2 | 2120 ± 2520 | 2 | 19.7, 35.8* | 252, 5450* |
| 10 | Male | 5 | 411 ± 233 | 36,700 ± 30,600 | 4 | 496 ± 158 | 45,700 ± 26,500 |
| | Female | 5 | 496 ± 47.0 | 51,200 ± 11,000 | 5 | 496 ± 47.0 | 51,200 ± 11,000 |
| 50 | Male | 5 | 1930 ± 632 | 196,000 ± 103,000 | 4 | 2150 ± 458 | 242,000 ± 19,500 |
| | Female | 5 | 2230 ± 445 | 224,000 ± 44,900 | 5 | 2230 ± 445 | 224,000 ± 44,900 |

Mean ± SD; *, individual values

Serum concentrations of nivolumab were measured by intravenously administering either 10 or 50 mg/kg of nivolumab twice a week for 13 weeks to male and female cynomolgus monkeys. Serum trough concentrations of nivolumab increased with each dose, reaching a steady state generally within 9 weeks. Serum trough concentrations generally exhibited dose proportionality and showed no clear sex differences. In 1 male in the 10 mg/kg group, anti-nivolumab antibodies were detected in serum after the Week 4 of administration; the serum concentration of nivolumab in this male monkey was lower than that in other monkeys without antibodies.

Based on the PK parameters estimated from the serum concentrations following the first dose in cynomolgus monkeys in which 10 or 50 mg/kg of nivolumab had been administered intravenously once a week for 4 weeks, chronological changes in the serum concentrations of nivolumab following repeated intravenous dosing of 10 or 50 mg/kg twice a week for 13 weeks were estimated. The $C_{max}$ and $AUC_{168h}$ values of nivolumab at Week 13 of administration calculated from the estimated chronological changes were 801 μg/mL and 117,000 μg × h/mL, respectively, for the 10 mg/kg group, and 3610 μg/mL and 531,000 μg × h/mL, respectively, for the 50 mg/kg group.

### 3.(ii).A.(3) Distribution

Nivolumab at 10 or 50 mg/kg was administered intravenously twice weekly to pregnant cynomolgus monkeys from Days 20 to 22 of gestation up to Day 165 of gestation. Serum nivolumab concentrations in maternal animals on Day 14 after parturition for the 10 and 50 mg/kg groups were 371 and 1280 μg/mL, respectively, while those were 271 and 1120 μg/mL in newborn animals, respectively. Serum nivolumab concentrations were generally comparable between maternal and newborn animals. Based on these results, the applicant stated that nivolumab may be transferred to fetuses via the placenta.

The tissue distribution of nivolumab has not been investigated.

### 3.(ii).A.(4) Metabolism and excretion

The metabolism and excretion of nivolumab have not been investigated. Nivolumab is a human monoclonal antibody belonging to the IgG4 subclass. Like other types of IgG, after being metabolized into low molecular peptides and amino acids, nivolumab is thought to be either excreted or reused to synthesize proteins and peptides *in vivo*. The applicant therefore did not conduct investigation on the metabolism and excretion of nivolumab also in consideration of "Preclinical Safety Evaluation of

Biotechnology-derived Pharmaceuticals" (Notification No. 0323-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 23, 2012).

Endogenous IgG4s have been reported to be excreted into milk (*PLoS ONE*. 2012;7:e42942), and the applicant explains that nivolumab is also thought to be excreted into milk like other types of endogenous IgG4s.

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

Based on the submitted data and the following review, PMDA accepted the applicant's explanation regarding the absorption, distribution, metabolism, and excretion of nivolumab.

**Tissue distribution**

The applicant explained that the tissue distribution of nivolumab was not investigated because the following factors are indicative that nivolumab is distributed mainly in circulating blood as well as to activated lymphocytes and myeloid cells expressing PD-1:

- In a single-dose study in cynomolgus monkeys, the steady-state volume of the distribution ($V_{ss}$) of nivolumab suggests that the level of tissue distribution is low [see "3.(ii).A.(2) Absorption"].
- PD-1, the target molecule of nivolumab, is reported to be expressed on activated lymphocytes and myeloid cells (*Int Immunol*. 2007;19:813-24, *Annu Rev Immunol*. 2008;26:677-704). Tissue cross-reactivity studies of normal human and cynomolgus monkey tissue show that nivolumab generally cross-reacts with lymphocytes and myeloid cells [see "3.(iii).A.(6).1) Cross-reactivity studies"].

PMDA's considerations are as follows:

While tissue distribution in the appropriate animal models is useful in predicting latent toxicity in clinical settings, PMDA accepted the applicant's explanations, taking into account the fact that the safety profile of nivolumab in animals and humans has been adequately evaluated.

## 3.(iii) Summary of toxicology studies

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

#### 3.(iii).A.(1) Single-dose toxicity

Male and female cynomolgus monkeys (n = 3/sex/group) received a single dose of intravenous nivolumab at 1 mg/kg and 3 male cynomolgus monkeys at 10 mg/kg. No changes or deaths due to nivolumab were observed in any group.

Acute toxicity of nivolumab was evaluated based on findings between the first and second doses (3 or 7 days) in 4- and 13-week repeated intravenous dose toxicity studies. [see "3.(iii).A.(2) Repeated-dose toxicity"]. Since no deaths occurred at the maximum dose of 50 mg/kg, the approximate lethal dose was determined to be >50 mg/kg.

#### 3.(iii).A.(2) Repeated-dose toxicity

##### 3.(iii).A.(2).1) Four-week repeated intravenous dose toxicity study in cynomolgus monkeys

Cynomolgus monkeys (n = 5/sex/group) received 0 (saline), 1, 10, or 50 mg/kg of nivolumab intravenously once a week for 5 weeks. A 4-week recovery period followed the final dose for 2 males and 2 females in each group. This study included tests of peripheral blood immunophenotyping and thyroid function (thyroid stimulating hormone [TSH], triiodothyronine [$T_3$], thyroxin [$T_4$] assays). No deaths or nivolumab-associated changes occurred in any treatment group. The study also investigated the binding of nivolumab to PD-1 expressed on the membrane of CD3+ T cells in the peripheral blood of monkeys following the recovery period. The result confirmed the binding of nivolumab in animals that were free of anti-nivolumab antibody expression.

Based on the above results, the no observed adverse effect level (NOAEL) for the study was determined to be 50 mg/kg/dose.

### 3.(iii).A.(2).2) Thirteen-week repeated intravenous dose toxicity study in cynomolgus monkeys

Cynomolgus monkeys (n = 6/sex/group) received 0 (saline), 10, or 50 mg/kg of nivolumab intravenously twice a week for a total of 27 times. A 4-week recovery period followed the final dose in 2 males and 2 females in each group. This study included tests of peripheral blood immunophenotyping, thyroid function (TSH, $T_3$, $T_4$ assays), and blood pituitary hormone assay (growth hormone, adrenocorticotropic hormone, α-melanocyte stimulating hormone).

No deaths occurred in any treatment group. Thyroid function tests confirmed low $T_3$ values during Week 13 of administration in female monkeys in the 50 mg/kg group. For the following reasons, these low $T_3$ values were deemed not to be suggestive of thyroid or pituitary impairments, and their toxicological significance was deemed low: no changes occurred in $T_4$ and pituitary hormone levels; no abnormalities were observed in the organ weight of the thyroid and pituitary or in histopathological findings; and no changes associated with low $T_3$ values were noted in body temperatures, heart rates, clinical conditions, body weights, or serum cholesterol levels. Immunophenotyping showed increases in CD4+ effector memory T cells, CD8+ effector memory T cells, and CD8+ central memory T cells in the 50 mg/kg group. These increases were due to the pharmacological effects of nivolumab, but their toxicological significance was considered low because of the absence of changes indicating excessive immunoresponse such as inflammatory changes or tissue damage. Furthermore, the binding of nivolumab to PD-1 was confirmed in CD3+ T cells in the peripheral blood of monkeys following the recovery period.

Based on these results, the NOAEL for the study was determined to be 50 mg/kg/dose. The estimated 3-week steady state exposure of nivolumab (AUC) following 50 mg/kg administered twice weekly for a total of 27 doses was 1593 mg × h/mL, approximately 105 times the clinical exposure* [see "3.(ii).A.(2).2) Repeated-dose administration"].

* In the ONO-4538-02 study, the 3-week steady state exposure of nivolumab (AUC) following intravenous dosing at 2 mg/kg every 3 weeks was estimated to be 15,204 μg × h/mL in Japanese patients with malignant melanoma.

### 3.(iii).A.(3) Genotoxicity

Nivolumab, an antibody-based pharmaceutical, is highly unlikely to pass through cell membranes to act directly on DNA or other chromosomal components. Thus, no genotoxicity studies were conducted.

### 3.(iii).A.(4) Carcinogenicity

Since nivolumab is a pharmaceutical product used to treat advanced malignant melanoma, no carcinogenicity studies were conducted.

### 3.(iii).A.(5) Reproductive and developmental toxicity

#### 3.(iii).A.(5).1) Study of fertility and early embryonic development

Since nivolumab is a pharmaceutical product used to treat advanced malignant melanoma, no studies of fertility or early embryonic development were conducted.

According to the applicant, nivolumab is unlikely to affect male or female reproductive organs or fertility for the following reasons:

- A repeated-dose toxicity study investigated the effect of nivolumab on female reproductive organs but yielded no notable histopathological findings attributable to nivolumab [see "3.(iii).A.(2) Repeated-dose toxicity"]. However, the effect of nivolumab on male reproductive organs could not be adequately evaluated in the study because the male monkeys used had not reached sexual maturity.
- The effect of nivolumab on male reproductive organs in monkeys was investigated in a 4-week repeated intravenous dose toxicity study using nivolumab and [redacted], a human anti-LAG-3 monoclonal antibody [see "3.(iii).A.(6).2) Four-week repeated intravenous dose toxicity study with [redacted] co-administration in cynomolgus monkeys"]. No notable histopathological findings attributable to nivolumab were noted in the male reproductive organs.
- A tissue cross-reactivity study using normal human tissue showed nivolumab does not react with male or female reproductive organs [see "3.(iii).A.(6).1) Cross-reactivity studies"].

- Fertility was maintained when male and female PD-1-/- or PD-L1-/- mice were mated (*Int Immunol.* 1998;10:1563-72, *J Exp Med*. 2005;202:231-37).

**3.(iii).A.(5).2) Extended study of pre- and postnatal development in cynomolgus monkeys**

To investigate the effects of nivolumab on embryo–fetal and pre- and postnatal development, 0 (saline), 10, or 50 mg/kg of nivolumab was intravenously administered twice weekly to pregnant cynomolgus monkeys (n = 16/group) from Days 20 to 22 of gestation (start of fetal organogenesis) through delivery. Maternal and newborn monkeys were subjected to immunophenotyping, immunoglobulin, and antinuclear antibody assays. Newborn monkeys were subjected to T cell-dependent antibody response assays.

Nivolumab had no observable effects on maternal monkeys. For the 10 and 50 mg/kg groups, the mortality rates of embryos, fetuses, and newborns increased during the third trimester (from Day 101 of gestation to delivery). In 1 dead fetus in the 10 mg/kg group, thyroid interstitial inflammation and follicular cell hypertrophy/hyperplasia due to CD3+ T cells were found. Dead neonates were all delivered prematurely, and died or were sacrificed and necropsied on the day of delivery or at 12 days after delivery. External observations, skeletal tests, and necropsies of the dead fetuses and neonates did not reveal any abnormalities.

In the 50 mg/kg group, aside from 1 death due to umbilical cord thrombosis during the first trimester (from Days 20 to 50 of gestation), embryo or fetal death was confirmed in 3 of 16 monkeys (18.8%). However, 2 of 16 monkeys in the control group also died during the first trimester, and the mortality in the 50 mg/kg group was comparable with the upper limit of the historical data from the study laboratory (16.7%). Thus, the embryo–fetal deaths during the first trimester were considered potentially unrelated to nivolumab.

No teratogenicity was observed. No effects on neonatal growth, behavior, or immune function were observed.

Based on these results, the NOAEL of nivolumab for embryos, fetuses, and neonates was determined to be <10 mg/kg. The estimated 3-week exposure (AUC) in maternal animals during the third trimester (Days 132 to 141 of gestation) for the 10 mg/kg group was 351,000 μg × h/mL, or about 23 times the clinical exposure.*

The applicant's explanation was as follows:

The involvement of regulatory T cells with immunological tolerance and pregnancy maintenance in human fetuses has been reported (*Mol Hum Reprod*. 2004;10:347-53), suggesting that nivolumab may affect pregnancy maintenance in humans. The reproductive and developmental toxicity study in monkeys confirmed the increased mortality of embryos, fetuses, and neonates in late pregnancy. Therefore, in principle, nivolumab should not be administered to pregnant women or to women who may be pregnant. However, the reproductive and developmental toxicity study in monkeys did not document any cases of teratogenicity, and nivolumab had no effect on neonatal growth. Based on these findings and the seriousness of the disease, if the potential therapeutic benefits outweigh the risks, the clinical use of nivolumab is considered acceptable. The applicant plans to include this information in the package insert.

* In Study ONO-4538-02, the 3-week steady state exposure of nivolumab (AUC) following intravenous dosing at 2 mg/kg every 3 weeks was estimated to be 15,204 μg × h/mL in Japanese patients with malignant melanoma.

**3.(iii).A.(6) Other toxicity studies**

**3.(iii).A.(6).1) Cross-reactivity studies**

**(a) Cross-reactivity study using normal human and cynomolgus monkey tissue**

The cross reactivity of nivolumab against various tissues was investigated by immunohistochemical staining using frozen normal human and cynomolgus monkey tissue fragments and fluorescein isothiocyanate (FITC)-labeled nivolumab. The result confirmed the presence of nivolumab in the cell membranes of lymphocytes in various organs and the cytoplasm of endocrine cells in the anterior pituitary. In normal monkey tissue, nivolumab was detected in the cytoplasm and cell membranes of

myelopoietic cells and in the cytoplasm of mesothelial cells in the small intestine, pancreas, liver, lung, spleen, and uterine corpus.

**(b) Tissue cross-reactivity study using human pituitary (reference data, non-GLP study)**
In a tissue cross-reactivity study using normal human tissue, nivolumab was detected in the cytoplasm of pituitary endocrine cells [see "(a) Cross-reactivity study using normal human and cynomolgus monkey tissue"]. To investigate the specificity of positive nivolumab response, a tissue cross-reactivity study was conducted using human pituitary endocrine cells, FITC-labeled nivolumab, and unlabeled nivolumab. Commercially available mouse anti-human PD-1 monoclonal antibodies (hereinafter referred to as "[redacted]") were used as positive control for human PD-1.

The result showed the presence of FITC-labeled nivolumab and unlabeled nivolumab in human pituitary endocrine cells at the concentrations of ≥5 and ≥1 μg/mL, respectively. These concentration levels were higher than the concentration levels of FITC-labeled nivolumab and unlabeled nivolumab in human tonsillar lymphoid tissue expressing PD-1 (0.2 μg/mL). [redacted] was detected in human tonsillar lymphoid tissue but not in human pituitary endocrine cells.

Based on these results, the applicant stated that nivolumab may have bound nonspecifically to human pituitary endocrine cells.

**3.(iii).A.(6).2) Four-week repeated intravenous dose toxicity study with ipilimumab co-administration in cynomolgus monkeys (reference data, GLP study)**
Nivolumab and ipilimumab (a human anti-CTLA-4 monoclonal antibody) were administered intravenously once weekly to cynomolgus monkeys (n = 5/sex/group) which were allocated to the following dose groups: 0/0 mg/kg (saline), 10/3 mg/kg, and 50/10 mg/kg of nivolumab/ipilimumab. In the 10/3 and 50/10 mg/kg groups, inflammatory changes occurred in the colon and increased antibody production against keyhole limpet hemocyanin (KLH) was observed in a T-cell dependent antibody production study. Lymphocyte subset variability was noted in the 50/10 mg/kg group. No inflammatory change was observed in the colon in the repeated-dose toxicity study of nivolumab monotherapy [see "3.(iii).A.(2) Repeated-dose toxicity"]. The inflammatory changes in the colon in the concomitant groups were considered attributable to the activation of immune cells enhanced by the co-administration.

**3.(iii).A.(6).3) Four-week repeated intravenous dose toxicity with [redacted] co-administration in cynomolgus monkeys**
Nivolumab and [redacted] were administered intravenously once weekly to cynomolgus monkeys (n = 5/sex/group) in the following dose groups: 0/0 mg/kg (vehicle control), 0/30 mg/kg, 0/100 mg/kg, 50/0 mg/kg, and 50/100 mg/kg of nivolumab/[redacted]. In 2 males and 2 females in each dose group, a 6-week recovery period followed the final dose. Each dose group exhibited in *ex vivo* immune response studies an elevated immunoresponse of CD4+ T cells against KLH. In the monotherapy and co-administration groups, the infiltration of lymphocytes and plasma cells into the choroid plexus occurred (3 of 6 monkeys following the end of monotherapy, 2 of 4 monkeys following the end of the recovery period, and 8 of 10 monkeys following concomitant therapy) [see "3.(iii).B Outline of the review by PMDA, Effects on choroid plexus"].

Of the 5 male monkeys in the co-administration group, 1 was sacrificed moribund. The sacrificed monkey was found to have inflammation of the central nervous system (brain parenchyma, meningeal and spinal vessels) and male reproductive organs. The surviving monkeys also experienced lymphoid tissue inflammation in brain parenchymal vessels. These inflammatory changes in the concomitant groups were considered attributable to the activation of immune cells enhanced by co-administration.

## *3.(iii).B Outline of the review by PMDA*
Based on the submitted data and the following review, PMDA concluded that the clinical use of nivolumab is acceptable.

**Effects on choroid plexus**
Because of the infiltration of lymphocytes and plasma cells into the choroid plexus occurred with nivolumab monotherapy [see "3.(iii).A.(6).3) Four-week repeated intravenous dose toxicity with [redacted] co-administration in cynomolgus monkeys"], PMDA asked the applicant to explain the need to promote awareness of the effects of nivolumab on the choroid plexus in clinical settings.

The applicant replied as follows:
Based on the following fact, the applicant considered that the infiltration of lymphocytes and plasma cells into the choroid plexus associated with nivolumab monotherapy is not toxicologically significant.
- In the animal study that found lymphocyte and plasma cell infiltration into the choroid plexus associated with nivolumab monotherapy, no findings emerged to suggest elevated or decreased production of cerebrospinal fluid (an indicator of choroid plexus function) or choroid plexus tissue damage.

