Report on Deliberation Results

June 3, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Yervoy Injection 50 mg (for intravenous use)
[Non-proprietary name]	Ipilimumab (Genetical Recombination)
[Applicant]	Bristol-Meyers Squibb K.K.
[Date of application]	September 19, 2014

[Results of deliberation]

In the meeting held on May 28, 2015, 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 is 10 years. The drug substance and the drug product are both classified as powerful drugs and biological products.

[Conditions for approval]

1 The applicant is required to establish and appropriately implement a risk management plan.
2. An extremely small number of patients were involved in the Japanese clinical studies. The applicant is therefore required to conduct a use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients are available, to identify the characteristics of these patients and to promptly collect safety and efficacy data so that necessary measures are taken for the proper use of the product.

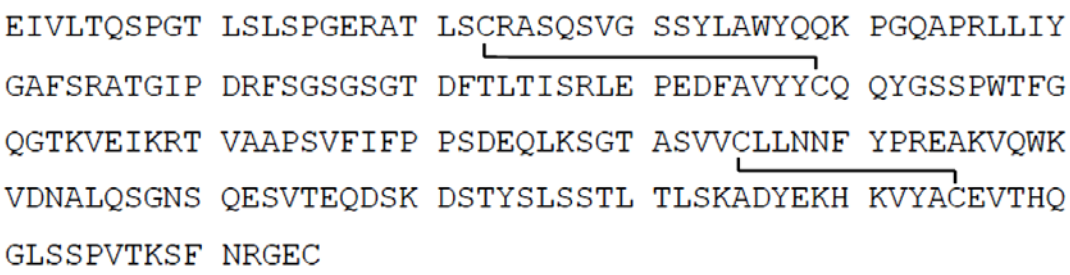
Review Report

May 19, 2015
Pharmaceuticals and Medical Devices Agency

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

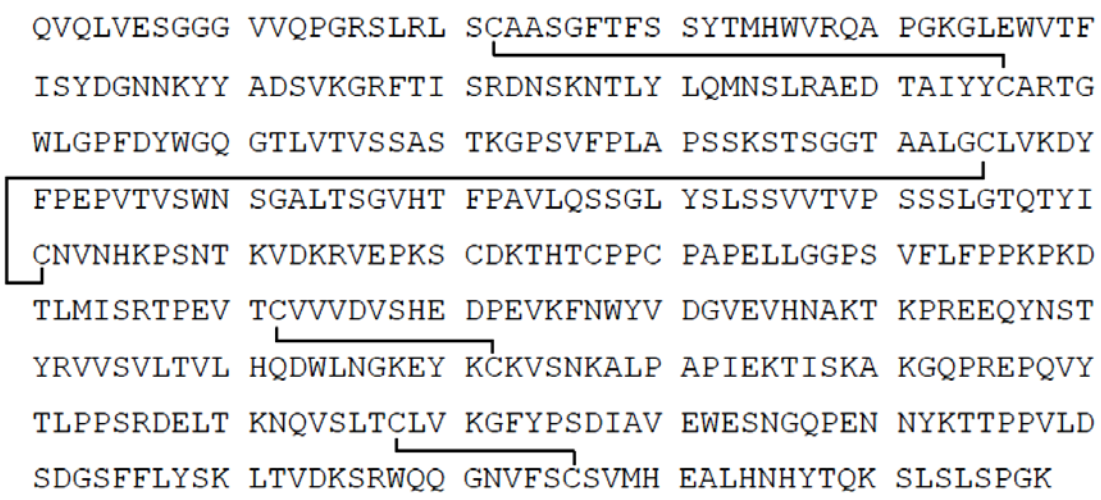
[Brand name]	Yervoy Injection 50 mg (for intravenous use)
[Non-proprietary name]	Ipilimumab (Genetical Recombination)
[Applicant]	Bristol-Meyers Squibb K.K.
[Date of application]	September 19, 2014
[Dosage form/Strength]	Injection: One 10 mL vial contains 50 mg of ipilimumab (genetical recombination).
[Application classification]	Prescription drug (1): Drug with a new active ingredient
[Definition]	Ipilimumab is a recombinant human IgG1 monoclonal antibody against human cytotoxic T-lymphocyte-associated antigen 4. Ipilimumab is produced in Chinese hamster ovary cells. Ipilimumab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 448 amino acid residues each and 2 L-chains (κ-chains) consisting of 215 amino acid residues each.

[Chemical structure]



L-chain

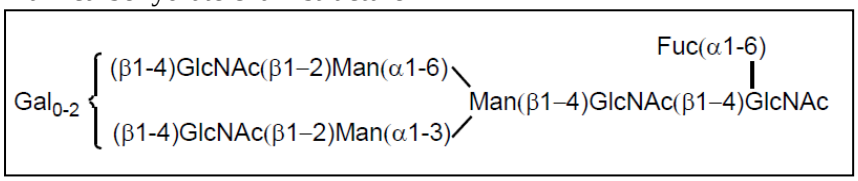
This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.



H-chain

Intramolecular disulfide bonds: solid line
Intermolecular disulfide bonds: L-chain C215-H-chain C221, H-chain C227-H-chain C227, H-chain C230-H-chain C230
Partial pyroglutamic acid: H-chain Q1
Partial processing: H-chain K448
Glycosylation: H-chain N298

Main carbohydrate chain structure



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

Molecular formula: $C_{6472}H_{9972}N_{1732}O_{2004}S_{40}$ (protein segment)
Molecular weight: approximately 148,000

[Items warranting special mention]

Orphan drug (Drug Designation No. 300 of 2013 [*25 yaku*], PFSB/ELD Notification No. 0315-2 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 15, 2013)

[Reviewing office] Office of New Drug V

Review Results

May 19, 2015

[Brand name]	Yervoy Injection 50 mg (for intravenous use)
[Non-proprietary name]	Ipilimumab (Genetical Recombination)
[Applicant]	Bristol-Meyers Squibb K.K.
[Date of application]	September 19, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that a certain level of efficacy of the product in the treatment of unresectable malignant melanoma has been demonstrated and its safety is acceptable in view of its observed benefits. The following events should be further studied through post-marketing surveillance, etc.: diarrhoea, colitis, and gastrointestinal perforation; skin disorders; hepatic disorders; hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency; peripheral neuropathy; renal disorders; interstitial lung disease; and infusion reactions.

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

[Indication] Unresectable malignant melanoma

[Dosage and administration] The usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 times.

[Conditions for approval]

1. The applicant is required to establish and appropriately implement a risk management plan.
2. An extremely small number of patients were involved in the Japanese clinical studies. The applicant is therefore required to conduct a use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients are available, to identify the characteristics of these patients and to promptly collect safety and efficacy data so that necessary measures are taken for the proper use of the product.

Review Report (1)

April 2, 2015

I. Product Submitted for Registration

[Brand name]	Yervoy Injection 50 mg (for intravenous use)
[Non-proprietary name]	Ipilimumab (Genetical Recombination)
[Applicant]	Bristol-Meyers Squibb K.K.
[Date of application]	September 19, 2014
[Dosage form/Strength]	Injection: One 10 mL vial contains 50 mg of ipilimumab (genetical recombination).
[Proposed indication]	Unresectable or metastatic malignant melanoma
[Proposed dosage and administration]	The usual adult dosage is 3 mg/kg of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 times.

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

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

(1) Outline of the proposed product

Ipilimumab (Genetical Recombination) (hereafter referred to as ipilimumab) is a human monoclonal antibody of immunoglobulin G1 (IgG1) subclass against CD152 (cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4]) discovered by Medarex (currently Bristol-Myers Squibb [BMS]) in the United States.