Based on the following facts, the findings on the choroid plexus is considered unlikely to be due to the administration of nivolumab.
- Lymphocyte and plasma cell infiltration into the choroid plexus has been reported to occur naturally in monkeys (*Toxicol Pathol*. 2010;38:642-57, *J Toxicol Pathol*. 2012;25:63-101).
- No changes in the choroid plexus were observed in 4- and 13-week repeated-dose toxicity studies on nivolumab [see "3.(iii).A.(2) Repeated-dose toxicity"].

However, the possibility to have lymphocyte and plasma cell infiltration into the choroid plexus in clinical settings cannot be ruled out because this finding on the choroid plexus was not observed at the study laboratory prior to this study (a total of 438 cases used as the historical data), and its developmental mechanism has yet to be elucidated. Therefore, the package insert will state the effects of nivolumab on the choroid plexus.

PMDA accepted the applicant's explanation.

## 4. Clinical data
### 4.(i) Summary of biopharmaceutical studies and associated analytical methods
### *4.(i).A Summary of the submitted data*
**Analytical methods**
#### 4.(i).A.1) Nivolumab assay
Nivolumab (Genetical Recombination) (hereinafter referred to as "nivolumab") in human serum was quantified by one of the following 3 assays that were demonstrated to be equivalent by cross validation:
(a) Enzyme-linked immunosorbent assay (ELISA) using solid-phase bound human recombinant CD279 (programmed cell death 1, PD-1)/Fc fusion protein and alkaline phosphatase (ALP)-labeled mouse anti-human immunoglobulin (Ig) G4 antibody (lower limit of quantification, 1.2 μg/mL)
(b) ELISA using solid-phase bound human recombinant PD-1/Fc fusion protein and ALP-labeled goat anti-human IgG4 antibody (lower limit of quantification, 1.2 μg/mL)
(c) Electrochemical luminescence immunoassay (ECLIA) using solid-phase bound streptavidin, biotin-labeled anti-nivolumab antibodies, and ruthenium-labeled anti-nivolumab antibodies (lower limit of quantification, 0.2 μg/mL)

#### 4.(i).A.2) Anti-nivolumab antibody assay
Anti-nivolumab antibodies in human serum were quantified by ECLIA using solid-phase bound streptavidin, biotin-labeled nivolumab, and ruthenium-labeled nivolumab. During the development of nivolumab, the ECLIA method was modified so as to reduce the impact of serum nivolumab on anti-nivolumab antibody measurements. In the clinical studies, 4 kinds of ECLIA methods were employed (Method A [overseas phase I study (CA209001), assay code, STM-4669]; Method B [domestic phase I study (ONO-4538-01*), assay code, [redacted]]; Method C [overseas phase I study (CA209003), assay code, [redacted]]; and Method D [ONO-4538-01*, domestic phase II study (ONO-4538-02), assay code, [redacted]]). The upper concentration limits that are free of the impact of

nivolumab in the anti-nivolumab antibody assay for Methods A, B, C, and D were 0.1, 5, 12.5, and 800 μg/mL, respectively.

Maximum nivolumab serum concentrations as measured by anti-nivolumab antibody assays in Study CA209001, ONO-4538-01, CA209003, and ONO-4538-02 were 105, 319, 594, and 49.9 μg/mL, respectively. The applicant explained that while the impact of serum nivolumab on anti-nivolumab antibody assays with Methods A, B, and C could not be ruled out, the impact was minimal with Method D.

* Following measurement by Method B, all specimens were retested by Method D.

**4.(ii) Summary of clinical pharmacology studies**

***4.(ii).A Summary of the submitted data***

**4.(ii).A.(1) Domestic phase I study (5.3.3.2-1: ONO-4538-01, from February 2009 to present, [Data cutoff date, [redacted], 20[redacted]])**

In 17 patients with advanced solid tumors resistant to conventional therapies, an open-label study was conducted to investigate the pharmacokinetics (PK) of nivolumab. In the single dosing period, 1, 3, 10, or 20 mg/kg of nivolumab was administered intravenously over at least 1 hour.

The following table shows the PK parameters for single-dose nivolumab. Within the dose range investigated, $AUC_{last}$ values were generally dose proportional. $C_{max}$ values were generally dose proportional in the dose range of 1 to 10 mg/kg, but the $C_{max}$ increased in a less-than-dose-proportional manner in the dose range of 10 to 20 mg/kg. According to the applicant, this trend is due to significant inter-subject variability of $C_{max}$ values in the 20 mg/kg group. The $t_{1/2}$ of nivolumab was comparable with that of endogenous IgG4 (504 hours) (*Clin Pharmacokinet*. 2010;49:633-59). CL and $V_{ss}$ were generally constant, regardless of dose. $V_{ss}$ values were almost comparable with human plasma volume (approximately 50 mL/kg) (*Pharm Res*. 1993;10:1093-5).

**PK parameters for single-dose nivolumab**

| Dose (mg/kg) | n | $C_{max}$ (μg/mL) | $t_{max}$*1 (h) | $AUC_{last}$*2 (μg × h/mL) | $AUC_{inf}$ (μg × h/mL) | $t_{1/2}$ (h) | CL (mL/h/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|---|---|---|
| 1 | 3 | 24.4 ± 4.5 | 3.0 (1.0, 9.0) | 4950 ± 580 | 8000 ± 1390 | 360 ± 10 | 0.127 ± 0.020 | 64.6 ± 6.7 |
| 3 | 5 | 68.8 ± 10.9 | 1.0 (1.0, 3.0) | 12,300 ± 4500 | 20,000 ± 11,300 | 320 ± 170 | 0.210 ± 0.152 | 69.7 ± 10.2 |
| 10 | 6 | 192 ± 36 | 3.0 (1.0, 9.0) | 43,900 ± 7200 | 82,700 ± 18,700 | 520 ± 270 | 0.126 ± 0.027 | 83.6 ± 27.4 |
| 20 | 3 | 214 ± 68 | 9.0 (3.0, 25) | 67,400 ± 15,500 | 126,000 ± 62,000 | 410 ± 230 | 0.206 ± 0.143 | 96.8 ± 12.1 |

Arithmetic mean ± SD; *1, median (range); *2, $AUC_{21day}$

**4.(ii).A.(2) Overseas phase I study (5.3.3.2-2: CA209001, from October 2006 to [redacted] 20[redacted])**

In 39 patients with castration-resistant prostate cancer, advanced or recurrent non-small cell lung cancer, colorectal cancer, malignant melanoma, or renal cell cancer resistant to conventional therapies, an open-label study was conducted to investigate the PK and other endpoints of nivolumab. In the single dosing period, 0.3, 1, 3, or 10 mg/kg of nivolumab was administered intravenously over at least 1 hour. In the PK analysis set, PK parameters were calculated for patients from whom an adequate number of blood samples were collected.

The following table summarizes PK parameters for the single-dose administration of nivolumab. $C_{max}$ and $AUC_{inf}$ of nivolumab were dose proportional in the dose range investigated.

**PK parameters for single-dose nivolumab**

| Dose (mg/kg) | n | $C_{max}$ (μg/mL) | $t_{max}$*1 (h) | $AUC_{last}$*2 (μg × h/mL) | $AUC_{inf}$ (μg × h/mL) | $t_{1/2}$ (day) | CL (mL/h/kg) | $V_z$ (mL/kg) |
|---|---|---|---|---|---|---|---|---|
| 0.3 | 6 | 6.8 ± 1.5 | 3.0 (1.0, 6.8) | 1118 ± 525 | 2364*3 ± 384 | 18.9*2, 3 ± 7.05 | 0.13*3 ± 0.022 | 82.8*3 ± 27.19 |
| 1 | 6 | 16.8 ± 5.4 | 1.9 (1.0, 7.0) | 3904 ± 2414 | 6217*4 ± 1847 | 17.0*4 ± 2.36 | 0.17*4 ± 0.051 | 99.6*4 ± 23.04 |
| 3 | 5 | 62.0 ± 17.1 | 3.1 (1.0, 5.0) | 15,066 ± 6616 | 17,134 ± 7622 | 17.0 ± 4.70 | 0.20 ± 0.087 | 112.7 ± 39.50 |
| 10 | 21 | 199.7 ± 38.9 | 1.6 (0.9, 7.0) | 61,064 ± 23,715 | 79,327*5 ± 21,775 | 24.8*5 ± 7.22 | 0.13*5 ± 0.038 | 109.4*5 ± 26.70 |

Arithmetic mean ± SD; *1, median (range), *2, $AUC_{84day}$, *3, n = 3, *4, n = 4, *5, n = 19

### 4.(ii).A.(3) Overseas phase I study (5.3.3.2-3: CA209003, from October 2008 to ■ 20■)

In 306 patients with castration-resistant prostate cancer, advanced or recurrent non-small cell lung cancer, colorectal cancer, malignant melanoma, or renal cell cancer resistant to conventional therapies, an open-label study was conducted to investigate the PK and other endpoints of nivolumab (PK analysis set consisting of 305 patients). In each cycle, 0.1, 0.3, 1, 3, or 10 mg/kg of nivolumab was administered as an intravenous infusion over at least 1 hour every 2 weeks for 8 weeks. In the PK analysis set, PK parameters were calculated for patients from whom an adequate number of blood samples were collected.

The following table summarizes the PK parameters of nivolumab. For the first and third cycles, the $C_{max}$ and $AUC_{tau}$ of nivolumab were dose proportional, and the CL values were generally constant regardless of dose. Furthermore, the accumulation indices of $C_{max}$ and $AUC_{tau}$ (first to third cycle ratio) were 2.0 to 2.4 and 2.9 to 3.3, respectively, and remained constant regardless of dose.

**PK parameters of nivolumab following the first dosing in the first and third cycles**

| Dose (mg/kg) | Cycle | n | $C_{max}$ (μg/mL) | $t_{max}$*1 (h) | $AUC_{tau}$ (μg × h/mL) | CL (mL/h/kg) |
|---|---|---|---|---|---|---|
| 0.1 | 1 | 15 | 2.0 ± 0.5 | 1.1 (0.3, 51.0) | 295*2 ± 96 | - |
| | 3 | 5 | 4.1 ± 1.7 | 8.0 (0.6, 24.0) | 1138*3 ± 303 | 0.093*3 ± 0.0299 |
| 0.3 | 1 | 17 | 7.3 ± 2.4 | 1.2 (0.9, 24.3) | 993*4 ± 267 | - |
| | 3 | 2 | 18.1 ± 4.8 | 24.7 (1.3, 48.0) | 3420 ± 437 | 0.089 ± 0.0113 |
| 1 | 1 | 17 | 20.4 ± 6.0 | 1.2 (0.9, 48.0) | 3679*5 ± 876 | - |
| | 3 | 10 | 48.2 ± 12.6 | 1.0 (0.9, 24.1) | 10,510*6 ± 2712 | 0.101*6 ± 0.0264 |
| 3 | 1 | 13 | 63.1 ± 16.7 | 2.1 (0.8, 8.0) | 9003 ± 2045 | - |
| | 3 | 7 | 134.6 ± 26.7 | 4.0 (1.0, 8.0) | 30,998*7 ± 5418 | 0.101*7 ± 0.0141 |
| 10 | 1 | 14 | 203.8 ± 81.4 | 3.9 (1.0, 48.2) | 32,159*8 ± 8160 | - |
| | 3 | 5 | 487.6 ± 119.8 | 22.3 (1.0, 24.5) | 101,968*9 ± 26,552 | 0.105*9 ± 0.0259 |

Arithmetic mean ± SD; -, not calculated; *1, median (range); *2, n = 13; *3, n = 4; *4, n = 15; *5, n = 10; *6, n = 9; *7, n = 5; *8, n = 12; *9, n = 3

### 4.(ii).A.(4) Domestic phase II study (5.3.5.2-1: ONO-4538-02, from December 2011 to present [data cutoff date, ■ ■, 20■])

In 35 patients with unresectable advanced (stage III/IV) or recurrent malignant melanoma and a history of chemotherapy with dacarbazine, an open-label study was conducted to investigate the PK and other endpoints of nivolumab. The patients received 2 mg/kg of nivolumab as an intravenous infusion of at least 1 hour every 3 weeks.

After Week 18 of administration, serum nivolumab concentrations following intravenous dosing were 44.3 to 51.6 μg/mL and serum trough concentrations were 25.1 to 36.5 μg/mL (the averages of values obtained at all time points of measurements). The values were generally constant, regardless of time point of measurement. The applicant therefore stated that nivolumab serum concentrations is expected to reach a steady state before Week 18 of administration.

**4.(ii).A.(5) Effects on QT/QTc intervals**

The ONO-4538-02 study investigated the effect of nivolumab on QT/QTc intervals. A linear mixed effect model was used to examine the relationship between serum nivolumab concentrations and the change from the baseline in QT corrected for heart rate by the Fridericia's correction formula (QTcF) (ΔQTcF). The result showed no clear correlation between serum nivolumab concentrations and ΔQTcF. In the ONO-4538-02 study, ΔQTcF with $C_{max}$ of 53.6 μg/mL was −2.39 msec (90% confidence interval [CI], −6.49 msec, 1.70 msec).

Based on the result, the applicant stated that nivolumab is unlikely to have clinically significant effect on QT/QTc intervals when administered intravenously at the dose of 2 mg/kg every 3 weeks.

**4.(ii).A.(6) Population pharmacokinetics (PPK) analysis**

Based on the PK data obtained from Studies ONO-4538-01, ONO-4538-02, CA209001, and CA209003 (5028 measurements from 395 patients), a population pharmacokinetics (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.

The following covariates for nivolumab PK parameters (CL and $V_1$) were assessed: body weight, ethnicity, age, sex, baseline blood lactic dehydrogenase (LDH), serum albumin, estimated glomerular filtration rate (eGFR), Eastern Cooperative Oncology Group Performance Status (ECOG PS), C-reactive protein (CRP), total lymphocyte count, liver function based on the National Cancer Institute (NCI) Organ Dysfunction Group classification, dosage, and cancer type. The result identified body weight, sex, serum albumin, and CRP as significant covariates for nivolumab CL. Body weight and sex were also identified as significant covariates for $V_1$.

Based on the analysis, the applicant stated the following:

- The effects of body weight, sex, serum albumin, and CRP on the CL of nivolumab were within the inter-subject variability of CL (coefficient of variation, 42.0%). Thus, the effects of these covariates on PK of nivolumab are limited.
- The estimated $V_1$ values for patients in relation to body weights of 50.0 kg (5th percentile), 77.0 kg (median), and 115.8 kg (95th percentile) were 3.82, 4.89, and 6.17 L, respectively. The effect of body weight on $V_1$ was greater than the inter-subject variability of $V_1$ (coefficient of variation, 24.9%). The $V_1$ of nivolumab is thought to increase with body weight because nivolumab is mainly distributed in the circulating blood [see "3.(ii).A.(2).1) Single-dose administration"]. Thus, the $V_1$ of nivolumab increases with body weight.

A simulation using the above-mentioned PPK model estimated the 3-week steady-state AUC following intravenous nivolumab every 3 weeks at the dose of 2 mg/kg to be 15,204 μg × h/mL.

**4.(ii).A.(7) Effects of anti-nivolumab antibodies on the PK of nivolumab**

The expression of anti-nivolumab antibodies was investigated in Studies ONO-4538-01 (n = 17), ONO-4538-02 (n = 35), CA209001 (n = 39), and CA209003 (n = 243). Serum anti-nivolumab antibodies were measured by Method A in Study CA209001; by Methods B and D in Study ONO-4538-01; by Method C in Study CA209003; and by Method D in Study ONO-4538-02 [see "4.(i).A.2) Anti-nivolumab antibody assay"]. In Study ONO-4538-01, specimens were first measured by Method B, then retested by Method D (Method D has a higher upper limit of concentration level that is free of the impact of nivolumab in anti-nivolumab antibody assay). The specimens in Studies CA209001 and CA209003 were not retested by Method D.

The numbers of persistent-positive patients (anti-nivolumab antibodies detected in at least 2 consecutive measurements and post-dosing antibody titers at least 4-fold greater than the pre-dosing

antibody titer) in Studies ONO-4538-01, ONO-4538-02, and CA209003 were 0 of 17 patients (0%), 0 of 35 patients (0%), and 2 of 243 patients (0.8%), respectively. According to the applicant, persistent-positive cases were not investigated in Study CA209001 because the antibody titers were not quantified.

Anti-nivolumab antibodies were detected in at least 1 measurement in 2 of 17 patients (11.8%) in Study ONO-4538-01, 0 of 35 patients (0%) in Study ONO-4538-02, 4 of 39 patients (10.3%) in Study CA209001, and 21 of 243 patients (8.6%) in Study CA209003.

To investigate the effect of anti-nivolumab antibodies on the nivolumab PK, the CL of nivolumab estimated by the final model obtained by the above-mentioned PPK analysis was compared between patients without anti-nivolumab antibodies and those with anti-nivolumab antibodies (at least 1 positive measurement) [see "4.(ii).A.(6) Population pharmacokinetics (PPK) analysis"]. In Study CA209003, the CL in patients with anti-nivolumab antibodies was higher than in those without anti-nivolumab antibodies, but the distribution of individual values of the 2 groups of patients overlapped.

Based on the analysis, the applicant stated that anti-nivolumab antibodies do not markedly impact the PK of nivolumab.

**4.(ii).A.(8) Relationship of nivolumab exposure to efficacy and safety**

**4.(ii).A.(8).1) Relationship of nivolumab exposure to efficacy**

Based on the result of Study ONO-4538-02 in patients with malignant melanoma, a logistic regression analysis was conducted to investigate the relationship of nivolumab exposure (AUC, $C_{max}$, $C_{min}$) to efficacy. The result showed no statistically significant relationship between nivolumab exposure (AUC, $C_{max}$, $C_{min}$) and efficacy.

Among the patients with malignant melanoma enrolled in Study CA209003, a relationship was observed between nivolumab $C_{min}$ values and response rates. The effect of exposure level gradually stabilized with 1 mg/kg of nivolumab every 2 weeks.