CTLA-4 is a costimulatory receptor expressed on T cells (i.e., a negative regulator of T-cell activity). Ipilimumab is expected to suppress tumor growth by inhibiting the binding of CTLA-4 to CD80 (B7.1) and CD86 (B7.2) expressed on antigen presenting cells to promote the immune response of T cells against tumors, and by other mechanisms.

(2) History of development, etc.

In other countries, Medarex (currently BMS) conducted a phase I study (Study MDXCTLA4-01) in patients with hormone-refractory advanced prostate cancer from [redacted] 20[redacted] and a phase I study (Study MDXCTLA4-02) in patients with unresectable malignant melanoma from [redacted] 20[redacted]. Medarex and BMS then conducted a joint foreign phase III study (Study MDX010-20) from [redacted] 20[redacted] in patients with unresectable malignant melanoma who had received prior therapy.

An application for ipilimumab approval was filed in June 2010 in the US and in May 2010 in the EU, with main data from Study MDX010-20. Ipilimumab was approved in March 2011 in the US and in July 2011 in the EU for the following indications: "YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma." in the US; and "YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy." in the EU. In the EU, an additional application was filed in August 2012 for approval in the treatment of untreated malignant melanoma. In October 2013, the EU indication was changed to state that "YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults."

As of February 2015, ipilimumab has been approved for the treatment of malignant melanoma in 51 countries or regions.

In Japan, the applicant conducted a phase II study (Study CA184202) to assess the efficacy and safety of ipilimumab 10 mg/kg plus dacarbazine (DTIC) from [redacted] 20[redacted]. However, Study CA184202 was discontinued due to a safety issue [see "4. (iii).A-2.(2) Japanese clinical studies"], and the development of the combination therapy of ipilimumab 10 mg/kg and DTIC was discontinued. From [redacted] 20[redacted], the applicant conducted a phase II study (Study CA184396) to assess the efficacy and safety of ipilimumab monotherapy at 3 mg/kg in patients with unresectable malignant melanoma.

This application for ipilimumab marketing approval was filed with main data from Studies MDX010-20 and CA184396.

Of note, in April 2012, the Ministry of Health, Labour and Welfare requested the applicant to develop ipilimumab based on discussions at the 11th meeting of the Study Group on Unapproved and Off-label Drugs of High Medical Need held in March 2012 (http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/kaihatsuyousei/list120423.html). Ipilimumab was also designated an orphan drug in March 2013 for the anticipated indication of malignant melanoma (Designation No. [25 yaku] No. 300).

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 substrate

[redacted] A hybridoma clone having a high ability to produce antibodies with a neutralizing activity against CTLA-4 was selected from the hybridoma cell line. Gene fragments encoding human H-chains and L-chains were prepared from the hybridoma clone. The gene fragments and a plasmid containing the constant region of human IgG1 were used to generate an expression construct for

ipilimumab. This expression construct was transfected into a Chinese hamster ovary (CHO) cell line in a serum-free medium. The master cell bank (MCB) and the working cell bank (WCB) were prepared from a clone with high antibody-producing capacity selected from the CHO cell line.

The characterization (isozyme analysis, cytogenetic analysis, cDNA base sequence analysis, Northern blot analysis, Southern blot analysis, or copy number) of MCB, WCB, and cells cultured up to the limit of the *in vitro* cell age (CAL) demonstrated genetic stability of ipilimumab during the manufacturing period.

Purity tests (sterility testing, bacteriostatic/fungistatic activity test, mycoplasma testing, *in vitro* virus test, *in vivo* virus test, test for minute virus of mice (MVM), antibody production test in mice, antibody production test in hamsters, *in vitro* focus assay, extended XC plaque assay, transmission electron microscopy, bovine virus test, porcine parvovirus test, reverse transcriptase activity test, or co-culture assay using *Mus dunni* cells) were performed on MCB, WCB, and CAL. The results showed neither viral nor nonviral adventitious agents.

MCB and WCB are stored in the gas phase of liquid nitrogen. The MCB is used to derive all working cell banks, while a new WCB is prepared as needed.

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

[redacted]

[redacted]

The manufacturing process was developed by the method of quality by design (QbD). The following were the main focuses of investigations.

- [redacted]
- Identification of critical process parameters (CPPs) and key process parameters (KPPs) based on risk assessment

[redacted]

Process validation was performed for the manufacturing process of the drug substance at commercial scale.

2.A.(1).3) Safety evaluation of adventitious agents

The manufacturing process of the drug substance does not use biological raw materials other than CHO cell line as the host cell line.

Purity tests have been performed on MCB, WCB, and CAL [see "2.A.(1).1) Preparation and control of cell substrate"]. Further, bioburden testing, endotoxin testing, mycoplasma testing, and exogenous virus test (*in vitro*) were performed for an unprocessed bulk before harvesting at commercial scales. No contamination of viral nor non-viral adventitious agents was observed in the tests performed. Bioburden testing, mycoplasma testing, and exogenous virus test (*in vitro*) of unprocessed bulk have been specified as in-process testing.

Purification process was subject to virus clearance studies using model virus. The studies showed certain levels of virus-clearing capability in the purification process.

Results of virus clearance studies

Manufacturing process	Virus reduction factor (log_{10})			
	Amphotropic murine leukemia virus	Herpes simplex virus type 1	Porcine parvovirus	Reovirus type 3
Virus inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Filtration of virus	[redacted]	[redacted]	[redacted]	[redacted]
Minimum total viral clearance factor	> 17.43	> 15.67	> 10.66	> 11.87

* This figure was not used to calculate the minimum total viral clearance factor.

2.A.(1).4) History of development of manufacturing process (comparability)

The main changes in the manufacturing process during the development of the drug substance are shown below. (The manufacturing processes are referred to as A, B ([redacted]L), B ([redacted]L), C, and C.1 [the proposed manufacturing process].) The drug product containing the drug substance produced by Process B ([redacted]L) was mainly used in foreign clinical studies. The drug product containing the drug substance produced by Process C or Process C.1 was mainly used in Japanese clinical studies.

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

When the manufacturing process was changed, the comparability between pre-change and post-change product in quality was evaluated. [redacted]

The above results of evaluation confirmed the comparability before and after the changes in the manufacturing process.

* The drug substance produced by a method comparable to Process B ([redacted]L) at the scale of [redacted]L was used.

2.A.(1).5) Properties

(a) Structure

- The primary structures were analyzed by amino acid composition analysis, reductive trypsin digestion and Asp-N digestion peptide mapping, and amino terminal (N-terminal) and carboxyl terminal (C-terminal) amino acid sequencing by liquid chromatography-tandem mass spectrometry (LC-MS/MS) of peptide fragments.
- Higher order structures were analyzed by non-reductive alkylation trypsin digestion and Lys-C digestion peptide mapping, free thiol assay, sedimentation velocity analytical ultracentrifugation, far-ultraviolet circular dichroism (CD) spectrometry, differential scanning calorimetry (DSC), and hydrogen deuterium exchange mass spectrometry (HDX-MS).
- The glycosylation site and carbohydrate structure were confirmed by trypsin digestion peptide mapping and liquid chromatography-electrospray ionization mass spectroscopy (LC-ESI-MS).

(b) Physicochemical properties

- [redacted]
- Charge variants were confirmed by isoelectric focusing (IEF), imaging capillary isoelectric focusing (iCIEF), and CEX.
- [redacted]
- Absorptivity and ultraviolet visible absorption spectrum were confirmed.

(c) Biological properties

- Binding activity to CTLA-4 was confirmed by enzyme-linked immunosorbent assay (ELISA).
- [redacted]
- The dissociation constant against CTLA-4 was confirmed by surface plasmon resonance (SPR).
- [redacted]
- [redacted]
- [redacted]

(d) Product-related substances/product-related impurities

[redacted]

(e) Process-related impurities

[redacted] Adequate removal of all process-related impurities was confirmed in the manufacturing process.