**4.(ii).A.(8).2) Relationship between nivolumab exposure and safety**

Based on the result of Study ONO-4538-02, a logistic regression analysis was conducted to examine the relationship of nivolumab exposure (AUC, $C_{max}$, $C_{min}$) to (a) ≥ Grade 3 adverse events with a reasonable suspected causal relationship to nivolumab, and (b) ≥ Grade 3 autoimmune disease-related symptoms that were considered to be due to immunomodulatory activities based on the mechanism of action of nivolumab [see "4.(iii).B.(3).7).(a) Excessive immunoreaction"]. The result showed no statistically significant relationship between nivolumab exposure (AUC, $C_{max}$, $C_{min}$) and the development of (a) or (b). No clear difference was observed in nivolumab exposure (AUC, $C_{max}$, $C_{min}$) between patients experiencing and not experiencing the development of (a) or (b).

These findings suggest that the efficacy of nivolumab may diminish when nivolumab exposure is lower than that is achieved by intravenous dosing at 1 mg/kg every 2 weeks. According to the applicant, no clear relationship has been found between nivolumab exposure and the efficacy and safety of nivolumab in the range of exposure levels associated with intravenous dosing at 2 mg/kg every 3 weeks.

**4.(ii).A.(9) Effects of impaired liver and kidney function on nivolumab PK**

The applicant stated that decreased liver and kidney functions are less likely to affect the PK of nivolumab for the reasons given below:

- Nivolumab, a human IgG4, is thought to be metabolized into peptides and amino acids in reticuloendothelial cells, which are generally seen not only in the liver but also in other tissues (*Drug Discov Today*. 2006;11:81-8, *Clin Pharmacol Ther*. 2008;84:548-58).
- As a high molecular compound (molecular weight, approximately 145,000), nivolumab is unlikely to be excreted unmetabolized via the kidneys.

- A PPK analysis did not identify baseline eGFR (an indicator of liver and kidney functions as assessed by the NCI Organ Dysfunction Group classification) as a significant PK covariate for nivolumab [see "4.(ii).A.(6) Population pharmacokinetics (PPK) analysis"].

### *4.(ii).B Outline of the review by PMDA*

#### 4.(ii).B.(1) Differences in the nivolumab PK between Japanese and foreign patients

The applicant explained that there are no clear differences in the PK of nivolumab between Japanese and foreign patients: (a) In comparisons of the PK parameters obtained in Study ONO-4538-01 (Japanese phase I study) and Study CA209001 (foreign phase I study), $C_{max}$ and AUC were comparable between the 2 studies with 1, 3, or 10 mg/kg of nivolumab; and (b) a PPK analysis did not identify ethnicity (Japanese or non-Japanese) as a significant covariate for the PK of nivolumab [see "4.(ii).A.(6) Population pharmacokinetics (PPK) analysis"].

PMDA accepted the applicant's explanation.

#### 4.(ii).B.(2) Effects of anti-nivolumab antibodies on the PK of nivolumab

The applicant stated that no clear effects of anti-nivolumab antibodies on the PK of nivolumab were observed in clinical studies of nivolumab [see "4.(ii).A.(7) Effects of anti-nivolumab antibodies on nivolumab PK"].

PMDA's considerations are as follows:
Because of the following facts, it is difficult to reach a conclusion on the effects of anti-nivolumab antibodies on the PK of nivolumab based on the results of the submitted studies. The collection of PK data must be continued and new relevant information must be provided to the medical community.

- With the anti-nivolumab assays used in Studies CA209001 and CA209003 (Methods A and C, respectively), the possibility that nivolumab in specimens had affected anti-nivolumab antibody measurements could not be ruled out [see "4.(i).A.2) Anti-nivolumab antibody assay"].
- In Studies ONO-4538-01 and ONO-4538-02, the number of patients with anti-nivolumab antibodies was extremely low [see "4.(ii).A.(7) Effects of anti-nivolumab antibodies on nivolumab PK"].

## 4.(iii) Summary of clinical efficacy and safety

### *4.(iii).A Summary of the submitted data*

The results from a total of 4 studies were submitted as efficacy and safety data: 1 Japanese phase I study, 1 Japanese phase II study, and 2 foreign phase I studies.

**Summary of clinical studies on safety and efficacy**

| Data classification | Region | Study | Phase | Subjects | Enrollment number | Summary of dosage and administration | Main endpoints |
|---|---|---|---|---|---|---|---|
| Assessment | Japanese | ONO-4538-01 | I | Advanced solid cancer patients | 17 | Intravenous dosing at 1, 3, 10, or 20 mg/kg once or every 2 weeks for a total of 2 administrations | Safety<br>PK |
| | | ONO-4538-02 | II | Patients with unresectable advanced or recurrent MEL patients with a past history of chemotherapy | 35 | Intravenous dosing of 2 mg/kg every 3 weeks | Efficacy<br>Safety<br>PK |
| | Foreign | CA209001 | I | Patients with advanced or recurrent NSCLC, CRC, MEL, RCC, or CRPC | 39 | Intravenous dosing of 0.3, 1, 3, or 10 mg/kg once or every 4 weeks | Safety<br>PK |
| | | CA209003 | I | Patients with advanced or recurrent NSCLC, CRC, MEL, RCC, or CRPC | 395 | Intravenous dosing of 0.1, 0.3, 1, 3, or 10 mg/kg every 2 weeks | Safety<br>PK |

MEL, malignant melanoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; RCC, renal cell carcinoma; CRPC, castration-resistant prostate cancer; PK, Pharmacokinetics

A summary of each clinical study is given below:
The major adverse events other than death confirmed in each clinical study are listed in "4.(iv) Adverse events observed in clinical studies" and the PK data in "4.(i) Summary of biopharmaceutical studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

***Evaluation Data***

**4.(iii).A.(1) Japanese clinical study**

**4.(iii).A.(1).1) Japanese phase I study (5.3.3.2-1: ONO-4538-01, from February 2009 to present [data cutoff date, [redacted], 20[redacted]])**

In patients with advanced solid cancer resistant to conventional therapies (target sample size, a maximum of 24), a domestic open-label uncontrolled study was conducted at 1 domestic institution to investigate the safety, tolerance, and PK of nivolumab.

In this study, 1, 3, 10, or 20 mg/kg of nivolumab was administered as an intravenous infusion of at least 1 hour (single dosing period). After a 3-week washout period, patients without dose limiting toxicities (DLT) were treated with the same dose by an intravenous infusion of at least 1 hour twice at a 2-week interval (multiple dosing period). In patients without DLT who met the criteria for either partial response (PR) or stable disease (SD) as determined by RECIST version 1.0 after the end of the multiple dosing period, the same dose used during the single dosing period was administered as an intravenous infusion of at least 1 hour for a total of 4 times at 2-week intervals (continuous dosing period).

All 17 patients enrolled in this study received nivolumab and served as the safety analysis set.

DLT was assessed during the single and multiple dosing periods. DLT was not seen in any of the treatment groups.

No deaths occurred during the dosing or follow-up periods (up to 28 days after the final dose).

**4.(iii).A.(1).2) Japanese phase II study (5.3.5.2-1: ONO-4538-02, from December 2011 to present [data cutoff date, [redacted], 20[redacted]])**

In patients with unresectable advanced (stage III or IV) or recurrent malignant melanoma with a history of chemotherapy with dacarbazine, an open-label uncontrolled study was conducted at 11 domestic institutions to investigate the efficacy, safety, and PK of nivolumab.

In this study, 2 mg/kg of nivolumab was administered as intravenous infusion over at least 1 hour every 3 weeks, which may have been continued until unacceptable toxicities emerged.

All 35 patients enrolled in the study received nivolumab and served as the full analysis set (FAS) to assess both efficacy and safety.

The following table summarizes response rates (primary endpoint) as assessed by a central image analysis organization (central assessments).

* The pre-determined threshold for response rate in this study was 12.5%.

**Best overall assessments and response rates (RECIST Ver. 1.1, Central assessments, FAS, n = 35)**

| | n (%) |
|---|---|
| Best overall assessments | |
| Complete response (CR) | 1 (2.9) |
| Partial response (PR) | 7 (20.0) |
| Stable disease (SD) | 15 (42.9) |
| Progressive disease (PD) | 11 (31.4) |
| Not evaluable (NE) | 1 (2.9) |
| Response (CR + PR) | 8 |
| (Response rate [90% CI*][%]) | (22.9 [13.4, 36.2]) |

* Wilson's normal approximation; CI, Confidence interval

No deaths occurred during the dosing or follow-up periods (up to 28 days after final dosing).

**4.(iii).A.(2) Foreign clinical study**

**4.(iii).A.(2).1) Foreign phase I study (5.3.3.2-2: CA209001, from October 2006 to [redacted] 20[redacted])**

In patients with castration-resistant prostate cancer, advanced or recurrent non-small cell lung cancer, colorectal cancer, malignant melanoma, or renal cell cancer resistant to conventional therapies (target

sample size, n = 39), an open-label uncontrolled study was conducted at 4 overseas institutions to investigate the safety, tolerance, and PK of nivolumab.

In this study, 0.3, 1, 3, or 10 mg/kg of nivolumab was administered as an intravenous infusion over at least 1 hour (single dosing period). In patients who met the criteria for stable disease (SD) as determined by RECIST version 1.0 after a 4-week washout period, the same dose was administered as an intravenous infusion over at least 1 hour every 4 weeks (repeated dosing period).

All 39 patients enrolled in the study received nivolumab and served as the analysis set for safety data.

DLT did not occur in any of the treatment groups.

The number of deaths during the dosing and follow-up periods (up to 28 days after final dosing) was 12. The causes of the deaths were disease progression in 10 patients, hepatic failure in 1 patient, and pneumonia in 1 patient. A causal relationship to nivolumab was ruled out in all cases.

**4.(iii).A.(2).2) Foreign phase I study (5.3.3.2-3: CA209003, from October 2008 to [redacted] 20[redacted])**

In patients with castration-resistant prostate cancer, advanced or recurrent non-small cell lung cancer, colorectal cancer, malignant melanoma, or renal cell cancer resistant to conventional therapies (target sample size, n = 290), an open-label uncontrolled study was conducted at 13 overseas institutions to investigate the safety, efficacy, and PK of nivolumab.

In a single cycle, 0.1, 0.3, 1, 3, or 10 mg/kg of nivolumab was administered intravenously over at least 1 hour every 2 weeks for 8 weeks. Nivolumab was allowed to be administered for up to 12 cycles.

Of the 395 patients enrolled in this study, 89 patients did not meet the study inclusion criteria or died before dosing, and 306 patients received nivolumab and served as the analysis set for safety data.

A total of 75 patients died during the dosing and follow-up periods (up to 100 days after final dosing). The causes of the deaths were disease progression in 70 patients, unknown in 2 patients, ischemic myocardiopathy in 1 patient, cardiorespiratory arrest in 1 patient, and sepsis in 1 patient. In the case of sepsis, a causal relationship to nivolumab could not be ruled out.*

* A 59-year-old male patient with colorectal cancer had pneumonitis on Day 90 of dosing, acute respiratory distress syndrome (ARDS) on Day 103 of dosing, and sepsis on Day 124 of dosing. He died on Day 126 of dosing.

## *4.(iii).B Outline of the review by PMDA*

### 4.(iii).B.(1) Data for review

Considering that Study ONO-4538-02 (a Japanese phase II study of patients with unresectable advanced or recurrent malignant melanoma who have a past history of chemotherapy with dacarbazine) is the most important clinical study for assessing the efficacy and safety of nivolumab, PMDA decided to prioritize the results of Study ONO-4538-02 for the assessment of safety and efficacy.

### 4.(iii).B.(2) Efficacy

Based on the following review, PMDA concluded that nivolumab exhibited some degree of efficacy in patients with unresectable advanced or recurrent malignant melanoma and a history of chemotherapy with dacarbazine.

**Efficacy endpoints and assessment results**

The lower limit of 90% CI of the response rate (22.9%) assessed centrally, the primary endpoint of Study ONO-4538-02, was 13.4%, which was above the threshold response rate established based on the results of dacarbazine studies (12.5%) [see "4.(iii).A.(1).2) Japanese phase II study"]. As for secondary endpoints, the investigator-assessed response rate was 22.9% (90% CI; 13.4%, 36.2%), the median overall survival (OS) was 473.0 days (90% CI; 276.0 days, unable to be estimated), and the median progression-free survival (PFS) assessed centrally was 169.0 days (90% CI; 72.0, 277.0 days).

The applicant explained the clinical significance of the efficacy of nivolumab in patients with unresectable, advanced or recurrent malignant melanoma who have a history of chemotherapy with dacarbazine as follows:
Malignant melanoma has the following characteristics, which reduce patients' quality of life (QOL).The potential of nivolumab to shrink tumors and to improve QOL would be of clinical significance.

- Hemorrhaging is likely to occur on primary and dermal disseminated lesions and is accompanied by foul smell, which causes psychological distress to the patient.
- Malignant melanoma frequently occurs in the hands and legs, resulting in axillary and inguinal lymph node metastases and causing edema.
- Malignant melanoma frequently occurs also in the body trunk, face, and arms, resulting in mediastinal lymph node metastasis and causing dyspnea due to tracheal compression.
- Tumors arising near joints restrict the range of joint movements.

PMDA's considerations are as follows:
OS should be the true endpoint for patients with unresectable advanced or recurrent malignant melanoma with a history of chemotherapy with dacarbazine. Nevertheless, the relationship between the OS and response rate is unclear, and it is difficult to assess the life-prolonging effect of nivolumab in patients with malignant melanoma at present.

However, in Study ONO-4538-02, the primary endpoint of the centrally assessed response rate exceeded the predetermined threshold response rate [see "4.(iii).A.(1).2) Japanese phase II study"]. Nivolumab may be clinically effective in reducing the size of tumors in patients with unresectable advanced or recurrent malignant melanoma and with a history of chemotherapy with dacarbazine. These findings indicate some degree of efficacy of nivolumab in the subjects of Study ONO-4538-02.

**4.(iii).B.(3) Safety [see "4.(iv) Adverse events observed in clinical studies" for adverse events.]**
Based on the following reviews, PMDA concluded that adverse events that require attention while using nivolumab are hepatic function disorder, abnormal thyroid function, interstitial lung disease, infusion reaction, and skin disorder. The onset of these adverse events must be monitored when using nivolumab.

At the same time, PMDA concluded that while the monitoring of the onset of these adverse events is essential, nivolumab can be used as long as physicians with sufficient knowledge of and experience with cancer chemotherapy take appropriate actions, including the observation and management of adverse events and drug interruption. However, available safety information for nivolumab is very limited. The applicant should continue gathering information after the market launch to promptly provide relevant new safety information to the medical community.

**4.(iii).B.(3).1) Safety profile of nivolumab**
According to the applicant, nivolumab has the following safety profile in patients with malignant melanoma.

The safety of nivolumab in Study ONO-4538-02 is summarized below:

**Safety summary (Study ONO-4538-02)**

| | n (%)<br>n = 35 |
|---|---|
| All adverse events | 35 (100) |
| ≥ Grade 3 adverse events | 19 (54.3) |
| Death | 1 (2.9) |
| Serious adverse events | 17 (48.6) |
| Adverse events leading to drug discontinuation | 10 (28.6) |
| Adverse events leading to drug interruption | 6 (17.1) |

The following table lists adverse events with an incidence of ≥20%.

**Adverse events with an incidence of ≥20% (Study ONO-4538-02)**

| System organ class<br>Preferred term<br>(MedDRA/J ver.16.0) | n (%)<br>n = 35 | |
|---|---|---|
| | All grades | ≥ Grade 3 |
| All adverse events | 35 (100) | 19 (54.3) |
| Gastrointestinal disorders | | |
| Constipation | 8 (22.9) | 0 |
| Nausea | 9 (25.7) | 2 (5.7) |
| General disorders and administration site conditions | | |
| Fatigue | 7 (20.0) | 1 (2.9) |
| Malaise | 10 (28.6) | 1 (2.9) |
| Fever | 7 (20.0) | 0 |
| Investigations | | |
| ALT increased | 8 (22.9) | 1 (2.9) |
| AST increased | 10 (28.6) | 2 (5.7) |
| Blood albumin decreased | 8 (22.9) | 2 (5.7) |
| Blood LDH increased | 12 (34.3) | 1 (2.9) |
| Blood TSH increased | 7 (20.0) | 0 |
| CRP increased | 13 (37.1) | 1 (2.9) |
| γ-GTP increased | 9 (25.7) | 4 (11.4) |
| Haematocrit decreased | 7 (20.0) | 3 (8.6) |
| Haemoglobin decreased | 8 (22.9) | 3 (8.6) |
| Lymphocyte count decreased | 7 (20.0) | 2 (5.7) |
| Total protein decreased | 7 (20.0) | 0 |
| Red blood cell count decreased | 7 (20.0) | 3 (8.6) |
| $T_3$ free decreased | 9 (25.7) | 0 |
| $T_4$ free decreased | 7 (20.0) | 0 |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 9 (25.7) | 4 (11.4) |
| Skin and subcutaneous tissue disorders | | |
| Pruritus | 11 (31.4) | 0 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactic dehydrogenase; TSH, thyroid stimulating hormone; CRP, C-reactive protein; γ-GTP, gamma-glutamyltransferase; $T_3$, triiodothyronine; $T_4$, thyroxine

A total of 17 patients (48.6%) experienced serious adverse events including liver disorder, malignant melanoma (5.7%, n = 2 each), anaemia, hypothyroidism, optic nerve disorder, malaise, pain, urinary tract infection, pneumonia bacterial, pubis fracture, hypercalcaemia, metastatic pain, tumour haemorrhage, cancer pain, metastases to central nervous system, paralysis, interstitial lung disease, pleural effusion, and psoriasis (2.9%, n = 1 each). A causal relationship to nivolumab could not be ruled out for liver disorder (n = 2), hypothyroidism, pneumonia bacterial, interstitial lung disease, and psoriasis (n = 1 each).

A total of 10 patients (28.6%) experienced adverse events leading to drug discontinuation including malignant melanoma (5.7%, n = 2), γ-glutamyltransferase (γ-GTP) increased, tri-iodothyronine ($T_3$) free decreased, thyroxin ($T_4$) free decreased, blood thyroid stimulating hormone (TSH) increased, hypothyroidism, blood creatine phosphokinase (CK) increased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, liver disorder, CRP increased, cell marker increased, pneumonia bacterial, surfactant protein increased, cancer pain, depressed level of consciousness, delirium, interstitial lung disease, metastases to central nervous system, brain oedema, and hypercalcaemia (2.9%, n = 1 each). A causal relationship to nivolumab could not be ruled out for γ-GTP increased, $T_3$ free decreased, $T_4$ free decreased, blood TSH increased, hypothyroidism, blood CK increased, ALT increased, AST increased, liver disorder, CRP increased, cell markers increased, pneumonia bacterial, surfactant protein increased, and interstitial lung disease (n = 1).