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

[redacted]

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

The results of main stability tests of the drug substance are shown in the following table.

Summary of main stability tests of drug substance

	Manufacturing process	Number of batches	Storage condition	Period	Form of storage
Long-term	C.1	4	5 ± 3°C	36 months*	[redacted]
Accelerated			[redacted]	[redacted]	
Stress			[redacted]		
			[redacted]	[redacted]	
Photostability	[redacted]	1	Overall illumination of ≥1.2 million lux·h, integrated near ultraviolet energy of ≥200 W·h/m^2		[redacted]

* [redacted] months; a stability test is underway and will continue for 36 months.

In the long-term testing, no clear changes in quality attributes were observed throughout the study period.

In the stress testing (°C), a decrease in the main peak in SEC was observed, in addition to the above-mentioned changes observed in accelerated testing and stress testing (°C).

Photostability testing showed the drug substance to be photolabile.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is an injection containing 50 mg of ipilimumab per glass vial (10 mL). It contains trometamol hydrochloride, sodium chloride, D-mannitol, diethylenetriamine-pentaacetic acid, polysorbate 80, mol/L hydrochloric acid solution, mol/L sodium hydroxide solution, and water for injection as excipients.

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

The manufacturing process for the drug product consists of mixing, sterile filtration, filling and packaging, labeling, storing, and testing.

Process validation was performed on the manufacturing process of the drug product at commercial scale.

2.A.(2).3) History of development of manufacturing process (comparability)

The manufacturing site was changed during the development of the drug product. Comparability of the drug product before and after the change was confirmed.

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

Foreign insoluble matter and insoluble particulate matter were specified during the review.

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

The following table shows the results of the main stability tests of the drug product.

Summary of main stability tests of drug product

	Manufacturing process of drug substance	Number of batches	Storage condition	Period	Form of storage
Long-term	C	3	5 ± 3°C	36 months	
	C.1	2		30 months*	
Accelerated					
Stress					
Photostability	B	1	Overall illumination of 1.2 million lux·h, an integrated near ultraviolet energy of 200 W·h/m^2		

* Stability testing is underway and will continue for 36 months.

In the long-term testing, no clear change in quality attributes was observed throughout the study period.

In the stress testing (°C), a decrease in main peak in SEC was observed, in addition to the above-mentioned changes observed in accelerated testing and stress testing (°C).

Photostability testing showed the drug product to be photolabile.

Thus, the shelf life of the drug product was determined to be 24 months when stored in glass vials at 2°C to 8°C without freezing in a light-shielded state.

2.A.(3) Reference material

The reference material has been shown to be stable for up to months. Stability during storage is evaluated at months first, and then every months.

2.B Outline of the review by PMDA

Based on the data submitted and the results of the examination presented below, PMDA considered the quality of the drug substance and the drug product to be appropriately controlled.

New excipients

The drug product contains new excipients: mol/L hydrochloric acid solution, mol/L sodium hydroxide solution, and diethylenetriamine-pentaacetic acid.

Based on the results of the examination described in (a) and (b) below, PMDA considered the use of the above excipients in the drug product would pose no particular issues.

(a) Specification, testing method, and stability

Based on the data submitted, PMDA considered the specifications, testing methods, and stability of [redacted]mol/L hydrochloric acid solution, [redacted]mol/L sodium hydroxide solution, and diethylenetriamine-pentaacetic acid would pose no particular issues.

(b) Safety

Based on the data submitted, PMDA considered that the proposed content of [redacted]mol/L hydrochloric acid solution, [redacted]mol/L sodium hydroxide solution, and diethylenetriamine-pentaacetic acid is unlikely to pose safety problems.

3. Non-clinical data

3.(i) Summary of pharmacology studies

Ipilimumab is a human monoclonal antibody of immunoglobulin G1 (IgG1) subclass against CD152 (CTLA-4). Because ipilimumab exhibits no cross-reaction to CTLA-4 of mice [see "3.(i).A.(1).1) Binding properties to CTLA-4"], 9D9 (mouse IgG2b), an anti-mouse CTLA-4 antibody, and UC10 (hamster IgG1) were also used in pharmacology studies.

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

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

3.(i).A.(1).1) Binding properties to CTLA-4 (Reports 930019518, 930019520, 930021444, 930043090, MDX-010-011-R, MDX-010-013-R [all are reference data])

Ipilimumab binding to the fusion protein of human CTLA-4 and Fc fragment of human IgG1 subclass was examined by surface plasmon resonance. The dissociation constant (K_D) of ipilimumab was 5.25 ± 3.62 nmol/L (mean ± standard deviation, n = 4).

Ipilimumab binding to lymphocytes derived from human peripheral blood activated *in vitro* was examined by flow cytometry (FCM). Ipilimumab was shown to bind to activated lymphocytes derived from human peripheral blood.

The following test results and other data showed that ipilimumab binds to monkey CTLA-4 but not to rodent or rabbit CTLA-4.

- Ipilimumab did not bind to a mouse T cell hybridoma BW-mCTLA-4/CD3ζ cell line forcibly expressing CTLA-4 proteins or a CHO cell line forcibly expressing rat CTLA-4 proteins. In contrast, ipilimumab bound to an L cell line derived from mouse dermal fibroblasts forcibly expressing rhesus CTLA-4 proteins (evaluated by FCM).
- Ipilimumab bound to lymphocytes expressing CTLA-4 derived from cynomolgus monkey peripheral blood activated *in vitro*. In contrast, ipilimumab did not bind to lymphocytes expressing CTLA-4 derived from rabbit or mouse peripheral blood (evaluated by FCM).

3.(i).A.(1).2) Inhibition of binding of CTLA-4 and B7.1 or B7.2 (Report MDX-010-008-R)

FCM was used to examine the inhibition by ipilimumab of the binding of human CTLA-4 protein expressed on cell surfaces to its ligands, B7.1 and B7.2 proteins. Ipilimumab inhibited the binding of mouse T cell hybridoma forcibly expressing human CTLA-4 proteins to fluorescent-labeled human B7.1-Fc fragment and B7.2-Fc fragment fusion proteins. The 50% effective concentrations (EC_{50}) of ipilimumab were 1.13 nmol/L (B7.1) and 1.41 nmol/L (B7.2).

3.(i).A.(1).3) Effects on the immune system (Reports 930031729, TIB-06-001, MDX-1106/010-006-R [reference data], MDX-1106/010-007-R [reference data], 930031040 [reference data])

The following results of a study of cynomolgus monkeys confirmed ipilimumab's immunoenhancing effect:

- Ipilimumab promoted the enhanced proliferation of T cells activated by proteins derived from simian immunodeficiency virus (SIV).
- Ipilimumab enhanced the immune response induced by inoculation of the hepatitis B surface antigen (HBsAg), a SK-mel cell line derived from human malignant melanoma (SK-mel cells), and keyhole limpet hemocyanin (KLH), a T cell-dependent antigen [see "3.(iii).A.(2).2) Toxicity study of 1-month intermittent repeated intravenous administration in monkeys," etc.]

CTLA-4 is an inhibitory modulator of immune reaction mediated by T cells. Ipilimumab may worsen T cell-mediated autoimmune diseases. Therefore, anti-mouse CTLA-4 antibodies were administrated to mice to examine the effects on various autoimmune diseases. The results are summarized in (a) to (c) below.

(a) Following the administration of 9D9 (0.5 mg) to normal mice and mice deficient in IgG-specific Fc receptor (FCγR) IIb twice weekly for 6 weeks, serum antinuclear antibody (ANA) increased. The amount of ANA produced by ipilimumab in FCγRIIb-deficient mice was greater than that in normal mice.