A total of 6 patients (17.1%) experienced adverse events led to drug interruption including hypothyroidism, blood TSH increased, $T_3$ free decreased, $T_4$ free decreased (8.6%, n = 3 each), γ-GTP increased (5.7%, n = 2), nausea, hepatic disorder, blood LDH increased, CRP increased, AST

increased, platelet count decreased, haematocrit decreased, haemoglobin decreased, red blood cell (RBC) count decreased, blood CK increased, diarrhoea, neutrophil count decreased, and anti-thyroid antibody positive (2.9%, n = 1 each). A causal relationship to nivolumab could not be ruled out for all the events.

PMDA asked the applicant to summarize the safety of nivolumab in domestic and overseas clinical studies because the safety of nivolumab patients with malignant melanoma has only been investigated in a very limited number of patients. The applicant responded as follows:

Because the results of domestic and overseas phase I clinical studies suggested no difference in safety among the doses from 1 to 10 mg/kg, the safety was analysed based on the combined data of these different dosage and administration. The following table summarizes adverse events with a difference of ≥10% in the incidences between Japanese patients (combined data from Studies ONO-4538-01 and ONO-4538-02, n = 52) and overseas patients (combined data from Studies CA209001 and CA209003, n = 345). Except for malaise and cancer pain, adverse events which occurred ≥10% more frequently in Japanese patients than in foreign patients were of the SOC of "investigations".

**Summary of safety data from Japanese and foreign studies (Studies ONO-4538-01, ONO-4538-02, CA209001, CA209003)**

| System organ class<br>Preferred term<br>(MedDRA/J ver.16.0) | n (%) | | | |
|---|---|---|---|---|
| | All grades | | ≥ Grade 3 | |
| | Japanese patients n = 52 | Overseas patients n = 345 | Japanese patients n = 52 | Overseas patients n = 345 |
| Blood and lymphatic system disorders | | | | |
| Anaemia | 3 (5.8) | 55 (15.9) | 3 (5.8) | 11 (3.2) |
| Lymphopenia | 0 | 35 (10.1) | 0 | 9 (2.6) |
| Gastrointestinal disorders | | | | |
| Diarrhoea | 11 (21.2) | 113 (32.8) | 1 (1.9) | 3 (0.9) |
| Dry mouth | 1 (1.9) | 43 (12.5) | 0 | 1 (0.3) |
| General disorders and administration site conditions | | | | |
| Fatigue | 11 (21.2) | 190 (55.1) | 1 (1.9) | 23 (6.7) |
| Malaise | 13 (25.0) | 8 (2.3) | 1 (1.9) | 0 |
| Oedema peripheral | 1 (1.9) | 67 (19.4) | 0 | 1 (0.3) |
| Investigations | | | | |
| ALT increased | 12 (23.1) | 28 (8.1) | 2 (3.8) | 7 (2.0) |
| AST increased | 14 (26.9) | 28 (8.1) | 3 (5.8) | 6 (1.7) |
| Blood albumin decreased | 16 (30.8) | 11 (3.2) | 3 (5.8) | 0 |
| Blood CK increased | 10 (19.2) | 3 (0.9) | 3 (5.8) | 1 (0.3) |
| Blood LDH increased | 17 (32.7) | 11 (3.2) | 1 (1.9) | 0 |
| Blood TSH increased | 9 (17.3) | 19 (5.5) | 0 | 1 (0.3) |
| CRP increased | 20 (38.5) | 19 (5.5) | 1 (1.9) | 0 |
| Eosinophil count increased | 12 (23.1) | 7 (2.0) | 0 | 0 |
| γ-GTP increased | 12 (23.1) | 0 | 5 (9.6) | 0 |
| Haematocrit decreased | 13 (25.0) | 4 (1.2) | 4 (7.7) | 0 |
| Blood urine present | 8 (15.4) | 2 (0.6) | 0 | 0 |
| Haemoglobin decreased | 14 (26.9) | 53 (15.4) | 4 (7.7) | 2 (0.6) |
| Lymphocyte count decreased | 17 (32.7) | 12 (3.5) | 4 (7.7) | 6 (1.7) |
| Protein total decreased | 12 (23.1) | 3 (0.9) | 0 | 0 |
| Red blood cell count decreased | 11 (21.2) | 4 (1.2) | 4 (7.7) | 0 |
| Weight decreased | 4 (7.7) | 66 (19.1) | 0 | 1 (0.3) |
| White blood cell count increased | 8 (15.4) | 14 (4.1) | 0 | 3 (0.9) |
| T3 free decreased | 11 (21.2) | 0 | 0 | 0 |
| T4 free decreased | 8 (15.4) | 2 (0.6) | 0 | 0 |
| Metabolism and nutrition disorders | | | | |
| Hyperglycaemia | 2 (3.8) | 50 (14.5) | 0 | 6 (1.7) |
| Musculoskeletal, and connective tissue disorders | | | | |
| Arthralgia | 2 (3.8) | 69 (20.0) | 0 | 4 (1.2) |
| Back pain | 3 (5.8) | 81 (23.5) | 1 (1.9) | 9 (2.6) |
| Musculoskeletal pain | 0 | 48 (13.9) | 0 | 8 (2.3) |
| Neoplasms benign, malignant and unspecified | | | | |
| Malignant neoplasm progression | 1 (1.9) | 54 (15.7) | 1 (1.9) | 54 (15.7) |
| Cancer pain | 6 (11.5) | 0 | 3 (5.8) | 0 |

| System organ class<br>Preferred term<br>(MedDRA/J ver.16.0) | n (%) | | | |
|---|---|---|---|---|
| | All grades | | ≥ Grade 3 | |
| | Japanese patients<br>n = 52 | Overseas patients<br>n = 345 | Japanese patients<br>n = 52 | Overseas patients<br>n = 345 |
| Nervous system disorders | | | | |
| Headache | 3 (5.8) | 68 (19.7) | 0 | 1 (0.3) |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Cough | 5 (9.6) | 98 (28.4) | 0 | 5 (1.4) |
| Dyspnoea | 2 (3.8) | 90 (26.1) | 1 (1.9) | 32 (9.3) |
| Skin and subcutaneous tissue disorders | | | | |
| Leukoderma | 6 (11.5) | 0 | 0 | 0 |
| Rash | 7 (13.5) | 84 (24.3) | 0 | 0 |
| Vascular disorders | | | | |
| Hypotension | 0 | 37 (10.7) | 0 | 6 (1.7) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine phosphokinase; LDH, lactic dehydrogenase; TSH, thyroid stimulating hormone; CRP, C-reactive protein; γ-GTP, γ-glutamyltransferase; $T_3$, triiodothyronine; $T_4$, thyroxine

PMDA's considerations are as follows:
The adverse events that occurred in the clinical studies of nivolumab warrant monitoring, and it is necessary to provide appropriate information on these adverse events to the medical community. PMDA concluded that nivolumab can be tolerated by patients if physicians with sufficient knowledge of and experience with cancer chemotherapy take appropriate actions, including drug interruption.

The following section discusses major adverse events that occurred in Study ONO-4538-02.

**4.(iii).B.(3).2) Hepatic function disorders**

The applicant explained about hepatic function disorders associated with the administration of nivolumab as follows:
Adverse events indicative of hepatic function disorders were summarized by corresponding MedDRA preferred terms, which were "acute hepatic failure," "ALT increased," "AST increased," "bilirubin conjugated increased," "blood bilirubin increased," "hepatic enzyme increased," "hepatic failure," "hepatitis," "hyperbilirubinaemia," "liver disorder," "liver function test abnormal" and "transaminase increased."

In Study ONO-4538-02, hepatic function disorders occurred in 10 of the 35 patients (28.6%; AST increased [n = 10], ALT increased [n = 8], liver disorder [n = 2], blood bilirubin increased, conjugated bilirubin increased [n = 1 each]; more than 1 event/patient were reported). Serious hepatic function disorders occurred in 2 of the 35 patients (5.7%; liver disorder [n =2]), for which a causal relationship to nivolumab could not be ruled out. No hepatic function disorder that satisfies Hy's law (Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009) occurred.

The following table lists patients who experienced hepatic function disorders in Study ONO-4538-02:

**Patients who experienced hepatic function disorders (Study ONO-4538-02)**

| Age | Sex | PS | Preferred term (MedDRA/J ver.16.0) | Grade | Onset (days) | Dosing count | Duration (days) | Therapy details | Seriousness | Causal relationship | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 74 | Female | 1 | ALT increased | 1 | 23 | 2 | 22 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | AST increased | 1 | 23 | 2 | 22 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | AST increased | 2 | 65 | 3 | 106 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | ALT increased | 1 | 104 | 5 | 46 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| 31 | Female | 0 | Liver disorder | 3 | 2 | 1 | 46 | Prednisolone<br>Betamethasone<br>Glycyrrhizinate | Serious | Yes | Recovering/ resolving |
| | | | AST increased | 3 | 10 | 1 | 35 | Glycyrrhizinate | Not serious | Yes | Recovering/ resolving |
| | | | ALT increased | 2 | 15 | 1 | 33 | Glycyrrhizinate | Not serious | Yes | Lost to follow-up |
| | | | Bil Conjugated increased | 1 | 44 | 1 | 4 | Follow-up | Not serious | No | Lost to follow-up |
| | | | Blood Bil increased | 1 | 44 | 1 | 4 | Follow-up | Not serious | No | Lost to follow-up |
| 64 | Female | 0 | ALT increased | 4 | 41 | 3 | 141 | Prednisolone<br>Glycyrrhizinate | Not serious | Yes | Recovered/ Resolved |
| | | | AST increased | 4 | 62 | 3 | 57 | Prednisolone<br>Glycyrrhizinate | Not serious | Yes | Recovered/ Resolved |
| | | | Liver disorder | 3 | 83 | 3 | 113 | Prednisolone | Serious | Yes | Recovered/ Resolved |
| 65 | Female | 1 | AST increased | 1 | 3 | 1 | 21 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| 61 | Male | 1 | ALT increased | 1 | 64 | 2 | 18 | Follow-up | Not serious | No | Recovered/ Resolved |
| | | | AST increased | 1 | 81 | 2 | 1 | Follow-up | Not serious | No | Unchanged |
| 59 | Female | 0 | ALT increased | 2 | 98 | 4 | 23 | Glycyrrhizinate | Not serious | No | Recovered/ Resolved |
| | | | AST increased | 2 | 98 | 4 | 23 | Glycyrrhizinate | Not serious | No | Recovered/ Resolved |
| 28 | Female | 0 | ALT increased | 1 | 71 | 4 | 24 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | AST increased | 1 | 71 | 4 | 24 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| 59 | Female | 0 | ALT increased | 1 | 26 | 2 | 11 | Follow-up | Not serious | No | Recovered/ Resolved |
| | | | AST increased | 1 | 26 | 2 | 11 | Follow-up | Not serious | No | Recovered/ Resolved |
| | | | ALT increased | 1 | 42 | 2 | 1 | Follow-up | Not serious | No | Unchanged |
| | | | AST increased | 1 | 42 | 2 | 1 | Follow-up | Not serious | No | Unchanged |
| 60 | Female | 0 | ALT increased | 1 | 211 | 10 | 24 | Follow-up | Not serious | No | Recovered/ Resolved |
| | | | AST increased | 1 | 211 | 10 | 24 | Follow-up | Not serious | No | Recovered/ Resolved |
| 69 | Male | 1 | AST increased | 1 | 193 | 9 | 12 | Follow-up | Not serious | No | Unchanged |

PS, ECOG performance status; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bil, bilirubin

In Study ONO-4538-02, the median onset for hepatic function disorders was 52.5 days (range, 2–211 days). There was no consistent trend in the time of onset.

In Study ONO-4538-02, hepatic function disorders led to drug discontinuation in 1 of 35 patients (2.9%; liver disorder, ALT increased, AST increased [n = 1 each]; more than 1 event/patient was reported). Hepatic function disorders led to drug interruption in 1 of 35 patients (2.9%; liver disorder, AST increased [n = 1 each]; more than 1 event/patient was reported), none of whom resumed the treatment.

In Studies ONO-4538-01, CA209001, and CA209003, hepatic function disorders occurred in 5 of 17 patients (29.4%), 14 of 39 patients (35.9%), and 34 of 306 patients (11.1%), respectively.

These findings reveals that, while most hepatic function disorders observed in Japanese and foreign studies represent liver function test abnormal, hepatotoxicity including hepatitis was also observed,

and the conduct of periodic blood test should be therefore considered. Once any hepatic function disorder occurs, the patient should undergo a thorough examination so that the cause of the disorder is identified and appropriate actions are taken. Actions such as drug interruption and liver support therapy should be taken in a case of hepatic function disorder associated with nivolumab. Corticosteroid therapy should be considered for severe hepatic function disorder.

PMDA's considerations are as follows:
Throughout the clinical studies, blood tests were conducted periodically and appropriate actions including drug interruption were taken for hepatic function disorders. As a result, in most cases, the events were mild in severity and treatment with nivolumab was continued. Similarly in clinical practice, most hepatic function disorders associated with nivolumab should be controllable by periodical blood tests and appropriate actions.

However, the safety of nivolumab has only been investigated in a very small number of patients. Because of hepatic failure with a fatal outcome* in Study CA209001 and the potential difficulty in assessing a causal relationship between nivolumab and a hepatic function disorder, the package insert must mention the circumstances of hepatic function disorders in clinical studies. Furthermore, awareness of hepatic function disorders should be promoted among healthcare professionals through informative materials so that they will be prepared to take appropriate measures for the onset of disorders.

* A 63 year-old woman with malignant melanoma received 10 mg/kg of nivolumab. On Day 50 of the administration of nivolumab, the patient discontinued the study due to tumor progression. The patient suffered Grade 4 acute hepatic failure on Day 60. Dexamethasone was administered for sepsis on Day 64. The patient died on Day 66. Computed tomography (CT) conducted on Day 63 confirmed a liver tumor occupying 70%-90% of the left and right lobes. A causal relationship between nivolumab and acute hepatic failure was ruled out.

### 4.(iii).B.(3).3) Thyroid function abnormality

The applicant explained about abnormal thyroid function associated with the administration of nivolumab as follows: Thyroid function abnormality was analyzed by summarizing adverse events corresponding to the following MedDRA preferred terms: "autoimmune thyroiditis," "blood TSH decreased," "blood TSH increased," "hyperthyroidism," "hypothyroidism," "thyroid function test abnormal," "thyroiditis," "$T_4$ decreased," "$T_4$ free decreased," "$T_4$ free increased," "$T_4$ increased," and "$T_3$ increased."

In Study ONO-4538-02, abnormal thyroid function was observed in 9 of 35 patients (25.7%; blood TSH increased, free $T_4$ decreased [n = 7 each], hypothyroidism [n = 5], blood TSH decreased [n = 4]; more than 1 event/patient were reported). Serious thyroid function abnormality was observed in 1 of 35 patients (2.9%; hypothyroidism), for which a causal relationship to nivolumab could not be ruled out.

The following table lists patients in whom abnormal thyroid function was observed in Study ONO-4538-02.

**Patients in whom abnormal thyroid function was observed (Study ONO-4538-02)**

| Age | Sex | PS | Preferred term (MedDRA/J ver.16.0) | Grade | Onset (days) | Dosing count | Duration (days) | Therapy details | Seriousness | Causal relationship | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Blood TSH increased | 1 | 94 | 4 | 238 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| 79 | Female | 0 | Hypothyroidism | 1 | 94 | 4 | 238 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | $T_4$ free decreased | 1 | 94 | 4 | 196 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH increased | 2 | 65 | 3 | 127 | Levothyroxine | Not serious | Yes | Recovered/ Resolved |
| 74 | Female | 1 | Hypothyroidism | 2 | 65 | 3 | 334 | Levothyroxine | Not serious | Yes | Recovering/ Resolving |
| | | | $T_4$ free decreased | 2 | 65 | 3 | 127 | Levothyroxine | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH increased | 2 | 41 | 3 | 323 | Levothyroxine | Not serious | Yes | Recovered/ Resolved |
| 64 | Female | 0 | Hypothyroidism | 2 | 41 | 3 | 323 | Levothyroxine | Not serious | Yes | Recovering/ Resolving |
| | | | $T_4$ free decreased | 2 | 41 | 3 | 323 | Levothyroxine | Not serious | Yes | Recovered/ Resolved |
| 56 | Female | 0 | Blood TSH increased | 2 | 5 | 1 | 438 | Levothyroxine | Not serious | Yes | Recovering/ |

| Age | Sex | PS | Preferred term (MedDRA/J ver.16.0) | Grade | Onset (days) | Dosing count | Duration (days) | Therapy details | Seriousness | Causal relationship | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Resolving |
| | | | $T_4$ free decreased | 2 | 5 | 1 | 438 | Levothyroxine | Not serious | Yes | Recovering/ Resolving |
| | | | Hypothyroidism | 2 | 169 | 8 | 274 | Levothyroxine | Serious | Yes | Recovering/ Resolving |
| 61 | Male | 1 | Blood TSH decreased | 1 | 45 | 2 | 37 | Follow-up | Not serious | No | Recovering/ Resolving |
| | | | $T_4$ free decreased | 1 | 57 | 2 | 25 | Follow-up | Not serious | No | Unchanged |
| 65 | Female | 0 | Blood TSH decreased | 1 | 44 | 3 | 50 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| 59 | Female | 0 | $T_4$ free increased | 1 | 7 | 1 | 71 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH decreased | 1 | 21 | 1 | 57 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH increased | 1 | 77 | 4 | 103 | Levothyroxine | Not serious | Yes | Lost to follow-up |
| | | | $T_4$ free decreased | 1 | 77 | 4 | 103 | Levothyroxine | Not serious | Yes | Lost to follow-up |
| 28 | Female | 0 | Blood TSH decreased | 1 | 15 | 1 | 34 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | $T_4$ free increased | 1 | 15 | 1 | 34 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH increased | 2 | 48 | 3 | 159 | Levothyroxine | Not serious | Yes | Recovered/ Resolved |
| | | | $T_4$ free decreased | 2 | 48 | 3 | 80 | Levothyroxine | Not serious | Yes | Recovered/ Resolved |
| | | | Hypothyroidism | 2 | 86 | 4 | 176 | Levothyroxine | Not serious | Yes | Lost to follow-up |
| | | | Free $T_4$ increased | 1 | 136 | 6 | 55 | Follow-up | Not serious | No | Recovered/ Resolved |
| 78 | Male | 0 | Blood TSH increased | 1 | 45 | 3 | 20 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH increased | 1 | 93 | 5 | 21 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH increased | 1 | 156 | 8 | 43 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH increased | 1 | 218 | 10 | 22 | Follow-up | Not serious | Yes | Recovered/ Resolved |
| | | | Blood TSH increased | 1 | 247 | 12 | 15 | Follow-up | Not serious | Yes | Recovered/ Resolved |

PS, ECOG performance status; TSH, thyroid stimulating hormone; $T_4$: thyroxine; levothyroxine, levothyroxine sodium hydrate

In Study ONO-4538-02, abnormal thyroid function led to drug discontinuation in 1 of 35 patients (2.9%; blood TSH increased, hypothyroidism, $T_4$ free decreased [n = 1 each]; more than 1 event/patient were reported). Abnormal thyroid function resulted in drug interruption in 3 of 35 patients (8.6%; blood TSH increased, hypothyroidism, $T_4$ free decreased [n = 3 each]; more than 1 event/patient were reported).

In Studies ONO-4538-01, CA209001, and CA209003, abnormal thyroid function was observed in 4 of 17 patients (23.5%), 18 of 39 patients (46.2%), and 30 of 306 patients (9.8%), respectively.

PMDA asked the applicant to explain how thyroid function was monitored during the administration of nivolumab and actions taken when any abnormal thyroid function was noted, as well as the need for caution against thyroid function abnormalities.

The applicant responded as follows:
In the ONO-4538-02 study, thyroid function was monitored by measuring TSH, free $T_3$, and free $T_4$ every 3 weeks. When thyroid function abnormality was observed, early treatment was recommended after thorough testing, including anti-thyroglobulin antibody assays. The administration of nivolumab was to be discontinued when (a) a Grade 3 adverse event with a reasonable suspected causal relationship to nivolumab persisted for ≥7 days, (b) a Grade 4 adverse event with a reasonable suspected causal relationship to nivolumab occurred, or (c) the severity of the adverse event was not reduced to Grade 1 or did not return to the baseline level after hormone replacement therapy within 6 weeks of drug interruption. Hormone replacement therapy was considered for the treatment of thyroid function abnormalities. The interruption of nivolumab and treatment with corticosteroid were

recommended for patients with moderate to severe thyroid function abnormality possibly attributable to elevated autoimmune reactions.

Thyroid function abnormality requires regular monitoring because it can be asymptomatic even when clinical tests are abnormal. It is important to keep healthcare professionals informed about the "Algorithm for treating endocrine disorders" to facilitate appropriate management including hormone replacement therapy and corticosteroid therapy in the event of symptomatic thyroid function abnormality.

PMDA's considerations are as follows:
In Study ONO-4538-02, thyroid function was periodically monitored. When abnormal thyroid function was observed, either nivolumab was interrupted or levothyroxine sodium hydrate was administered. As a result, the observed thyroid function abnormalities were mild and the administration of nivolumab was continued. Similarly in clinical practice, thyroid function abnormality associated with nivolumab should be controllable as long as blood tests are performed regularly and appropriate measures are taken.

However, the safety of nivolumab has only been investigated in a limited number of patients. The result has shown the following: (a) In some patients, the administration of nivolumab was discontinued because of abnormal thyroid function; (b) abnormal thyroid function takes a long time to resolve or improve. Subsequently, the package insert should explain the cases of abnormal thyroid function observed in clinical studies and methods of monitoring thyroid function. Furthermore, awareness of thyroid function abnormalities should be promoted through informative materials so that appropriate measures are taken to manage abnormal thyroid function.

### 4.(iii).B.(3).4) Interstitial lung diseases

The applicant explained about the interstitial lung diseases associated with the administration of nivolumab as follows:
Interstitial lung diseases were analyzed by summarizing adverse events corresponding to the following MedDRA preferred terms: "acute respiratory distress syndrome," "acute respiratory failure," "interstitial lung disease," "lung infiltration," and "pneumonitis."

The following table lists patients with interstitial lung diseases in Study ONO-4538-02:

**Patients in whom interstitial lung disease was observed (Study ONO-4538-02)**

| Age | Sex | PS | Preferred term (MedDRA/J ver.16.0) | Grade | Onset (days) | Dosing count | Duration (days) | Therapy details | Seriousness | Causal relationship | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 69 | Female | 1 | Interstitial lung disease | 2 | 80 | 4 | 148 | Prednisolone<br>Antibiotic<br>Oxygen inhalation | Serious | Yes | Resolved/ Recovered |
| 72 | Male | 0 | Lung infiltration | 1 | 125 | 6 | 166 | Follow-up | Not serious | No | Resolved/ Recovered |

PS, ECOG performance status

In Study ONO-4538-02, interstitial lung disease led to the discontinuation of nivolumab in 1 of 35 patients (2.9%; interstitial lung disease).

No cases of interstitial lung diseases were observed in Studies ONO-4538-01 and CA209001. In Study CA209003, interstitial lung disease occurred in 21 of 306 patients (6.9%; pneumonitis [n = 12], lung infiltration [n = 5], acute respiratory failure [n = 3], interstitial lung disease, ARDS [n = 1 each]; more than 1 event/patient were reported.

PMDA asked the applicant to explain countermeasures for interstitial lung disease associated with the administration of nivolumab.

The applicant responded as follows:
In Study ONO-4538-02, when an interstitial lung disease was suspected in a patient, an early diagnosis was made based on the consultation with a respiratory specialist. When a patient had a diagnosis of

≥Grade 2 interstitial lung disease, the administration of nivolumab was discontinued and a corticosteroid was introduced. If there was no improvement in the symptoms, the addition of an immunosuppressant was also considered.

Interstitial lung diseases observed in Study ONO-4538-02 were all mild and resolved after an appropriate action was taken. Nevertheless, interstitial lung diseases are potentially fatal. In Study CA209003, some patients died of adverse events occurring after contracting nivolumab-induced pneumonitis [see the following table]. Thus, the "Careful Administration" section of the package insert should specify the need of special attention to a history of and complications involving interstitial lung diseases. The "Important Precaution" section should recommend the careful monitoring of clinical symptoms associated with interstitial lung diseases following the administration of nivolumab and conduct appropriate tests as needed. To ensure that an appropriate action is taken, including cooperation with a respiratory specialist and the use of corticosteroid, healthcare professionals must be duly informed of the "Algorithm for treating lung-related adverse events" used in the clinical studies.

**Patients who died of adverse events occurring after pneumonitis (Study CA209003)**

| Age | Sex | Primary disease | Dose (mg/kg) | Preferred term (MedDRA ver.15.1) | Grade | Onset (days) | Causal relationship | Therapy (days) | Therapy details | Death* (days) |
|---|---|---|---|---|---|---|---|---|---|---|
| 62 | Male | NSCLC | 1 | Pneumonitis | 4 | 22 | Yes | 22 | Antibiotic | |
| | | | | | | | | 23 | Endotracheal intubation | |
| | | | | | | | | 23 | Methylprednisolone | |
| | | | | | | | | 26 | Infliximab | |
| | | | | | | | | 26 | Methylprednisolone, etc. | |
| | | | | Sepsis | 5 | 29 | Yes | | | 30 |
| 59 | Male | CRC | 10 | Pneumonitis | 3 | 91 | Yes | 92 | Antibiotic | |
| | | | | | | | | 92 | Oxygen therapy | |
| | | | | | | | | 99 | Methylprednisolone | |
| | | | | ARDS | 4 | 103 | Yes | 109 | Infliximab, etc. | |
| | | | | Sepsis | 5 | 124 | Yes | | | 126 |
| 40 | Female | NSCLC | 1 | Myalgia | 3 | 28 | Yes | | | |
| | | | | Pneumonitis | 4 | 29 | Yes | 29 | Methylprednisolone | |
| | | | | | | | | 29 | Prednisolone | |
| | | | | Pneumonitis | 4 | 86 | Yes | 86 | Oxygen therapy | |
| | | | | | | | | | Methylprednisolone | |
| | | | | | | | | 89 | Infliximab | |
| | | | | Respiratory failure | 5 | 118 | Yes | | | 120 |

* Day 1 was the date on which administration commenced; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; ARDS, acute respiratory distress syndrome

PMDA's considerations are as follows:
The safety of nivolumab has only been investigated in a limited number of patients. The result has shown the following: (a) In some patients, the administration of nivolumab was discontinued because of interstitial lung diseases; (b) some patients in an overseas clinical study died after contracting pneumonitis. Thus, the package insert must mention the past cases of interstitial lung diseases. Healthcare professionals should carefully select eligible patients and continue monitoring for the onset of interstitial lung diseases during treatment. Furthermore, awareness of interstitial lung diseases should be promoted through informative materials so that appropriate actions are taken in the event of a clinical symptom indicating an interstitial lung disease.

**4.(iii).B.(3).5) Infusion reactions**

The applicant explained about the infusion reactions associated with the administration of nivolumab as follows:
Infusion reactions were analyzed by summarizing adverse events corresponding to the following MedDRA preferred terms: "anaphylactic reaction," "hypersensitivity," and "infusion related reaction."

No infusion reactions associated with the administration of nivolumab were observed in Studies ONO-4538-02, ONO-4538-01, and CA209001.

In Study CA209003, infusion reactions occurred in 18 of 306 patients (5.9%; infusion related reaction [n = 14], hypersensitivity [n = 5]; more than 1 event/patient were reported). Serious infusion reactions occurred in 2 of 306 patients (0.7%; hypersensitivity [n = 2]), for which a causal relationship to nivolumab could not be ruled out.

Symptoms related to infusion reaction were as follows: coughing in 9 patients, headache in 6 patients, dyspnoea in 6 patients, pruritus in 5 patients, rash in 5 patients, nausea in 4 patients, chills in 4 patients, dizziness in 4 patients, vomiting in 3 patients, fever in 3 patients, pneumonia in 2 patients, hypoxia in 2 patients, hypotension in 2 patients, tachycardia in 1 patient, face oedema in 1 patient, and hypertension in 1 patient.

Infusion reactions occurred on the first day of dosing in 7 patients and following the second day of dosing in the other patients. The prophylactic use of acetaminophen or diphenhydramine was recommended prior to subsequent doses of nivolumab in patients experiencing infusion reactions, and the use of a corticosteroid was also encouraged as needed. Of 6 patients who received the prophylactic treatment, 3 patients experienced infusion reactions (infusion related reaction [n = 2], hypersensitivity [n = 1]). Infusion reactions also resulted in the discontinuation of nivolumab in 4 of 306 patients (1.3%; infusion related reaction, hypersensitivity [n = 2 each]).

These results suggest that the administration of nivolumab can cause infusion reactions such as fever, chills, pruritus, rash, hypertension, hypotension, and dyspnoea. Patient condition must be carefully monitored during and after the administration of nivolumab. When any infusion reaction develops, appropriate actions should be taken, and the use of prophylactic acetaminophen and diphenhydramine, and a corticosteroid as needed, is encouraged prior to subsequent doses of nivolumab.

PMDA's considerations are as follows:
In Study CA209003, infusion reactions due to nivolumab led to the discontinuation of treatment in some patients. There was no definite trend in the time of onset. Thus, close monitoring for potential infusion reactions is required during and after the administration of nivolumab. The need for the prophylactic medication in patients who experienced an infusion reaction is unclear at this time in light of the incidence of infusion reactions in patients who underwent the prophylactic medication in the clinical studies.

Based on the above, it is necessary to provide appropriate information to the medical community concerning the incidence of infusion reactions reported in the clinical studies and measures that should be taken for infusion reactions. Awareness of infusion reactions should also be promoted thorough informative materials so that appropriate actions are taken in the event of an infusion reaction.

**4.(iii).B.(3).6) Skin disorders**

The applicant explained about the skin disorders associated with the use of nivolumab as follows:
Skin disorders were analyzed by summarizing adverse events corresponding to the following MedDRA preferred terms: "blisters," "dermatitis," "dermatitis exfoliative," "drug eruption," "eczema," "erythema," "exfoliative rash," "palmar-plantar erythrodysaesthesia syndrome," "photosensitivity reaction," "pruritus," "allergic pruritus," "generalized pruritus," "psoriasis," "rash," "rash erythematous," "rash generalized," "rash macular," "rash maculo-papular," "rash papular," "rash pruritic," "skin exfoliation," "skin irritation," and "urticaria."

In Study ONO-4538-02, skin disorders occurred in 19 of 35 patients (54.3%; pruritus [n = 11], eczema [n = 4], rash, maculopapular rash [n = 2 each], urticaria, psoriasis [n = 1 each]; more than 1 event/patient was reported). A serious skin disorder occurred in 1 of 35 patients (2.9%; psoriasis [n = 1]), for which a causal relationship to nivolumab could not be ruled out. In this study, Grade 1 or 2 skin disorders were treated by symptomatic therapy (e.g., antihistamines, topical corticosteroids). If symptoms persisted or were exacerbated or if Grade 3 or 4 skin disorders occurred, the administration of nivolumab was interrupted and corticosteroids were administered. Skin disorders did not lead to drug discontinuation in any patients.

In Studies ONO-4538-01, CA209001, and CA209003, skin disorders occurred in 7 of 17 patients (41.2%), 16 of 39 patients (41.0%), and 123 of 306 patients (40.2%), respectively. Serious skin disorders occurred in 2 of 306 patients (0.7%) in the CA209003 study. Skin disorders leading to drug discontinuation did not occur in Study ONO-4538-01 or CA209001 but occurred in 1 of 306 patients (0.3%; due to rash [n = 1]) in the CA209003 study.

PMDA's considerations are as follows:
In Study ONO-4538-02, skin disorders were treated at onset according to the study protocol, so they were mild and did not lead to the discontinuation of nivolumab. Nivolumab can be tolerated if the same actions are taken. Therefore, considering that the safety of nivolumab has only been investigated in a very small number of patients, appropriate information should be provided to the medical community concerning the incidence of skin disorders, and awareness of skin disorders should be promoted through informative materials so that appropriate actions are taken in the event of a skin disorder.

**4.(iii).B.(3).7) Other**
**4.(iii).B.(3).7).(a) Excessive immunoreaction**
Based on the mechanism of action of nivolumab, some specific adverse events are expected to occur. The applicant defined those events as "autoimmune disease-related symptoms." Autoimmune disease symptoms were analyzed by summarizing not only the aforementioned hepatic function disorders, thyroid function abnormal, interstitial lung diseases, infusion reactions, and skin disorders but also adverse events categorized into gastrointestinal disorders (MedDRA Preferred Terms "colitis," "diarrhoea," "enteritis," "enterocolitis," "frequent bowel movements," "gastrointestinal perforation"), renal disorders (MedDRA Preferred Terms "blood creatinine increased," "creatinine renal clearance decreased," "hypercreatininaemia," "nephritis," "nephritis allergic," "renal failure," "acute renal failure," "renal tubular necrosis," "tubulointerstitial nephritis"), and endocrine disorders excluding thyroid function abnormal (MedDRA Preferred Terms "adrenal insufficiency," "adrenal suppression," "blood corticotrophin decreased," "blood corticotrophin increased," "diabetes mellitus," "hypophysitis," "latent autoimmune diabetes in adults," "secondary adrenocortical insufficiency").

In Study ONO-4538-02, autoimmune disease-related symptoms developed in 30 of 35 patients (85.7%). Autoimmune disease-related symptoms, excluding hepatic function disorders, thyroid function abnormal, interstitial lung diseases, infusion reactions, and skin disorders, were observed in 9 of 35 patients (25.7%; diarrhoea [n = 5], blood creatinine increased [n = 3], decreased corticotrophin, diabetes mellitus [n = 1 each]; more than 1 event/patient was reported). Serious autoimmune-related disease symptoms were observed in 5 of 35 patients (14.3%; hepatic disorder [n = 2], hypothyroidism, interstitial lung disease, psoriasis [n = 1 each]), for which a causal relationship to nivolumab could not be ruled out.

In Studies ONO-4538-01, CA209002, and CA209003, adverse drug reactions that were inferred to be associated with an excessive immunoreaction occurred in 13 of 17 patients (76.5%), 35 of 39 patients (89.7%), and 208 of 306 patients (68.0%), respectively.

The above-mentioned Japanese and foreign clinical studies confirmed the onset of autoimmune disease-related symptoms associated with nivolumab. The applicant intends to warn about the use of nivolumab in patients with an autoimmune disease or those with a history of a chronic or recurrent autoimmune disease in the "Careful Administration" section of the package insert.

PMDA's considerations are as follows:
It is unclear whether all events categorized as autoimmune disease-related symptoms by the applicant were attributable to excessive immunoreactions associated with nivolumab. However, due to the following reasons, an awareness of autoimmune disease-related symptoms should be raised through informative materials so that eligible patients can be chosen carefully; symptoms associated with excessive immunoreactions can be continuously monitored during the treatment with nivolumab; and appropriate actions can be taken in the event of a symptom suggestive of autoimmune diseases:
- The known pharmacological action of nivolumab suggests the possibility of post-dose adverse events caused by excessive immunoreaction.

- Adverse events thought to be attributable to excessive immunoreaction, such as autoimmune thyroiditis, have been documented.
- Japanese and foreign clinical studies of nivolumab excluded patients with autoimmune disease or those with a history of autoimmune disease. Thus, nivolumab has not been administered to patients with autoimmune diseases.

**4.(iii).B.(3).7).(b) Safety in anti-nivolumab antibody-positive patients**

The applicant stated the following with regard to the safety of nivolumab in anti-nivolumab antibody-positive patients:

In Studies ONO-4538-01, CA209001, and CA209003, anti-nivolumab antibodies were detected at least at 1 sampling point in 2 of 17 patients (11.8%), 4 of 39 patients (10.3%), and 21 of 306 patients (6.9%), respectively. No anti-nivolumab antibodies were detected in any patients in Study ONO-4538-02.

In these clinical studies, the number of patients with anti-nivolumab antibodies was small, but no marked differences were observed in the safety profile between the patients with anti-nivolumab antibodies and those without anti-nivolumab antibodies. This indicates that anti-nivolumab antibodies do not impact the safety of nivolumab.