(b) 9D9 (0.5 mg) and an anti-mouse PD-1 antibody 4H2 (0.5 mg) were administered alone or in combination intraperitoneally twice weekly for a total of 5 times to non-obese diabetic (NOD) mice, a mouse model of autoimmune diabetes, to study the onset of diabetes. No diabetes was observed following the administration of 9D9 alone, while diabetes was induced by the administration of 4H2 alone and in combination with 9D9. Time to the onset of diabetes was shorter in mice receiving 4H2 and 9D9 than in mice receiving 4H2 alone.

(c) The intraperitoneal administration of UC10 (20 and 40 mg/kg) to mice with oxazolone-induced colitis once every 3 days for a total of 3 times made colitis more serious.

3.(i).A.(1).4) Complement-dependent cytotoxicity and antibody-dependent cytotoxicity (Reports MDX-010-006-R, 930025694, STR-131, 930023602)

Complement-dependent cytotoxic (CDC) activity and antibody-dependent cytotoxic (ADCC) activity of ipilimumab on activated T cells expressing CTLA-4 were examined. The results are summarized in (a) to (c) below.

(a) Activated T cells expressing CTLA-4 derived from human peripheral blood mononuclear cells (PBMC) were cultured with ipilimumab in the presence of complement collected from newborn rabbits or human complement. Ipilimumab showed no CDC activity against activated T cells in the presence of either complement up to a concentration of 0.34 nmol/L.

(b) The FCγR-binding activity of ipilimumab was assessed by enzyme immunoassay. The EC_{50} of ipilimumab to FCγRI, a high-affinity receptor, was 1.8 nmol/L. The EC_{50} to FCγRII and FCγRIII, low-affinity receptors, was not calculated (EC_{50} > 5.4 μmol/L).

(c) The ADCC activity of ipilimumab was examined in an *in vitro* test system using activated T cells derived from human PBMCs as target cells and human PBMCs as effector cells by ^{51}Cr release assay. The samples exhibited negative (<1%*), low (1%-8%*), or moderate (8%-55%*) ADCC activity, showing inconsistency among the samples.

* Activity based on cytotoxic activity of 1% Triton X-100, which was regarded as 100%

The results in (c) do not accurately reflect the induction of CTLA-4 expression *in vivo*. A repeated-dose toxicity study in cynomolgus monkeys and the clinical studies of ipilimumab did not show a decrease in CTLA-4-expressing activated T cells [see "3.(iii).A.(2).3) Study of toxicity and biological activity comparability of 3-month intermittent repeated intravenous administration in monkeys" and "4.(ii).A.(7) Pharmacodynamics"]. The applicant therefore explains that ADCC activity is unlikely to be induced in immune cells in circulating blood, in which CTLA-4 expression level is expected to be low *in vivo*.

3.(i).A.(1).5) Actions against malignant tumors (Reports MDX-010-005-R, 930031045 [reference data], MDX-1106/010-002-R [reference data], MDX-1106/010-003-R [reference data], MDX-1106/010-004-R [reference data], MDX-1106/010-005-R [reference data])

(a) Malignant melanoma

Tumor growth inhibition by 9D9 was examined in C57BL/6 mice receiving subcutaneous transplantation of B16-F10 cell line derived from mouse malignant melanoma. The transplantation was performed on Day 0. On Day 8, tumor mass reached 67 mm^3, and the mice were divided into groups. On Days 8, 11, 14, and 17, 9D9 (10 mg/kg per dose) and 4H2 (10 mg/kg per dose), an anti-mouse PD-1 antibody, were intraperitoneally administered alone or in combination and the tumor mass was calculated. As compared with the control group (mouse IgG1), no tumor growth inhibitory effect was observed in the 9D9 or 4H2 alone or the combination therapy group.

Similarly, tumor growth inhibition was examined by the administration of UC10 alone and in combination with anti-mouse CD137 antibody in mice receiving transplantation of the B16-F10 cell line. No tumor growth inhibitory effect was observed.

(b) Malignant tumors other than malignant melanoma

Tumor growth inhibition by 9D9 was examined in A/J mice receiving subcutaneous transplantation of the SA1/N cell line derived from mouse fibrosarcoma. The transplantation was performed on Day 0. On Days 1, 4, 7, and 11, 9D9 (0.2 or 10 mg/kg per dose) and 4H2 (10 mg/kg per dose) were intraperitoneally administered alone or in combination (9D9, 0.2 mg/kg; 4H2, 10 mg/kg) and the tumor mass was

calculated. As compared with the control group (mouse IgG1), statistically significant tumor growth inhibition was observed in the 9D9 (10 mg/kg) group and the 4H2 group (data shown in the following table). The combination group showed a tendency to enhanced tumor growth inhibitory effect compared with the 4H2 group.

Tumor growth inhibition by 9D9 in mice receiving transplantation of SA1/N cell line

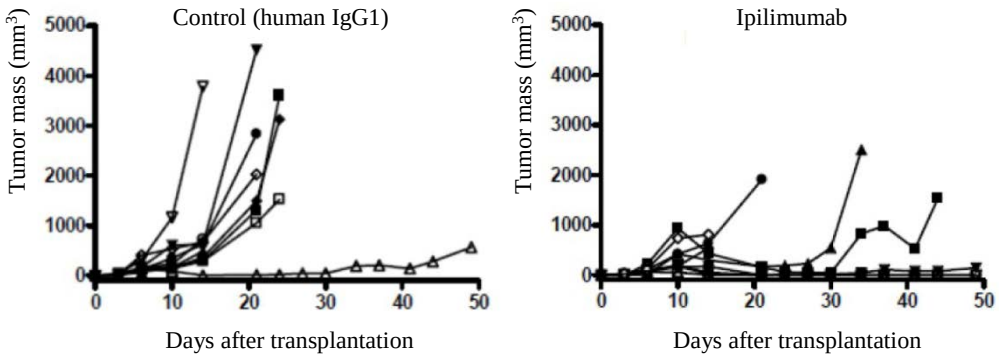
	Mean tumor mass (mm^3) on Day 14	Tumor growth inhibition rate (%) on Day 14[*1]	Survival (%) with tumor disappearance on Day 40[*2]
Control (mouse IgG1)	634	0	0
9D9 (0.2 mg/kg)	597	6	0
9D9 (10 mg/kg)	234	63	40[*3]
4H2 (10 mg/kg)	463	27	40[*3]
Combination	330	48	80[*3,*4]

n = 10, Measurement was discontinued when the tumor mass reached 1500 mm^3 or tumor ulceration was observed.
[*1] (1 – Mean tumor mass in the relevant treatment group/Mean tumor mass in the control group) × 100
[*2] Number of surviving animals with no tumor on the last day of study/Number of animals at the time of grouping × 100
[*3] $p < 0.05$ (log-rank test) in comparison with the control group
[*4] $p = 0.08$ (log-rank test) in comparison with the 4H2 alone group

Tumor growth inhibition by 9D9 was examined in BALB/c mice receiving subcutaneous transplantation of CT26 cell line derived from mouse colon cancer. The transplantation was performed on Day 0. On Day 10, the tumor mass reached 64 mm^3 and the mice were divided into groups. On Days 10, 14, 17, and 21, 9D9 (10 mg/kg) and 4H2 (10 mg/kg) were intraperitoneally administered alone or in combination (10 mg/kg each) and the tumor mass was calculated. On Day 21, as compared with the control group (mouse IgG1, 20 mg/kg), tumor growth inhibition was statistically significant in the 9D9 alone group but not in the 4H2 alone group. As compared with the 9D9 alone group, significantly enhanced tumor growth inhibition was observed in the combination group.

Tumor growth inhibitory effect of ipilimumab was examined in mouse *CTLA-4* knock-out human CTLA-4 knock-in transgenic mice (hCTLA-4 mice) subcutaneously transplanted with MC38 cell line derived from mouse colon cancer. Human IgG1 was used as control.