PMDA's considerations are as follows:

Few patients with anti-nivolumab antibodies have been found in the clinical studies of nivolumab. At this point in time, the effect of anti-nivolumab antibodies on the safety of nivolumab remains unclear. Thus, the collection of safety information from the ongoing study and other sources must be continued, and new relevant information must be provided to the medical community when available [see "4.(iii).B.(4).1) Clinical positioning and intended population"].

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

The proposed indication for nivolumab was "malignant melanoma." The "Precautions for Indications" section states that the efficacy and safety of nivolumab have not been established in chemotherapy-naïve patients.

After reviewing the issues described in "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety" and the following points, PMDA concluded that the indication for nivolumab should be "unresectable malignant melanoma." The "Clinical Studies" section of the package insert should include the details of the patients enrolled in Study ONO-4538-02 (e.g., a history of dacarbazine chemotherapy). The "Precautions for Indications" section should include the following statements in addition to the applicant's statements above:

- The efficacy and safety of nivolumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of nivolumab in postoperative adjuvant chemotherapy have not been established.
- Eligible patients should be selected based on a careful review of the contents of the Clinical Studies section, a thorough understanding of the efficacy and safety of nivolumab, and a thorough evaluation of the use of therapies other than nivolumab.

**4.(iii).B.(4).1) Clinical positioning and intended population**

PMDA confirmed that the following Japanese and foreign clinical practice guidelines and oncology publications do not mention nivolumab:

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Melanoma (hereinafter referred to as "the NCCN Guidelines") (v.3 2014)
- *Cutaneous Malignant Tumor Treatment Guidelines*, Version 1. Edited by the Japanese Skin Cancer Society (Kanehara & Co. Ltd., 2007) (hereinafter referred to as "the Japanese Clinical Practice Guidelines")
- DeVita, Hellman, and Rosenberg's Cancer: *Principles & Practice of Oncology*, 9th edition (Lippincott Williams & Wilkins 2011, PA, USA)
- *New Clinical Oncology for Cancer Medication Specialists*, 3rd Edition. Edited by the Japanese Society of Medical Oncology (Nankodo, 2012)

Based on the intended population and clinical positioning of nivolumab in patients with unresectable advanced or recurrent malignant melanoma and a history of chemotherapy with dacarbazine, the applicant specified the following indication for nivolumab:

The NCCN Guidelines (v.3.2014) recommend ipilimumab, vemurafenib, dabrafenib, and trametinib as antineoplastic agents for unresectable advanced or recurrent malignant melanoma. In Japan, none of these drugs have been approved. The Japanese Clinical Practice Guidelines state that there is no beneficial chemotherapy for unresectable advanced or recurrent malignant melanoma.

The result of Study ONO-4538-02 confirmed some degree of clinical usefulness of nivolumab in patients with unresectable advanced or recurrent malignant melanoma who have a history of chemotherapy with dacarbazine [see "4.(iii).B.(2) Efficacy," and "4.(iii).B.(3) Safety"].

No confirmatory clinical evidence has been obtained for nivolumab. However, given the current situation where therapeutic options are very limited for unresectable advanced or recurrent malignant melanoma, and based on the results of the currently available clinical studies, nivolumab may be a therapeutic option for the said disease.

Because of this situation, the applicant proposes that the indication for nivolumab be "malignant melanoma" and a warning that the efficacy and safety of nivolumab in chemotherapy-naïve patients have not been established be added in the "Precautions for Indications" section of the package insert.

A foreign phase III study (CA209066) is underway to compare the efficacy and safety of nivolumab with those of dacarbazine in chemotherapy-naïve patients with advanced or recurrent malignant melanoma, which uses a dosage (3 mg/kg every 2 weeks) that differs from the proposed dosage (2 mg/kg every 3 weeks). A Japanese phase II clinical study (ONO-4538-08) is being planned to investigate the efficacy and safety of the dosage used in Study CA209066 (3 mg/kg every 2 weeks) in Japanese chemotherapy-naïve patients with malignant melanoma.

PMDA's considerations are as follows:
The applicant's explanations were generally acceptable. However, given that the patients enrolled in Study ONO-4538-02 had unresectable malignant melanoma with a history of dacarbazine chemotherapy, PMDA concluded that the "Clinical Studies" section of the package insert should include details of patients enrolled in Study ONO-4538-02 (e.g., a history of dacarbazine chemotherapy), the "Precautions for Indications" section should note the following, and the indication for nivolumab should be "unresectable malignant melanoma."

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

Because the results of the ongoing Study CA209066 (a confirmatory study of nivolumab) are unavailable at this time, the use of an alternative therapy other than nivolumab should also be carefully considered, and this should be explained in the "Precautions for Indications" section.

**4.(iii).B.(4).2) Efficacy and safety in postoperative adjuvant chemotherapy**

Patients with resectable malignant melanoma have not been treated with drug therapy. No clinical studies have been conducted to investigate the efficacy and safety of nivolumab with neoadjuvant and adjuvant chemotherapy. Thus, the applicant concludes that the use of nivolumab as neoadjuvant and adjuvant chemotherapy is not currently recommended. This will be mentioned in the "Precautions for Dosage and Administration" section of the package insert.

PMDA's considerations are as follows:
The applicant's explanations were generally acceptable. However, since no neoadjuvant chemotherapy has been established for malignant melanoma, special precautionary statements for neoadjuvant chemotherapy are not necessary. Precautionary statements for adjuvant chemotherapy should rather be added in the "Precautions for Indications" section.

**4.(iii).B.(5) Dosage and administration**

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

Based on the following review, PMDA concluded that the dosage and administration of nivolumab should be set as proposed. Based on the methods for preparing nivolumab in Study ONO-4538-02 and other clinical studies, PMDA concluded that the "Precautions for Dosage and Administration" section should specify the following:

- The preparation method for the injection solution and the duration of infusion
  - 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.
  - 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.

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

The applicant explains the dosage and administration of nivolumab as follows:

Based on the results of the following studies, the dosage and administration of nivolumab in Study ONO-4538-02 was set to "intravenously infuse nivolumab in a single dose of 2 mg/kg body weight every 3 weeks." The study demonstrated some degree of clinical usefulness. Thus, the dosage and administration of nivolumab was proposed based on Study ONO-4538-02.

- Nivolumab is a human monoclonal antibody against PD-1 and thus for which PD-1 binding is important. Serum nivolumab concentration is one of the alternative indicators representing PD-1 binding.
- In Study CA209003, PD-1 binding in CD3+ cells was seen in all patients receiving ≥0.3 mg/kg of nivolumab.
- In Study ONO-4538-01, patients responded to the treatment with ≥1 mg/kg of nivolumab every 2 weeks, and nivolumab was tolerated.
- A simulation based on the PK data obtained from Study ONO-4538-01 suggested that 2 mg/kg of nivolumab administered every 3 weeks can maintain serum nivolumab concentrations comparable with 1 mg/kg of nivolumab administered every 2 weeks.

PMDA's considerations are as follows:

The efficacy and safety of nivolumab administered according to the dosage regimen other than the proposed one are unknown; it is therefore uncertain whether the proposed dosage and administration is optimal. However, Study ONO-4538-02 showed some degree of clinical usefulness of nivolumab in patients with malignant melanoma. PMDA concluded that the dosage and administration of nivolumab can be set as proposed.

In Studies CA209066 and ONO-4538-08 of malignant melanoma in chemotherapy-naïve patients, the dosage and administration of nivolumab was set to 3 mg/kg every 2 weeks. Investigation of the dosage and administration of nivolumab will continue.

**4.(iii).B.(5).2) Infusion time**

The durations of infusion of nivolumab are defined in the protocols as "administer nivolumab as an intravenous infusion over at least 1 hour" for Study ONO-4538-01 and "administer nivolumab as an intravenous infusion over about 1 hour" for Study ONO-4538-02. However, the "Precautions for Dosage and Administration" section at the time of application states: "administer nivolumab as an intravenous infusion over 30 minutes." The applicant considered the following points and explained that the infusion time for nivolumab:

- Shorter infusion time can reduce patient burden.
- Japanese and foreign phase I studies (ONO-4538-01 and CA209003 studies) confirmed tolerance at doses up to 10 mg/kg. The infusion rate for the proposed dosage and administration was lower than those in the studies.

PMDA's considerations are as follows:
Based on the following reasons, PMDA concluded that the infusion time for nivolumab at this point in time should be set to "administer nivolumab as an intravenous infusion over at least 1 hour":
- Very few patients were enrolled in Study ONO-4538-01.
- The dose interval of nivolumab in Study ONO-4538-01 differed from the proposed dosage and administration.
- Study ONO-4538-01, in which nivolumab was administered intravenous infusion over at least 1 hour, demonstrated some degree of clinical usefulness of nivolumab.

**4.(iii).B.(5).3) Concurrent administration with other antineoplastic drugs**
There is no efficacy and safety data on nivolumab co-administered with other antineoplastic drugs. The applicant intends to include this information in the "Precautions for Dosage and Administration" section.

PMDA accepted the applicant's explanation.

**4.(iii).B.(6) Post-marketing investigations**
According to the applicant, post-marketing surveillance is planned as follows:
To investigate the safety of nivolumab in routine clinical use, post-marketing surveillance covering all patients with malignant melanoma receiving nivolumab (hereinafter referred to as "the survey") is being planned.

The survey focuses on interstitial lung disease, hepatic function disorder, and abnormal thyroid function as priority items, which were adverse events observed in Studies ONO-4538-02 and CA209003.

The target number of patients is 300. This sample size was determined in order to achieve a 95% probability of detecting 1 patient experiencing an adverse drug reaction with an incidence of interstitial lung disease in Study ONO-4538-02 was 2.9% (1 of 35 patients), which was the lowest value among the priority items.

The follow-up period is planned to be 6 months because the priority items mostly occurred within 6 months after the start of dosing.

PMDA's considerations are as follows:
The safety of nivolumab has been examined in a very small number of patients with malignant melanoma. Considering surveillance feasibility based on the estimated number of target patients of nivolumab, the survey should cover all patients treated with nivolumab during a set period of time to collect safety information in a swift and unbiased manner, and to promptly provide relevant data to the medical community. The need for additional patients for the analysis and further surveys or studies should be discussed based on the survey result.

The priority items proposed by the applicant should include infusion reaction—an adverse event that requires monitoring during the administration of nivolumab.

Since serious interstitial lung diseases with a reasonable suspected causal relationship to nivolumab occurred after 6 months in Study CA209003, the follow-up period should be longer than 6 months.

**4.(iv) Adverse events observed in clinical studies**
Of the clinical study results submitted for safety evaluation, deaths are described in "4.(iii) Summary of clinical efficacy and safety." The following other major adverse events were also observed:

**4.(iv).(1) Japanese phase I study (ONO-4538-01)**
Adverse events were observed in all patients (100%). Adverse events with a reasonable suspected causal relationship to nivolumab were also observed in all patients (100%). The following table summarizes adverse events observed in at least 2 patients in any group:

**Adverse events seen in ≥2 patients in any group**

| System organ class<br>Preferred term<br>(MedDRA/J ver.16.0) | n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 mg/kg group<br>n = 3 | | 3 mg/kg group<br>n = 5 | | 10 mg/kg group<br>n = 6 | | 20 mg/kg group<br>n = 3 | |
| | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 |
| All adverse events | 3 (100) | 1 (33.3) | 5 (100) | 2 (40.0) | 6 (100) | 2 (33.3) | 3 (100) | 2 (66.7) |
| Cardiac disorders | | | | | | | | |
| Ventricular extrasystoles | 0 | 0 | 1 (20.0) | 0 | 2 (33.3) | 0 | 1 (33.3) | 0 |
| Gastrointestinal disorders | | | | | | | | |
| Constipation | 1 (33.3) | 0 | 2 (40.0) | 0 | 2 (33.3) | 0 | 1 (33.3) | 0 |
| Diarrhoea | 1 (33.3) | 0 | 3 (60.0) | 0 | 2 (33.3) | 0 | 0 | 0 |
| Nausea | 0 | 0 | 1 (20.0) | 0 | 1 (16.7) | 0 | 2 (66.7) | 0 |
| Vomiting | 0 | 0 | 2 (40.0) | 0 | 1 (16.7) | 0 | 1 (33.3) | 0 |
| General disorders and administration site conditions | | | | | | | | |
| Fatigue | 0 | 0 | 1 (20.0) | 0 | 2 (33.3) | 0 | 1 (33.3) | 0 |
| Malaise | 0 | 0 | 0 | 0 | 2 (33.3) | 0 | 1 (33.3) | 0 |
| Pain | 0 | 0 | 2 (40.0) | 0 | 0 | 0 | 0 | 0 |
| Fever | 1 (33.3) | 0 | 1 (20.0) | 0 | 2 (33.3) | 0 | 2 (66.7) | 0 |
| Investigations | | | | | | | | |
| ALT increased | 1 (33.3) | 0 | 0 | 0 | 2 (33.3) | 1 (16.7) | 1 (33.3) | 0 |
| AST increased | 0 | 0 | 1 (20.0) | 0 | 2 (33.3) | 1 (16.7) | 1 (33.3) | 0 |
| Blood albumin decreased | 1 (33.3) | 0 | 3 (60.0) | 1 (20.0) | 2 (33.3) | 0 | 2 (66.7) | 0 |
| Blood CK increased | 2 (66.7) | 0 | 0 | 0 | 2 (33.3) | 0 | 0 | 0 |
| Blood creatinine increased | 0 | 0 | 0 | 0 | 2 (33.3) | 0 | 1 (33.3) | 0 |
| Blood LDH increased | 1 (33.3) | 0 | 0 | 0 | 3 (50.0) | 0 | 1 (33.3) | 0 |
| Blood uric acid increased | 0 | 0 | 1 (20.0) | 0 | 3 (50.0) | 0 | 1 (33.3) | 0 |
| CRP increased | 1 (33.3) | 0 | 2 (40.0) | 0 | 2 (33.3) | 0 | 2 (66.7) | 0 |
| Eosinophil count increased | 2 (66.7) | 0 | 3 (60.0) | 0 | 2 (33.3) | 0 | 1 (33.3) | 0 |
| Haematocrit decreased | 1 (33.3) | 0 | 3 (60.0) | 1 (20.0) | 2 (33.3) | 0 | 0 | 0 |
| Haemoglobin decreased | 1 (33.3) | 0 | 3 (60.0) | 1 (20.0) | 2 (33.3) | 0 | 0 | 0 |
| Lymphocyte count decreased | 1 (33.3) | 0 | 2 (40.0) | 1 (20.0) | 5 (83.3) | 0 | 2 (66.7) | 1 (33.3) |
| Neutrophil count decreased | 0 | 0 | 2 (40.0) | 0 | 0 | 0 | 0 | 0 |
| Protein total decreased | 1 (33.3) | 0 | 3 (60.0) | 0 | 0 | 0 | 1 (33.3) | 0 |
| Red blood cell count decreased | 1 (33.3) | 0 | 3 (60.0) | 1 (20.0) | 0 | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | | | | | | |
| Decreased appetite | 1 (33.3) | 0 | 0 | 0 | 3 (50.0) | 0 | 2 (66.7) | 0 |
| Musculoskeletal and connective tissue disorders | | | | | | | | |
| Arthralgia | 0 | 0 | 2 (40.0) | 0 | 0 | 0 | 0 | 0 |
| Nervous system disorders | | | | | | | | |
| Dizziness | 0 | 0 | 1 (20.0) | 0 | 0 | 0 | 2 (66.7) | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | | | |
| Upper respiratory tract inflammation | 0 | 0 | 0 | 0 | 0 | 0 | 2 (66.7) | 0 |
| Skin and subcutaneous tissue disorders | | | | | | | | |
| Erythema | 1 (33.3) | 0 | 2 (40.0) | 0 | 1 (16.7) | 0 | 0 | 0 |
| Pruritus | 0 | 0 | 1 (20.0) | 0 | 2 (33.3) | 0 | 0 | 0 |
| Rash | 1 (33.3) | 0 | 2 (40.0) | 0 | 2 (33.3) | 0 | 0 | 0 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine phosphokinase; LDH, lactic dehydrogenase; CRP, C-reactive protein

Serious adverse events were observed in 1 of 3 patients (33.3%) in the 1 mg/kg group, 1 of 5 patients (20.0%) in the 3 mg/kg group, and 2 of 6 patients (33.3%) in the 10 mg/kg group. Pain in extremity (33.3%, n = 1) in the 1 mg/kg group; malignant neoplasm progression (20.0%, n = 1) in the 3 mg/kg group; and dehydration, ALT increased, AST increased, and blood bilirubin increased (16.7%, n = 1 each) in the 10 mg/kg group were observed. A causal relationship to nivolumab could not be ruled out for dehydration that was observed in the 10 mg/kg group.

The following adverse events leading to drug discontinuation occurred in 1 of 6 patients (16.7%) in the 10 mg/kg group,: bile duct stenosis, ALT increased, AST increased, bilirubin conjugated increased, blood LDH increased, and blood alkaline phosphatase increased (5.9%, n = 1 each). A causal relationship to nivolumab was ruled out for all the events.

### 4.(iv).(2) Japanese phase II study (ONO-4538-02)

Adverse events were observed in all patients (100%). Adverse events with a reasonable suspected causal relationship to nivolumab were observed in 30 of 35 patients (85.7%). The following table summarizes the adverse events with an incidence of ≥10%.