The following figures show the results of intraperitoneal administration of ipilimumab (10 mg/kg) and human IgG1 (10 mg/kg) on Days 0, 3, 6, and 10. Tumor growth inhibitory effect was observed in 8 of 10 animals receiving ipilimumab.



Tumor growth inhibition by ipilimumab in hCTLA-4 mice receiving transplantation of MC38 cell line
Changes in the tumor mass of each animal, n = 10

Measurement was discontinued when the tumor mass reached 1500 mm^3 or when tumor ulceration was observed.

In a study of C57BL/6 mice receiving subcutaneous transplantation of the MC38 cell line, tumor growth inhibitory effect was observed in mice receiving 9D9 and 4H2, but not in mice receiving 9D9 or 4H2 alone.

3.(i).A.(2) Safety pharmacology

A repeated-dose toxicity study in cynomolgus monkeys assessed the effects of ipilimumab (10 mg/kg) on clinical signs, body temperature, and the respiratory, central nervous, and cardiovascular systems of the animals and on electrocardiogram [see "3.(iii).A.(2) Repeated-dose toxicity"]. No effects of ipilimumab were observed.

3.(i).A.(3) Pharmacodynamic drug interactions (Reports TIB-06-001, 930031729, TIB-006-001, MDX-010-001-R, SUV00106 [reference data])

Pharmacological activity of ipilimumab in combination with BMS-663513, an immunomodulatory antibody to human CD137, or nivolumab (genetical recombination), an anti-human PD-1 antibody, was examined in cynomolgus monkeys.

- The combined effects of ipilimumab and BMS-663513 on immune reaction to SIV DNA antigen were examined. Ipilimumab promoted proliferation of SIV-specific T cells, while BMS-663513 increased the production of SIV-specific interferon (IFN)-γ. These effects were similar irrespective of whether ipilimumab or BMS-663513 was administered alone or in combination.
- A toxicity study was conducted to assess the safety of ipilimumab plus nivolumab. Serum ipilimumab or nivolumab concentrations did not clearly differ between monkeys receiving ipilimumab or nivolumab alone and those receiving both antibodies. Anti-ipilimumab antibodies were detected after the start of administration, and the expression rate of the antibodies (32%) was higher in monkeys receiving ipilimumab and BMS-663513 than in those receiving ipilimumab alone (0% -17%).

The combination of 9D9 with dexamethasone was examined in A/J mice receiving subcutaneous transplantation of the SA1/N cell line. Because the study did not involve ipilimumab, detailed findings of the study is omitted in this review report.

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

PMDA concluded that ipilimumab is effective against malignant melanoma based on the submitted data and the discussion described below.

Efficacy of ipilimumab against malignant melanoma

The applicant's explanation on the function of CTLA-4 and the mechanism of action of ipilimumab:

Activation of T cells (T cell proliferation, cytokine secretion, and induction of effector functions) is controlled by signals from T-cell receptors and costimulatory receptors (CD28 and CTLA-4) expressed on T cells. In particular, the positive costimulatory receptor CD28 and the negative costimulatory

receptor CTLA-4 (a negative regulator of T cell activation) have common ligands (CD80 [B7.1] and CD86 [B7.2] expressed on antigen-presenting cells). The balance between CD28 and CTLA-4 significantly influences T cell activation (*Nat Rev Immunol*. 2003; 3: 939-51). CTLA-4 has greater binding affinity to B7.1 and B7.2 expressed on antigen-presenting cells than CD28. CTLA-4 inhibits T cell proliferation and reduces cytokine expression, etc. by binding to B7.1 or B7.2 (*J Exp Med.* 1995; 182: 459-65, *Immunity*. 1994; 1: 405-13, etc.).

Ipilimumab, a human monoclonal antibody of IgG1 subclass against human CTLA-4, is considered to suppress tumor growth by inhibiting the binding of CTLA-4 expressed on T cells to B7.1 and B7.2 expressed on antigen-presenting cells, thereby promoting antitumor immune response of T cells. Several reports suggest that ipilimumab inhibits tumor growth by reducing the number of regulatory T-cells and their function (*Cancer Immunol Res.* 2013; 1: 32-42, *J Exp Med.* 2013; 210: 1695-710, etc.).

Anti-mouse CTLA-4 antibodies 9D9 and UC10 did not exhibit tumor growth inhibitory effect on the B16-F10 cell line derived from mouse malignant melanoma [see "3.(i).A.(1).5) Actions against malignant tumors"]. PMDA asked the applicant to explain ipilimumab's efficacy in the treatment of malignant melanoma in light of ipilimumab's mechanism of action described above.

The applicant's response:
Tumor growth inhibitory effect of an anti-mouse CTLA-4 antibody is mediated by the growth and activation of T cells specific to the tumor antigen and depends on the immunogenicity of the transplanted cell line. B16-F10 cell line has been reported to exhibit low immunogenicity (*Cancer Res.* 2000; 60: 5514-21, *Curr Opin Genet Dev.* 2014; 24: 46-51), and this low immunogenicity is considered the reason the anti-mouse CTLA-4 antibodies did not inhibited the proliferation of this cell line. The SA1/N cell line derived from mouse fibrosarcoma and the CT26 cell line derived from mouse colon cancer were reported to exhibit high immunogenicity (*J Immunol.* 2001; 167: 132-9, *J Immunother.* 2013; 36: 477-89), and anti-mouse CTLA-4 antibodies inhibited the proliferation of these cell lines [see "3.(i).A.(1).5) Actions against malignant tumors"].

The inoculation of a malignant melanoma-specific antigen resulted in enhanced antitumor immune response (*J Exp Med.* 1999; 190: 355-66, *Cancer Res.* 2003; 63: 3281-8). Generally, malignant melanoma is known to exhibit high immunogenicity that induces T cell response (*Annu Rev Immunol.* 2006; 24: 175-208, *N Engl J Med.* 2014; 371: 2189-99). Because of these factors, ipilimumab is expected to be effective against malignant melanoma.

PMDA's view:
The applicant's explanation that ipilimumab is expected to be effective against human malignant melanoma is reasonable, according to ipilimumab's mechanism of action. However, as the involvement of regulatory T cells in the mechanism is suggested, and there are unknown factors affecting the efficacy of ipilimumab. Such factors are important for the determination of patients' eligibility for the clinical

use of ipilimumab. For this reason, the efficacy of ipilimumab should be further investigated, and any new findings should be provided to healthcare professionals in an appropriate manner.

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetics (PK) of ipilimumab in animals was examined in cynomolgus monkeys.

3.(ii).A.(1) Analytical method

3.(ii).A.(1).1) Measurement method for ipilimumab

Ipilimumab in plasma and serum of monkeys was quantified by enzyme-linked immunosorbent assay (ELISA) using solid-phase human CTLA-4-Fc fusion protein and F (ab')$_2$ fragment of goat anti-human IgG labeled with alkaline phosphatase (ALP).

3.(ii).A.(1).2) Measurement method for anti-ipilimumab antibody

Anti-ipilimumab antibodies in monkey plasma and serum were detected by (a) ELISA using F (ab')$_2$ fragment of solid-phase ipilimumab and goat anti-human IgG labeled with ALP or (b) electrochemiluminescence (ECL) using solid-phase streptavidin, and biotin- or ruthenium-labeled ipilimumab.

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

Male and female cynomolgus monkeys (5/sex/group) received ipilimumab 10 mg/kg alone or in combination with 100 mg/kg BMS-663513, a human anti-CD137 monoclonal antibody, (the ipilimumab/BMS-663513 group) intravenously every week for 4 times to investigate serum ipilimumab concentration. On Day 10, T cell-dependent antigen KLH 10 mg was administered intramuscularly. According to the applicant, KLH is unlikely to affect the PK of ipilimumab because no clear differences were observed in the PK of ipilimumab between this study and other studies in which KLH was not used.