**Adverse events with an incidence of ≥10%**

| System organ class<br>Preferred term<br>(MedDRA/J ver.16.0) | n (%)<br>n = 35 | |
|---|---|---|
| | All grades | ≥ Grade 3 |
| All adverse events | 35 (100) | 19 (54.3) |
| Endocrine disorders | | |
| Hypothyroidism | 5 (14.3) | 0 |
| Gastrointestinal disorders | | |
| Constipation | 8 (22.9) | 0 |
| Diarrhoea | 5 (14.3) | 1 (2.9) |
| Nausea | 9 (25.7) | 2 (5.7) |
| Vomiting | 4 (11.4) | 1 (2.9) |
| General disorders and administration site conditions | | |
| Fatigue | 7 (20.0) | 1 (2.9) |
| Malaise | 10 (28.6) | 1 (2.9) |
| Oedema | 4 (11.4) | 1 (2.9) |
| Fever | 7 (20.0) | 0 |
| Infections and infestations | | |
| Nasopharyngitis | 4 (11.4) | 0 |
| Investigations | | |
| ALT increased | 8 (22.9) | 1 (2.9) |
| AST increased | 10 (28.6) | 2 (5.7) |
| Blood albumin decreased | 8 (22.9) | 2 (5.7) |
| Blood CK increased | 6 (17.1) | 3 (8.6) |
| Blood glucose increased | 4 (11.4) | 0 |
| Blood LDH increased | 12 (34.3) | 1 (2.9) |
| Blood TSH decreased | 4 (11.4) | 0 |
| Blood TSH increased | 7 (20.0) | 0 |
| CRP increased | 13 (37.1) | 1 (2.9) |
| Eosinophil count increased | 4 (11.4) | 0 |
| γ-GTP increased | 9 (25.7) | 4 (11.4) |
| Haematocrit decreased | 7 (20.0) | 3 (8.6) |
| Haematuria | 5 (14.3) | 0 |
| Haemoglobin decreased | 8 (22.9) | 3 (8.6) |
| Lymphocyte count decreased | 7 (20.0) | 2 (5.7) |
| Oxygen saturation decreased | 4 (11.4) | 1 (2.9) |
| Protein total decreased | 7 (20.0) | 0 |
| Red blood cell count decreased | 7 (20.0) | 3 (8.6) |
| White blood cell count decreased | 6 (17.1) | 0 |
| White blood cell count increased | 4 (11.4) | 0 |
| $T_3$ free decreased | 9 (25.7) | 0 |
| $T_4$ free decreased | 7 (20.0) | 0 |
| Blood ALP increased | 6 (17.1) | 1 (2.9) |
| Anti-thyroid antibody positive | 4 (11.4) | 0 |
| Surfactant protein increased | 4 (11.4) | 0 |
| Blood CK decreased | 4 (11.4) | 0 |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 9 (25.7) | 4 (11.4) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | | |
| Tumour haemorrhage | 4 (11.4) | 1 (2.9) |
| Cancer pain | 5 (14.3) | 3 (8.6) |
| Nervous system disorders | | |
| Peripheral neuropathy | 5 (14.3) | 1 (2.9) |
| Psychiatric disorders | | |
| Insomnia | 5 (14.3) | 0 |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | 4 (11.4) | 0 |

| System organ class<br>Preferred term<br>(MedDRA/J ver.16.0) | n (%)<br>n = 35 | |
|---|---|---|
| | All grades | ≥ Grade 3 |
| Skin and subcutaneous tissue disorders | | |
| Eczema | 4 (11.4) | 0 |
| Leukoderma | 6 (17.1) | 0 |
| Pruritus | 11 (31.4) | 0 |
| Skin hypopigmentation | 4 (11.4) | 0 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine phosphokinase; LDH, lactic dehydrogenase; TSH, thyroid stimulating hormone; CRP, C-reactive protein; γ-GTP, γ-glutamyltransferase; $T_3$, triiodothyronine; $T_4$, thyroxine; ALP, alkaline phosphatase

The following serious adverse events were observed in 17 of 35 patients (48.6%): hepatic disorder, malignant melanoma (5.7%, n = 2 each), anaemia, hypothyroidism, optic nerve neuropathy, malaise, pain, urinary tract infection, pneumonia bacterial, pubis fracture, hypercalcaemia, metastatic pain, tumour haemorrhage, cancer pain, metastases to central nervous system, paralysis, interstitial lung disease, pleural effusion, and psoriasis (2.9%, n = 1 each). A causal relationship to nivolumab could not be ruled out for hepatic disorder (5.7%, n = 2), hypothyroidism, pneumonia bacterial, interstitial lung disease, and psoriasis (2.9%, n = 1 each).

The following adverse events leading to drug discontinuation occurred in 10 of 35 patients (28.6%): malignant melanoma (5.7%, n = 2), hypothyroidism, hepatic disorder, pneumonia bacterial, ALT increased, AST increased, blood CK increased, blood TSH increased, CRP increased, γ-GTP increased, $T_3$ free decreased, $T_4$ free decreased, cell marker increased, surfactant protein increased, hypercalcaemia, cancer pain, metastases to central nervous system, depressed level of consciousness, brain oedema, delirium, interstitial lung disease (2.9%, n = 1 each). A causal relationship to nivolumab could not be ruled out for hypothyroidism, hepatic disorder, pneumonia bacterial, ALT increased, AST increased, blood CK increased, blood TSH increased, CRP increased, γ-GTP increased, $T_3$ free decreased, $T_4$ free decreased, cell marker increased, surfactant protein increased, and interstitial lung disease (2.9%, n = 1 each).

### 4.(iv).(3) Foreign phase I study (CA209001)

Adverse events were observed in all patients (100%). Adverse events with a reasonable suspected causal relationship to nivolumab were observed in 5 of 6 patients (83.3%) in the 0.3 mg/kg group, 5 of 6 patients (83.3%) in the 1 mg/kg group, all 6 patients (100%) in the 3 mg/kg group, and 19 of 21 patients (90.5%) in the 10 mg/kg group. The following table summarizes the adverse events with an incidence of ≥40% in any of the 4 treatment groups:

**Adverse events with an incidence of ≥40% in any group**

| System organ class<br>Preferred term<br>(MedDRA ver.10.1) | n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.3 mg/kg group<br>n = 6 | | 1.0 mg/kg group<br>n = 6 | | 3 mg/kg group<br>n = 6 | | 10 mg/kg group<br>n = 21 | |
| | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 |
| All adverse events | 6 (100) | 5 (83.3) | 6 (100) | 5 (83.3) | 6 (100) | 4 (66.7) | 21 (100) | 18 (85.7) |
| Blood and lymphatic system disorders | | | | | | | | |
| Anaemia | 1 (16.7) | 1 (16.7) | 4 (66.7) | 0 | 4 (66.7) | 1 (16.7) | 11 (52.4) | 2 (9.5) |
| Lymphocyte count decreased | 4 (66.7) | 0 | 1 (16.7) | 0 | 3 (50.0) | 1 (16.7) | 9 (42.9) | 2 (9.5) |
| Gastrointestinal disorders | | | | | | | | |
| Constipation | 0 | 0 | 1 (16.7) | 0 | 3 (50.0) | 0 | 9 (42.9) | 0 |
| Diarrhoea | 0 | 0 | 3 (50.0) | 0 | 1 (16.7) | 0 | 4 (19.0) | 0 |
| Nausea | 0 | 0 | 3 (50.0) | 1 (16.7) | 4 (66.7) | 0 | 10 (47.6) | 0 |
| General disorders and administration site conditions | | | | | | | | |
| Fatigue | 2 (33.3) | 0 | 5 (83.3) | 1 (16.7) | 4 (66.7) | 0 | 11 (52.4) | 2 (9.5) |
| Investigations | | | | | | | | |
| AST increased | 3 (50.0) | 0 | 2 (33.3) | 0 | 0 | 0 | 6 (28.6) | 1 (4.8) |
| Blood albumin decreased | 0 | 0 | 3 (50.0) | 0 | 1 (16.7) | 0 | 4 (19.0) | 0 |
| Blood bicarbonate decreased | 1 (16.7) | 0 | 4 (66.7) | 0 | 3 (50.0) | 0 | 5 (23.8) | 0 |
| Blood urea increased | 1 (16.7) | 0 | 3 (50.0) | 0 | 0 | 0 | 3 (14.3) | 0 |
| CRP increased | 1 (16.7) | 0 | 4 (66.7) | 0 | 4 (66.7) | 0 | 8 (38.1) | 0 |
| Carbon dioxide decreased | 0 | 0 | 4 (66.7) | 0 | 4 (66.7) | 0 | 6 (28.6) | 0 |
| CD4 lymphocytes decreased | 1 (16.7) | 1 (16.7) | 2 (33.3) | 0 | 1 (16.7) | 0 | 14 (66.7) | 7 (33.3) |

| System organ class<br>Preferred term<br>(MedDRA ver.10.1) | n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.3 mg/kg group<br>n = 6 | | 1.0 mg/kg group<br>n = 6 | | 3 mg/kg group<br>n = 6 | | 10 mg/kg group<br>n = 21 | |
| | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 |
| Haemoglobin decreased | 2 (33.3) | 0 | 3 (50.0) | 0 | 1 (16.7) | 0 | 4 (19.0) | 0 |
| Lymphocyte count decreased | 0 | 0 | 3 (50.0) | 1 (16.7) | 0 | 0 | 5 (23.8) | 3 (14.3) |
| Weight decreased | 5 (83.3) | 0 | 2 (33.3) | 0 | 3 (50.0) | 0 | 8 (38.1) | 0 |
| Urinary sediment present | 1 (16.7) | 0 | 3 (50.0) | 0 | 1 (16.7) | 0 | 6 (28.6) | 0 |
| Blood phosphorus increased | 0 | 0 | 1 (16.7) | 0 | 3 (50.0) | 0 | 3 (14.3) | 0 |
| Blood ALP increased | 2 (33.3) | 0 | 2 (33.3) | 0 | 2 (33.3) | 0 | 12 (57.1) | 2 (9.5) |
| Metabolism and nutrition disorders | | | | | | | | |
| Anorexia | 2 (33.3) | 1 (16.7) | 3 (50.0) | 0 | 1 (16.7) | 0 | 3 (14.3) | 0 |
| Hyperglycaemia | 3 (50.0) | 0 | 3 (50.0) | 1 (16.7) | 2 (33.3) | 0 | 4 (19.0) | 1 (4.8) |
| Hypocalcaemia | 1 (16.7) | 0 | 4 (66.7) | 0 | 3 (50.0) | 0 | 8 (38.1) | 1 (4.8) |
| Hyponatraemia | 4 (66.7) | 0 | 3 (50.0) | 1 (16.7) | 2 (33.3) | 1 (16.7) | 5 (23.8) | 0 |
| Musculoskeletal and connective tissue disorders | | | | | | | | |
| Back pain | 0 | 0 | 1 (16.7) | 0 | 3 (50.0) | 1 (16.7) | 9 (42.9) | 1 (4.8) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | | | | | | | | |
| Malignant neoplasm progression | 0 | 0 | 3 (50.0) | 3 (50.0) | 1 (16.7) | 1 (16.7) | 2 (9.5) | 2 (9.5) |
| Nervous system disorders | | | | | | | | |
| Dizziness | 0 | 0 | 3 (50.0) | 1 (16.7) | 0 | 0 | 5 (23.8) | 0 |
| Renal and urinary disorders | | | | | | | | |
| Proteinuria | 2 (33.3) | 0 | 3 (50.0) | 0 | 2 (33.3) | 0 | 8 (38.1) | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | | | |
| Dyspnoea | 0 | 0 | 2 (33.3) | 2 (33.3) | 3 (50.0) | 1 (16.7) | 5 (23.8) | 2 (9.5) |

AST, aspartate aminotransferase; CRP, C-reactive protein; ALP, alkaline phosphatase

The following serious adverse events occurred in 3 of 6 patients (50.0%) in the 0.3 mg/kg group, 5 of 6 patients (83.3%) in the 1 mg/kg group, 4 of 6 patients (66.7%) in the 3 mg/kg group, and 11 of 21 patients (52.4%) in the 10 mg/kg group: abdominal pain upper, dehydration, malignant neoplasm progression, metastases to spine, and spinal cord compression (16.7%, n = 1 each) in the 0.3 mg/kg group; malignant neoplasm progression (66.7%, n = 4), anaemia, colitis, gastritis, gastrointestinal haemorrhage, pneumonia, dehydration, hyperglycaemia, anorexia, hypercalcaemia, flank pain, metastatic pain, dizziness, nephrolithiasis, renal failure, chronic obstructive pulmonary disease, pleural effusion, and respiratory failure (16.7%, n = 1 each) in the 1 mg/kg group; anaemia (33.3%, n = 2), small intestinal obstruction, back pain, arthritis, malignant neoplasm progression, ureteric obstruction, and pulmonary embolism (16.7%, n = 1 each) in the 3 mg/kg group; and malignant neoplasm progression (19.0%, n = 4), abdominal pain (14.3%, n = 3), ascites, ileus, intestinal obstruction, rectal haemorrhage, pain, acute hepatic failure, pneumonia, sepsis, fracture, ALT increased, hyperglycaemia, metastases to central nervous system, spinal cord compression, aphasia, brain oedema, central nervous system lesion, myoclonus, anxiety, confusional state, mood variable, bladder obstruction, pelvic pain, and dyspnoea (4.8%, n = 1 each) in the 10 mg/kg group. A causal relationship to nivolumab could not be ruled out for anaemia and colitis (n = 1 each) observed in the 1 mg/kg group.

The following adverse events leading to drug discontinuation occurred in 2 of 21 patients (9.5%) in the 10 mg/kg group: polymyalgia rheumatica, metastases to central nervous system, brain oedema, aphasia, myoclonus, and confusional state (4.8%, n = 1 each). A causal relationship to nivolumab could not be ruled out for polymyalgia rheumatica.

**4.(iv).(4) Foreign phase I study (CA209003)**

Adverse events were observed in all 17 patients (100%) in the 0.1 mg/kg group, 17 of 18 patients (94.4%) in the 0.3 mg/kg group, 85 of 86 patients (98.8%) in the 1 mg/kg group, 53 of 54 patients (98.1%) in the 3 mg/kg group, and all 131 patients (100%) in the 10 mg/kg group. Adverse events with a reasonable suspected causal relationship to nivolumab were observed in 13 of 17 patients (76.5%) in the 0.1 mg/kg group, 14 of 18 patients (77.8%) in the 0.3 mg/kg group, 70 of 86 patients (81.4%) in the 1 mg/kg group, 40 of 54 patients (74.1%) in the 3 mg/kg group, and 93 of 131 patients (71.0%) in the 10 mg/kg group.

The following table summarizes adverse events with an incidence of ≥20% in any of the 5 treatment groups:

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

| System organ class<br>Preferred term<br>(MedDRA ver.15.1) | n (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0.1 mg/kg group<br>n = 17 | | 0.3 mg/kg group<br>n = 18 | | 1 mg/kg group<br>n = 86 | | 3 mg/kg group<br>n = 54 | | 110 mg/kg group<br>n = 131 | |
| | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 | All grades | ≥ Grade 3 |
| All adverse events | 17 (100) | 14 (82.4) | 17 (94.4) | 8 (44.4) | 85 (98.8) | 42 (48.8) | 53 (98.1) | 31 (57.4) | 131 (100) | 87 (66.4) |
| Gastrointestinal disorders | | | | | | | | | | |
| Constipation | 7 (41.2) | 1 (5.9) | 3 (16.7) | 0 | 18 (20.9) | 0 | 15 (27.8) | 0 | 35 (26.7) | 1 (0.8) |
| Diarrhoea | 3 (17.6) | 0 | 3 (16.7) | 0 | 37 (43.0) | 0 | 23 (42.6) | 0 | 39 (29.8) | 3 (2.3) |
| Nausea | 3 (17.6) | 1 (5.9) | 4 (22.2) | 0 | 23 (26.7) | 2 (2.3) | 17 (31.5) | 1 (1.9) | 45 (34.4) | 5 (3.8) |
| Vomiting | 3 (17.6) | 1 (5.9) | 3 (16.7) | 0 | 15 (17.4) | 0 | 13 (24.1) | 2 (3.7) | 36 (27.5) | 4 (3.1) |
| General disorders and administration site conditions | | | | | | | | | | |
| Fatigue | 10 (58.8) | 2 (11.8) | 8 (44.4) | 0 | 42 (48.8) | 8 (9.3) | 32 (59.3) | 2 (3.7) | 76 (58.0) | 8 (6.1) |
| Peripheral oedema | 4 (23.5) | 1 (5.9) | 2 (11.1) | 0 | 19 (22.1) | 0 | 10 (18.5) | 0 | 24 (18.3) | 0 |
| Fever | 4 (23.5) | 0 | 6 (33.3) | 0 | 14 (16.3) | 0 | 7 (13.0) | 0 | 30 (22.9) | 1 (0.8) |
| Investigations | | | | | | | | | | |
| Weight decreased | 4 (23.5) | 0 | 1 (5.6) | 0 | 11 (12.8) | 1 (1.2) | 10 (18.5) | 0 | 22 (16.8) | 0 |
| Metabolism and nutrition disorders | | | | | | | | | | |
| Hyperglycaemia | 5 (29.4) | 1 (5.9) | 1 (5.6) | 0 | 18 (20.9) | 1 (1.2) | 4 (7.4) | 1 (1.9) | 10 (7.6) | 1 (0.8) |
| Decreased appetite | 7 (41.2) | 0 | 6 (33.3) | 0 | 31 (36.0) | 2 (2.3) | 17 (31.5) | 0 | 46 (35.1) | 1 (0.8) |
| Musculoskeletal and connective tissue disorders | | | | | | | | | | |
| Arthralgia | 6 (35.3) | 1 (5.9) | 5 (27.8) | 0 | 21 (24.4) | 1 (1.2) | 10 (18.5) | 0 | 21 (16.0) | 2 (1.5) |
| Back pain | 6 (35.3) | 0 | 1 (5.6) | 0 | 14 (16.3) | 0 | 13 (24.1) | 2 (3.7) | 34 (26.0) | 5 (3.8) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | | | | | | | | | | |
| Malignant neoplasm progression | 3 (17.6) | 3 (17.6) | 1 (5.6) | 1 (5.6) | 12 (14.0) | 12 (14.0) | 5 (9.3) | 5 (9.3) | 27 (20.6) | 27 (20.6) |
| Nervous system disorders | | | | | | | | | | |
| Dizziness | 3 (17.6) | 0 | 4 (22.2) | 0 | 15 (17.4) | 0 | 9 (16.7) | 1 (1.9) | 25 (19.1) | 0 |
| Headache | 4 (23.5) | 1 (5.9) | 5 (27.8) | 0 | 14 (16.3) | 0 | 12 (22.2) | 0 | 24 (18.3) | 0 |
| Psychiatric disorders | | | | | | | | | | |
| Insomnia | 2 (11.8) | 0 | 3 (16.7) | 0 | 10 (11.6) | 0 | 13 (24.1) | 1 (1.9) | 17 (13.0) | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | | | | | |
| Cough | 6 (35.3) | 0 | 3 (16.7) | 0 | 21 (24.4) | 2 (2.3) | 17 (31.5) | 1 (1.9) | 43 (32.8) | 1 (0.8) |
| Dyspnoea | 0 | 0 | 3 (16.7) | 1 (5.6) | 24 (27.9) | 7 (8.1) | 17 (31.5) | 2 (3.7) | 36 (27.5) | 17 (13.0) |
| Skin and subcutaneous tissue disorders | | | | | | | | | | |
| Pruritus | 2 (11.8) | 0 | 4 (22.2) | 0 | 21 (24.4) | 0 | 8 (14.8) | 0 | 21 (16.0) | 1 (0.8) |
| Rash | 3 (17.6) | 0 | 5 (27.8) | 0 | 27 (31.4) | 0 | 13 (24.1) | 0 | 26 (19.8) | 0 |

Serious adverse events occurred in 9 of 17 patients (52.9%) in the 0.1 mg/kg group, 8 of 18 patients (44.4%) in the 0.3 mg/kg group, 37 of 86 patients (43.0%) in the 1 mg/kg group, 26 of 54 patients (48.1%) in the 3 mg/kg group, and 79 of 131 patients (60.3%) in the 10 mg/kg group. The following serious adverse events occurred in at least 2 patients in each group: malignant neoplasm progression (17.6%, n = 3) in the 0.1 mg/kg group; dyspnoea (11.1%, n = 2) in the 0.3 mg/kg group; malignant neoplasm progression (14.0%, n = 12), dyspnoea (5.8%, n = 5), pulmonary embolism, fever (4.7%, n = 4 each), dehydration, acute renal failure (3.5%, n = 3 each), hypoxia, pneumonitis, pleural effusion, deep vein thrombosis, anaemia, hypercalcaemia, neuralgia, and respiratory failure (2.3%, n = 2 each) in the 1 mg/kg group; malignant neoplasm progression (9.3%, n = 5), pneumonia (7.4%, n = 4), fever (5.6%, n = 3), dyspnoea, fatigue, dehydration, and myocardial infarction (3.7%, n = 2 each) in the 3 mg/kg group; and malignant neoplasm progression (20.6%, n = 27), dyspnoea (14.5%, n = 19), vomiting (7.6%, n = 10), nausea (5.3%, n = 7), diarrhoea, fever, dehydration (4.6%, n = 6 each), pneumonia (3.8%, n = 5), hypoxia, pleural effusion, pneumonitis, acute renal failure (3.1%, n = 4 each), pain, convulsions, hypotension, atrial fibrillation, confusional state (2.3%, n = 3 each), metastases to central nervous system, haemoptysis, colitis, fatigue, deep vein thrombosis, anaemia, abdominal pain upper, ascites, chest discomfort, chest pain, jaundice cholestatic, hypersensitivity, sepsis, hip fracture, blood creatinine increased, hypercalcaemia, hyponatraemia, back pain, flank pain, musculoskeletal pain, spinal cord compression, mental status changes, and coughing (1.5%, n = 2 each) in the 10 mg/kg group. A causal relationship to nivolumab could not be ruled out for pneumonitis (n = 2), fever and hypoxia (n = 1 each) in the 1 mg/kg group; malignant neoplasm progression, pneumonia, and fever (n = 1 each) in the 3 mg/kg group; and diarrhoea, pneumonitis (n =

4 each), vomiting, nausea, colitis, hypersensitivity (n = 2 each), dyspnoea, fever, dehydration, pneumonia, hypotension, fatigue, sepsis, flank pain, and coughing (n = 1 each) in the 10 mg/kg group.

Adverse events leading to drug discontinuation occurred in 3 of 17 patients (17.6%) in the 0.1 mg/kg group, 12 of 86 patients (14.0%) in the 1 mg/kg group, 12 of 54 patients (22.2%) in the 3 mg/kg group, and 30 of 131 patients (22.9%) in the 10 mg/kg group. The following adverse reactions leading to drug discontinuation occurred in at least 2 patients in at least 1 of each treatment group: pneumonitis (4.7%, n = 4), myalgia, and malignant neoplasm progression (2.3%, n = 2) in the 1 mg/kg group; abdominal pain, colitis, jaundice cholestatic, metastases to central nervous system, pneumonitis, and hypersensitivity (1.5%, n = 2 each) in the 10 mg/kg group. A causal relationship to nivolumab could not be ruled out for pneumonitis (n = 4) and myalgia (n = 2) in the 1 mg/kg group, and colitis, hypersensitivity, and pneumonitis (n = 2 each) in the 10 mg/kg 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

Compliance assessment is currently underway. The result of the assessment and PMDA's conclusion are to be reported in the Review Report (2).

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

Compliance assessment is currently underway. The result of the assessment and PMDA's conclusion are to be reported in the Review Report (2).

## IV. Overall evaluations

Based on the submitted data, PMDA has concluded that the efficacy of nivolumab in the treatment of unresectable malignant melanoma has been demonstrated and that its safety is acceptable in view of its observed benefits. Nivolumab is a drug with a new active ingredient that is a human monoclonal antibody belonging to the immunoglobulin G4 subclass against CD279 (programmed cell death 1, PD-1), and binds to PD-1 to block the interaction between PD-1 and PD-1 ligands and thereby to promote the activation of cancer antigen-specific T cells and the enhancement of cytotoxicity activity against cancer cells, resulting in the inhibition of tumor growth. Nivolumab is a clinically significant therapeutic option in treating unresectable malignant melanoma. The indication, dosage and administration, and post-marketing information to be studied on nivolumab will be further discussed in the Expert Discussion.

The product may be approved if it is concluded that there are no particular problems based on comments from the Expert Discussion.

**Review Report (2)**

June 13, 2014

## 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] | December 24, 2013 |

## II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described 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

Based on the results of the review in "II.4.(iii).B.(2) Efficacy" in Review Report (1), PMDA concluded that Study ONO-4538-02 (the Japanese phase II study of Nivolumab [Genetical Recombination] [hereinafter referred to as "nivolumab"] in patients with unresectable stage III/IV [advanced] or recurrent malignant melanoma who have a history of chemotherapy with dacarbazine) demonstrates some degree of efficacy of nivolumab in the treatment of unresectable malignant melanoma based on the response rate assessed centrally (primary endpoint) of 22.9% (90% confidence interval [CI], 13.4%, 36.2%), which exceeded the predetermined threshold response rate of 12.5%.

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

- The efficacy of nivolumab should be evaluated also taking into consideration the results of Study CA209066 (an ongoing foreign phase III study of chemotherapy-naïve patients with advanced or recurrent malignant melanoma).
- Non-clinical pharmacology studies have not demonstrated the effects of nivolumab on malignant melanoma cell lines while clinical studies have demonstrated the efficacy of nivolumab in patients without CD274 (Programmed cell death ligand 1, PD-L1) expression. At this point in time, no clear proof of concept has been demonstrated for nivolumab. The applicant should continue collecting information about molecular profiles (including PD-1 and PD-L1 expression in tumors) and tumor-infiltrating lymphocytes in patients receiving nivolumab from published literature and other sources to obtain robust evidence of the efficacy of nivolumab.

PMDA's considerations are as follows:
The clinical usefulness of nivolumab in treating malignant melanoma should essentially be demonstrated through comparative clinical studies that evaluate overall survival as their primary endpoint. The ongoing Study CA209066 is therefore expected to yield important data. Once available, the data must be promptly provided to the medical community and the package insert should be revised based on the data as needed.

PMDA considers it necessary to continue to proactively gather information on the efficacy of nivolumab, including that in published literature, and to promptly provide the medical community with any new useful information as appropriate.

PMDA instructed the applicant to positively consider the above matters. The applicant agreed to do so.

**(2) Safety**

Based on the review in "II.4.(iii).B.(3) Safety" in the Review Report (1), PMDA concluded that the following adverse events should be closely monitored when administering nivolumab: hepatic function disorders, abnormal thyroid function, interstitial lung diseases, infusion reactions, and skin disorders.

At the same time, PMDA concluded that despite the need of the monitoring of these adverse events, nivolumab is tolerated as long as appropriate actions, including the monitoring and management of adverse events or drug interruption, are taken by physicians with sufficient knowledge and experience with cancer chemotherapy.

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

- The clinical details of patients who experienced particularly serious infusion reactions in clinical studies should preferably be provided to the medical community.

The following table summarizes the details of the 4 patients who experienced infusion reactions leading to drug discontinuation in the foreign phase I study (CA209003).

**Patients who experienced infusion reactions leading to drug discontinuation (Study CA209003)**

| Age | Sex | Underlying disease | Dose (mg/kg) | Preferred term (MedDRA/J ver.16.0) | Grade | Onset (days) | Dose count | Causal relation-ship | Serious-ness | Prophylactic administra-tion | Other symptoms | Therapy details |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 61 | Male | NSCLC | 1 | Infusion-related reaction | 2 | 1 | 1 | Yes | Not serious | No | - | Nivolumab interrupted<br>Diphenhydramine<br>Ranitidine hydrochloride |
| | | | | Infusion-related reaction | 2 | 15 | 2 | Yes | Not serious | No | Dry mouth<br>Nausea | Hydrocortisone<br>Granisetron hydrochloride |
| 68 | Male | NSCLC | 10 | Infusion-related reaction | 2 | 1 | 1 | Yes | Not serious | No | Feeling of tight chest<br>Cough<br>Facial flush<br>Hypotension<br>Dyspnoea<br>Wheezing | Guaifenesin |
| | | | | Infusion-related reaction | 1 | 15 | 2 | Yes | Not serious | Yes | Nasal congestion<br>Rhinorrhea<br>Feeling of tight chest | Albuterol<br>Naproxen |
| | | | | Infusion-related reaction | 2 | 29 | 3 | Yes | Not serious | Yes | Lacrimation<br>Facial flush<br>Fatigue<br>Sneezing | Nivolumab interrupted<br>Hydrocortisone |
| | | | | Infusion-related reaction | 2 | 79 | 6 | Yes | Not serious | Yes | - | - |
| 80 | Female | NSCLC | 10 | Hypersensitivity | 3 | 568 | 41 | Yes | Serious | No | Chill<br>Tongue swelling | Hydroxyzine hydrochloride<br>Hydrocortisone<br>Diphenhydramine<br>Meperidine |
| 53 | Male | CRC | 10 | Hypersensitivity | 3 | 1 | 1 | Yes | Serious | No | Shortness of breath<br>Cough<br>Facial flush<br>Headache | Physiological saline<br>Diphenhydramine<br>Hydrocortisone<br>Famotidine<br>Acetaminophen<br>Albuterol<br>Oxygen therapy |

NSCLC, non-small cell lung cancer; CRC, colorectal cancer; Hydrocortisone, hydrocortisone sodium succinate

PMDA's considerations are as follows:
Besides the incidence of infusion reactions and the measures for infusion reactions in clinical studies [see "II.4.(iii).B.(3).5) Infusion reaction" in Review Report (I)], the details of the above-mentioned 4 patients should also be provided to the medical community appropriately through informative materials to raise awareness.

**(3) Clinical positioning and indication**
Based on the review in "II.4.(iii).B.(4) Clinical positioning and indication" in the Review Report (1), PMDA concluded that nivolumab is one of the therapeutic options for unresectable malignant melanoma and that nivolumab should be indicated for the treatment of "unresectable malignant melanoma." Furthermore, PMDA concluded that the "Clinical Studies" section of the package insert should state the details of the patients enrolled in Study ONO-4538-02 (e.g., a history of dacarbazine chemotherapy) and that the "Precautions for Indications" section should include the following:
- The efficacy and safety of nivolumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of nivolumab in adjuvant chemotherapy have not been established.
- Eligible patients must be selected based on a careful review of the contents of the Clinical Studies section, a thorough understanding of the efficacy and safety of nivolumab, and a thorough evaluation of the use of therapies other than nivolumab.

At the Expert Discussion, the expert advisors made the following comments and supported the above conclusion by PMDA:
- Unresectable advanced or recurrent malignant melanoma, the target disease of Study ONO-4538-02, is an orphan disease, for which the number of effective therapies is very limited. Nivolumab is a clinically significant therapeutic option for unresectable advanced or recurrent malignant melanoma, for which some degree of efficacy has been confirmed [see "(1) Efficacy"].

PMDA instructed the applicant to modify the "Indication" section and the "Precautions for Indications" section as mentioned above. The applicant agreed to do so.

**(4) Dosage and administration**
Based on the review in "II.4.(iii).B.(5) Dosage and administration" in the Review Report (1), PMDA concluded that the dosage and administration should be set to "The usual adult dosage of Nivolumab (Ggenetical Rrecombination) is 2 mg/kg body weight administered as an intravenous infusion every 3 weeks" and that the "Precautions for Dosage and Administration" should include the following:

- The preparation method for the injection solution and the duration of infusion
  - 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.
  - 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" section and the "Precautions for Dosage and Administration" section as mentioned above. The applicant agreed to do so.

**(5) Risk management plan (draft)**
The applicant plans to conduct a 6-month, all-case, post-marketing surveillance with a target number of 300 patients with malignant melanoma receiving nivolumab (hereinafter referred to as "the survey") to investigate the safety of nivolumab in routine clinical use. Based on the incidences of adverse events observed in Studies ONO-4538-02 and CA209003, the priority items of the survey will be interstitial lung disease, hepatic function disorder, and abnormal thyroid function.

Based on the review in "II.4.(iii).B.(6) Post-marketing investigations" in the Review Report (1), and given that the safety information of nivolumab in Japanese patients is extremely limited at this point in time, PMDA concluded that the safety of nivolumab should be investigated through post-marketing surveillance covering all patients receiving nivolumab in a specific period of time to collect safety information in a swift and unbiased manner and to promptly provide relevant data to the medical community. Furthermore, need for additional subjects for the analysis and further surveys or studies should be discussed based on the survey result.

PMDA concluded that the priority items should include not only the events proposed by the applicant but also infusion reactions (an adverse event that requires monitoring during the administration of nivolumab). The follow-up period of the survey should be longer than 6 months because an interstitial lung disease occurred in Study CA209003 more than 6 months after the initiation of nivolumab, and a causal relationship between the event and nivolumab could not be ruled out.

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

- Given that the median progression-free survival in Study ONO-4538-02 was 169.0 days [90% CI, 72.0, 277.0 days], the duration of treatment with nivolumab is expected to last more than 6 months in about half of patients. The duration of the survey should be therefore longer than 6 months.

Based on the above discussions, PMDA instructed the applicant to review the survey protocol. The applicant responded as follows:

- The enrollment period of the survey is planned to be 30 months, by which time the results of ongoing studies such as Study CA209066 will be available. During the 30 months, around 850 patients with malignant melanoma are expected to be enrolled. The results of the survey should be used to assess the need for additional subjects for the analysis, and further surveys or studies.
- The priority items should include not only interstitial lung disease, hepatic function disorder, and abnormal thyroid function but also infusion reaction.
- The duration of the follow-up period should be set to 1 year.
- An interim analysis should be conducted once data from a certain number of enrolled patients have been accumulated. Any relevant safety information from the survey should be promptly provided to the medical community.

PMDA accepted the applicant's response regarding the survey protocol.

Based on the above discussions, PMDA concluded that the draft of the risk management plan should include safety and efficacy investigations, as shown in the following table, and that additional pharmacovigilance activities and risk minimization activities should be implemented:

**Safety and efficacy investigations in the risk management plan (draft)**

| Safety Specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Interstitial lung disease<br>• Hepatic function disorder<br>• Abnormal thyroid function<br>• Infusion reaction | • Excessive immunoreaction | None |
| Efficacy follow-up | | |
| • Efficacy of nivolumab in routine clinical use | | |

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

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Early post-marketing phase vigilance<br>• Use-results survey (all-case surveillance)<br>[See the following table for a protocol outline.] | • Provision of data from early post-marketing phase vigilance<br>• Preparation and provision of materials for healthcare professionals (guidelines for proper use). |

**Outline of use-results survey plan (draft)**

| | |
|---|---|
| Objective | Investigation on the safety of nivolumab in routine clinical use |
| Methodology | All-case surveillance |
| Target patient population | Patients with unresectable malignant melanoma |
| Duration | 1 year |
| Planned number of patients | Approximately 850 patients |
| Main items to be investigated | Priority items: interstitial lung disease, hepatic function disorder, abnormal thyroid function, infusion reaction<br>Other major items: patientcharacteristics, status of use of nivolumab, concomitant drugs and therapy, adverse events (including laboratory test changes), efficacy, etc. |

## 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

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

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

A GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.2-1, 5.3.5.2-1). 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 findings were noted at some study sites and the sponsor's site (these findings do not markedly impact the overall assessment of the studies) and were notified to the respective heads of the study sites and the sponsor (i.e., the applicant):

Findings that require corrective actions:
Study sites
- Some parts of the review on the revision of the written information were conducted as expedited review although they were not subject to expedited review according to the Standard Operation Procedures.

Sponsor
- Some unexpected serious adverse drug reactions were not promptly reported to the investigators and the heads of the study sites.

## IV. Overall Evaluation

As a result of the above review, PMDA has concluded that nivolumab (Opdivo) may be approved with the following conditions after modifying the indication and the dosage and administration as shown below; provided that appropriate cautions are included in the package insert and information concerning the proper use of nivolumab is provided appropriately after the market launch; and that compliance with the proper use of nivolumab is ensured under the supervision of physicians with sufficient knowledge of and experience with cancer chemotherapy at medical institutions with adequate facilities to respond to emergencies. Since nivolumab is designated as an orphan drug, the re-examination period is 10 years. The drug substance and the drug product are both classified as powerful drugs and biological products.

[Indication]
Treatment of unresectable malignant melanoma

[Dosage and Administration]
The usual adult dosage of Nivolumab (Ggenetical Recombination) is 2 mg/kg body weight administered as an intravenous infusion every 3 weeks.

[Conditions for Approval]
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 Opdivo until data from a certain number of patients are accumulated following commercial introduction, in order to understand the characteristics of patients treated with Opdivo and compile the safety and efficacy data of Opdivo in the early postmarketing period, thereby taking necessary measures to ensure the proper use of Opdivo.

[Warnings]
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 well 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, fatigue) and examined by chest X-rays. In the event of an abnormality, the administration of Opdivo should be discontinued and an appropriate action such as the introduction of corticosteroid therapy should be taken.

[Contraindications]
Patients with a history of hypersensitivity to the ingredients of Opdivo

[Precautions for Indications]
(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 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.

[Precautions for Dosage and Administration]
(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.
    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 Opdivo.
(3) The efficacy and safety of Opdivo in combination with other antineoplastic drugs have not been established.