The table below summarizes the PK parameters of ipilimumab following the initial and fourth doses. No clear sex differences were seen in C_{max} or AUC. Accumulation of ipilimumab due to repeated administration was observed in both males and females. No anti-ipilimumab antibodies were detected.

PK parameters of ipilimumab
(male and female cynomolgus monkeys, repeated intravenous administration)

Administration	Drug	Sex	C_{max} (μg/mL)	AUC_{48h} (μg·h/mL)	AUC_{168h} (μg·h/mL)	$T_{1/2}$ (day)
Initial	Ipilimumab alone	Male	209 ± 14.9	7070 ± 622	17,500 ± 1830	–
		Female	233 ± 25.1	7220 ± 731	17,700 ± 1760	–
	Ipilimumab/ BMS-663513	Male	225 ± 19.3	7730 ± 1840	18,800 ± 4990	–
		Female	212 ± 38.4	6580 ± 548	16,100 ± 1470	–
Fourth	Ipilimumab alone	Male	352 ± 35.7	13,000 ± 1730	36,800, 36,000[*1]	10.3, 17[*1]
		Female	368 ± 25.6[*2]	12,600 ± 2170[*2]	32,000[*3]	14.1[*3]
	Ipilimumab/ BMS-663513	Male	351 ± 21.3	12,000 ± 1610	29,600, 37,300[*1]	5.4, 13.6[*1]
		Female	286 ± 55.3	10,100 ± 2470	27,800, 21,800[*1]	12.8, 14.8[*1]

Mean ± standard deviation, n = 5, [*1] n = 2 (individual value), [*2] n = 4, [*3] n = 1 (individual value), - not calculated

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

According to the applicant, tissue distribution of ipilimumab was not investigated for the following reasons:

- Since the V_{ss} of ipilimumab in a single-dose study in cynomolgus monkeys [see "3.(ii).A.(5) Effects of changes in drug substance manufacturing processes on PK"] was similar to the plasma volume of monkeys (45 mL/kg) (*Pharm Res.* 1993; 10: 1093-5), the amount of extravascular distribution of ipilimumab is considered small, and thus ipilimumab tissue distribution is unlikely.
- Ipilimumab's target molecule CTLA-4 has been reported to be expressed on lymphocytes (*Immunity.* 1996; 4: 535-43, *Am J Pathol.* 1998; 152: 963-73, *Cancer Immun.* 2013; 13: 1-14).
- In the tissue cross-reactivity study using normal human tissue, the cross-reactivity of ipilimumab was mainly observed in lymphocytes [see "3.(iii).A.(7).1) Tissue cross-reactivity study using normal human tissue"].

The applicant's explanation on placental transfer of ipilimumab:

Ipilimumab 10 or 30 mg/kg was intravenously administered to pregnant cynomolgus monkeys from Day 20 to Day 22 of gestation to delivery every 3 weeks. The ratio of serum ipilimumab concentrations in offspring to those in the dams on Day 7 post-partum was 1.1 in the 10 mg/kg group and 1.4 in the 30 mg/kg group. Since ipilimumab is extremely unlikely to be excreted in milk [see 3.(ii).A.(4) Metabolism and excretion"], ipilimumab detected in the serum of offspring is considered attributable to prenatal exposure to ipilimumab, not to milk ingestion. Thus, ipilimumab is considered to pass the placental barrier.

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

The applicant stated that metabolism and excretion of ipilimumab were not investigated according to "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012), because ipilimumab, a human monoclonal antibody of IgG1 subclass, is considered to be degraded to low-molecular-weight peptides and amino acids for reuse.

The applicant's explanation on the excretion of ipilimumab in milk:

Ipilimumab 10 or 30 mg/kg was intravenously administered to pregnant cynomolgus monkeys from Day 20 to Day 22 of gestation to delivery every 3 weeks. The ratios of ipilimumab concentrations in milk to serum ipilimumab concentrations on Days 3, 7, and 21 post-partum were 0.003, 0.002, and 0.004, respectively, in the 10 mg/kg group, and 0.002, 0.003, and 0.003, respectively, in the 30 mg/kg group. Ipilimumab is thus extremely unlikely to be excreted in milk.

3.(ii).A.(5) Effects of changes in drug substance manufacturing processes on PK

The manufacturing process of the drug substance was changed for a total of 4 times during the development process [see "2.A.(1).4) History of development of manufacturing process

(comparability)**”]**. The following studies were conducted to investigate the effects of the changes from Process A to Process B ([redacted]L) and from Process B ([redacted]L) to Process C on the PK of ipilimumab.

3.(ii).A.(5).1) Effects of change from Process A to Process B ([redacted]L)

Male and female cynomolgus monkeys intravenously received 10 mg/kg ipilimumab produced by Process A for 3 times every 4 weeks, or 0.1, 1, or 10 mg/kg ipilimumab produced by Process B ([redacted]L) for 3 times every 4 weeks to assess plasma ipilimumab concentrations. On Days 1, 29, and 57, HBsAg was administered intramuscularly and SK-mel cells subcutaneously.

The following table summarizes the PK parameters of ipilimumab following the initial dosing. The applicant stated that PK parameters could not be calculated for the group receiving 0.1 mg/kg ipilimumab produced by Process B ([redacted]L) because plasma ipilimumab concentrations at all time points of blood sample collection were around or below the lower limit of quantitation (1.2 μg/mL).

No clear difference was observed between Process A and Process B ([redacted]L) in the PK of ipilimumab 10 mg/kg. No clear sex differences were found in PK parameters of ipilimumab in any group. A comparison between 1 and 10 mg/kg ipilimumab, both produced by Process B ([redacted]L), revealed more than dose-proportional increases in C_{max} and AUC_t. According to the applicant, this may be due to the saturation of the elimination pathway mediated by binding to CTLA-4.

Anti-ipilimumab antibodies were detected in 1 of 6 animals receiving 10 mg/kg ipilimumab produced by Process A. No anti-ipilimumab antibodies were detected in a total of 18 animals receiving 0.1, 1, or 10 mg/kg ipilimumab produced by Process B ([redacted]L). Plasma ipilimumab concentrations (mean ± standard deviation) in 11 animals testing negative for anti-ipilimumab antibodies after receiving 10 mg/kg ipilimumab produced by either Process A or Process B ([redacted]L) were 14.6 ± 5.48, 64.6 ± 9.26, 19.0 ± 5.37, and 61.3 ± 17.5 μg/mL on Days 29, 43, 57, and 71, respectively. Plasma ipilimumab concentrations in animals testing positive for anti-ipilimumab antibodies were below the lower limit of quantitation (1.2 μg/mL) on Days 29, 43, 57, and 71.

PK parameters of ipilimumab following single intravenous administration of drug substance before and after changes in manufacturing process (in male and female cynomolgus monkeys)

Drug substance manufacturing process	Dose (mg/kg)	Sex	C_{max} (μg/mL)	AUC_t [*1] (μg·h/mL)	AUC_{inf} (μg·h/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	$T_{1/2}$ (day)	MRT (h)
A	10	Male	459 ± 68.7	44,900 ± 13,600[*2]	48,900 ± 15,200	0.217 ± 0.057	38.3 ± 5.76	7.0 ± 3.2	184 ± 44.5
		Female	420 ± 49.1	45,300 ± 7,980	48,200 ± 10,600	0.214 ± 0.043	43.1 ± 3.51	7.2 ± 2.2	207 ± 45.5
B [redacted]	1	Male	27.6 ± 2.97	1610 ± 109[*3]	–	–	–	–	–
		Female	21.7 ± 2.69	,730 ± 519[*4]	–	–	–	–	–
	10	Male	560 ± 97.4	51,600 ± 2,630	59,500 ± 4350	0.169 ± 0.012	50.0 ± 3.69	11.5 ± 1.6	298 ± 33.9
		Female	503 ± 96.6	49,600 ± 2,490	53,900 ± 1310	0.186 ± 0.005	44.9 ± 6.15	8.1 ± 1.0	241 ± 27.4

Mean ± standard deviation, n = 3, [*1] AUC_{672h}, [*2] AUC_{312h} in 1 animal, [*3] AUC_{312h}, [*4] AUC_{312h} in 2 animals, - not calculated

3.(ii).A.(5).2) Effects of change from Process B ([redacted]L) to Process C

Female cynomolgus monkeys received intravenously a single dose of 10 mg/kg ipilimumab produced by Process B ([redacted]L) or Process C, and serum ipilimumab concentration was assessed. No clear difference was observed in the PK parameters of ipilimumab between the group receiving ipilimumab produced by Process B ([redacted]L) and the group receiving ipilimumab produced by Process C (see the table below).

Anti-ipilimumab antibodies were detected in 1 of 4 animals (Day 42) in the group receiving ipilimumab produced by Process B ([redacted]L) and 1 of 4 animals (before administration and Days 29, 36, 42) in the group receiving ipilimumab produced by Process C. However, serum ipilimumab concentrations in the animals testing positive for anti-ipilimumab antibodies were similar to those in animals testing negative for anti-ipilimumab antibodies at the same blood sampling time points.

PK parameters of ipilimumab following single intravenous administration of drug substance before and after changes in manufacturing process (in male and female cynomolgus monkeys)

Drug substance manufacturing process	C_{max} (μg/mL)	AUC_{1008h} (μg·h/mL)	AUC_{inf} (μg·h/mL)	CL (mL/h/kg)	V_{ss} (mL/kg)	$T_{1/2}$ (day)	MRT (h)
B[redacted]	252 ± 13.0	52,100 ± 4810	57,500 ± 4950	0.175 ± 0.015	71.7 ± 10.6	12.8 ± 3.0	410 ± 48.8
C	234 ± 9.9	46,700 ± 4630	55,200 ± 12,100	0.187 ± 0.034	90.2 ± 9.98	15.4 ± 6.1	507 ± 173

Mean ± standard deviation, n = 4

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

Based on the submitted data, PMDA concluded that the applicant's explanation about absorption, distribution, metabolism, and excretion of ipilimumab was acceptable.

3.(iii) Summary of toxicology studies

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

In vivo toxicity studies were conducted in cynomolgus monkeys because ipilimumab was shown to bind to CTLA-4 of cynomolgus monkeys [see "3.(i).A.(1).1) Binding properties to CTLA-4"]. Ipilimumab produced by different manufacturing processes (Processes A, B [[redacted]L], B [[redacted]L], and C) was used [see "2.A.(1).4) History of development of manufacturing process (comparability)"].

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

No single-dose toxicity study was conducted. The acute toxicity of ipilimumab was assessed based on the results following the initial administration in repeated-dose toxicity studies in cynomolgus monkeys [see "3.(iii).A.(2) Repeated-dose toxicity"]. No toxicity findings associated with the administration of ipilimumab were obtained at any dose (0.1 to 30 mg/kg). Thus, the approximate lethal dose was determined to be > 30 mg/kg.

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

3.(iii).A.(2).1) Toxicity study of 2-week intermittent repeated intravenous administration in monkeys

Ipilimumab was intravenously administered to cynomolgus monkeys at 3 mg/kg (2 males) or 10 mg/kg (2 males and 2 females) on Days 1, 4, and 7. Autopsies were performed on Day 14. No deaths or toxicity associated with the administration of ipilimumab were observed during the study period. The no observed adverse effect level (NOAEL) was determined to be 10 mg/kg.

Ipilimumab was intravenously administered to cynomolgus monkeys at 3 mg/kg (2 males) or 30 mg/kg (2 males and 2 females) on Days 1, 4, and 7. Autopsies were performed on Day 14. No deaths or toxicity associated with the administration of ipilimumab were observed during the study period. The NOAEL was thus determined to be 30 mg/kg.

3.(iii).A.(2).2) Toxicity study of 1-month intermittent repeated intravenous administration in monkeys

Cynomolgus monkeys (5/sex/group) received 10 mg/kg ipilimumab alone or in combination with 100 mg/kg BMS-663513 (a human anti-CD137 monoclonal antibody) (the ipilimumab/BMS-663513 group) or a vehicle control[*1] intravenously every week (qw) for a total of 4 times. A 9-week recovery period was given to 2 males and 2 females following the last dose. As part of this study, peripheral blood lymphocyte phenotyping, tests of T cell-dependent antibody response (TDAR) to KLH, and antinuclear antibody tests were also performed.

[*1] Five mmol/L sodium succinate buffer solution (pH 5) containing normal saline as the ipilimumab solvent and 2 mg/mL normal saline solution of Pluronic F68 (poloxamer 188) as the BMS-663513 solvent

No animals were sacrificed moribund or died during the study period.

The TDAR revealed an increase in ability to produce antibodies to KLH in the ipilimumab alone group and the ipilimumab/BMS-663513 group (3.9-4.7-fold and 6.3-7.0-fold, respectively, as compared with the control group). No statistically significant differences were observed between these groups. Thus, the increased ability to produce antibodies to KLH is considered due primarily to the pharmacological action of ipilimumab.

Accordingly, the NOAEL of ipilimumab in this study was determined to be 10 mg/kg both in the ipilimumab alone group and the ipilimumab/BMS-663513 group. $AUC_{0\text{-}168h}$ at the NOAEL was 31.6 mg·h/mL, which is approximately 5.4-fold exposure in humans[*2] when dosing interval is converted to every 3 weeks.

[*2] The AUC (3 weeks) of ipilimumab administered at 3 mg/kg in Japanese patients with malignant melanoma estimated by population pharmacokinetic analysis was 17.5 mg·h/mL.

3.(iii).A.(2).3) Study of toxicity and biological activity comparability of 3-month intermittent repeated intravenous administration in monkeys

Cynomolgus monkeys (3/sex/group) received normal saline or 0.1, 1, or 10 mg/kg ipilimumab produced by Process B ([redacted]L) intravenously at 4-week intervals (q4w) for 3 times, 1 mg/kg ipilimumab produced by Process B ([redacted]L) intravenously qw for 10 times, or 10 mg/kg ipilimumab produced by Process A intravenously q4w for 3 times. All animals received SK-mel cells subcutaneously and HBsAg intramuscularly as vaccine antigens on Days 1, 29, and 57. To evaluate delayed type hypersensitivity (DTH), vaccine antigens or normal saline were subcutaneously administered on Day 41 or Days 44 and 71. The study also included DTH testing, TDAR to vaccine antigens, peripheral blood lymphocyte phenotyping (activated T cell subset), and intracellular staining of cytokines (tumor necrosis factor α ["TNF-α" hereinafter] and interferon γ ["IFN-γ" hereinafter]) known to be produced *in vitro* by CD8-positive T cells of peripheral blood of monkeys in response to HBsAg or polyclonal super antigen (*Staphylococcus* enterotoxin B).

No animals were sacrificed moribund or died for during the study period.

Following the administration of ipilimumab produced by Process B ([redacted]L), DTH response to HBsAg increased at 10 mg/kg (q4w) and 1 mg/kg (qw). TDAR tests showed increases in the ability to produce antibodies to SK-mel cells at 10 mg/kg (q4w) and the ability to produce antibodies to HBsAg at 10 mg/kg (q4w) and 1 mg/kg (qw and q4w). Production of antigen-specific cytokines (TNF-α and IFN-γ) was observed at 10 mg/kg (q4w) and 1 mg/kg (qw). Following the administration of ipilimumab produced by Process A (administered at 10 mg/kg [q4w]), increases in DTH response to HBsAg, the ability to produce antibodies to SK-mel cells and HBsAg in TDAR assay, and production of antigen-specific cytokines (TNF-α and IFN-γ) were observed.

Accordingly, DTH response, TDAR response, and toxicity profile of ipilimumab were comparable between Process A and Process B ([redacted]L). Since no toxicologically significant changes were observed in any treatment group regardless of the Process A or B ([redacted]L), the NOAEL in this study was determined to be 10 mg/kg for both manufacturing processes. The mean exposure (AUC_{inf}) at the NOAEL was 52.6 mg·h/mL for both Processes A and B ([redacted]L). This value (52.6 mg·h/mL) is approximately 2.3-fold exposure in humans* when dosing interval is converted to every 3 weeks.

* The AUC (3 weeks) of ipilimumab administered at 3 mg/kg in Japanese patients with malignant melanoma estimated by population pharmacokinetic analysis was 17.5mg·h/mL.

3.(iii).A.(2).4) Toxicity study of 6-month intermittent repeated intravenous administration in monkeys

Cynomolgus monkeys received normal saline (2 males and 2 females) or 10 mg/kg ipilimumab (5 males and 5 females) intravenously q4w for a total of 5 times. Some animals (3 males and 3 females) treated with ipilimumab also received SK-mel cells subcutaneously as a vaccine antigen on the same schedule as ipilimumab (the vaccine combination group). Cynomolgus monkeys (2 males and 2 females) received normal saline intravenously and SK-mel cells subcutaneously q4w for a total of 5 times (the vaccine

alone group). In this study, peripheral blood lymphocyte phenotyping and TDAR on SK-mel cells were performed. In the vaccine alone group and the vaccine combination group, DTH test was performed on 3 types of antigens (SK-mel cells, dendritic cells, and dendritic cells with antigen presentation by SK-mel cells).

No animals were sacrificed moribund or died during the study period.

Slight erythema or edema was observed at the sites of subcutaneous vaccination in the vaccine combination group. DTH tests showed increased response to SK-mel cells in the vaccine alone group and in the vaccine combination group. Response to dendritic cells with antigen presentation by SK-mel cells and dendritic cells also increased in the vaccine combination group. Generally, DTH response was stronger in the vaccine combination group than in the vaccine alone group. TDAR showed increased ability to produce antibodies to SK-mel cells in 1 of 6 animals in the vaccine alone group and in 5 of 6 animals in the vaccine combination group. DTH response and ability to produce antibodies were generally greater in the vaccine combination group than in the vaccine alone group.

Increases in antigen-specific TDAR and in DTH response to the subcutaneously administered antigen were attributable to ipilimumab's pharmacological actions. No changes suggesting nonspecific activation of immune cells were observed.

The NOAEL in this study was thus determined to be 10 mg/kg.

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

Ipilimumab is an antibody-based product and is unlikely to permeate cell membranes or act directly on DNA or other chromosomal components. Thus, no genotoxicity study was conducted.

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

Since ipilimumab is intended to treat unresectable malignant melanoma, no carcinogenicity study was conducted.

3.(iii).A.(5) Reproductive and developmental toxicity (extended study of prenatal and postnatal development in cynomolgus monkeys)

Pregnant cynomolgus monkeys (19-20/group) received normal saline (vehicle control) or 10 or 30 mg/kg ipilimumab intravenously once every 3 weeks from Day 20 to Day 22 of gestation to delivery, to investigate the effects of ipilimumab on embryos and fetuses and on prenatal and postnatal development. The study also included lymphocyte phenotyping, serum Ig concentration measurement, and antinuclear antibody measurement in dams and offspring, and TDAR to HBsAg and tetanus toxin in offspring.

Serum IgG increased 72 hours after administration from Day 125 to Day 127 of gestation in dams receiving ipilimumab ≥10 mg/kg. Glomerulopathy in the kidneys (enlarged and distorted glomerulus by

accumulated eosinophilic substances), mononuclear cell infiltration in the area around glomerulus, and mononuclear cellular inflammation with shrinking or disappearance of thyroid follicles were observed in the ipilimumab 30 mg/kg group.

Increased mortality of fetuses during the third trimester of gestation (Day 101 of gestation and thereafter), early deaths of offspring, and increased ability to produce antibodies to HBsAg and tetanus toxin in TDAR assay were observed in the ipilimumab ≥10 mg/kg groups. Premature births, decreased birth weight, unilateral defects of the left kidney and ureter in 1 animal born on Day 167 of gestation, and imperforate urethra, urinary tract obstruction, and subcutaneous edema of scrotum in 1 animal born prematurely were observed in the ipilimumab 30 mg/kg group. Nonspecific toxicity was observed, including aspiration of amniotic fluid, in fetuses that died during the third trimester of gestation and offspring that died soon after birth. No effects on offspring behavior or immune function were observed. The applicant stated that serum ipilimumab concentrations in dams and offspring [see "3.(ii).A.(3) Distribution"] suggested that ipilimumab exposure levels of the fetuses and the dams were similar during the third trimester.

Although a toxicity was found in the thyroid of a dam, the finding was considered to lack toxicological significance because (a) the toxicity in question was not reported from other toxicity studies of ipilimumab [see "3.(iii).A.(2) Repeated-dose toxicity"] and was found in only 1 animal in this study, and (b) such toxicity has been reported as spontaneous lesions (*Toxicol Pathol*. 2007; 35: 296-9). The NOAEL for clinical signs in dams was thus determined to be 30 mg/kg. The NOAEL for embryonic development was not determined. Exposure at the NOAEL in dams from Day 125 to Day 127 of gestation (AUC_t) was 146 mg·h/mL, or 8.3-fold the clinical exposure.*

* The AUC (3 weeks) of ipilimumab administered at 3 mg/kg in Japanese patients with malignant melanoma estimated by population pharmacokinetic analysis was 17.5 mg·h/mL.

3.(iii).A.(6) Local tolerance

No local tolerance studies were conducted. Studies of repeated intravenous administration were conducted in monkeys using doses that achieve concentrations comparable to clinical concentrations [see "3.(iii).A.(2) Repeated-dose toxicity"]. These studies showed no toxicity associated with the administration of ipilimumab.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Tissue cross-reactivity study using normal human tissue

The cross-reactivity of fluorescently labeled ipilimumab produced by Process A and Process B ([redacted]L) was investigated by immunohistochemical staining using normal human tissue sections.

A cross-reactivity test of ipilimumab produced by Process A showed positive reactions in the tonsils, a small number of lymphocytes in blood smears, and lymph nodes beneath the colonic mucosa. No positive reaction was observed in placental connective tissue. A cross-reactivity test of ipilimumab

produced by Process B ([redacted]L) showed positive reactions in the tonsils, large intestine, esophagus, small intestine, stomach, lung, kidneys, liver, and a small number of lymphocytes in blood smears.

The cross-reactivity observed in this study was generally consistent with the known immunohistological distribution of CTLA-4 receptors in human tissue (*Immunity.* 1996; 4: 535-43, *Am J Pathol.* 1998; 152: 963-73), and no unexpected cross-reactivity was observed.

3.(iii).A.(7).2) Tissue cross-reactivity study using normal tissue of mice, rats, rabbits, monkeys, and humans

The cross-reactivity of biotin-labeled ipilimumab was investigated by immunohistochemical staining using normal tissue sections of mice, rats, rabbits, monkeys, and humans. The following results were obtained:

- The digestive tract, lymphoid tissue, lymphocytes in skin, and placental connective tissue of cynomolgus monkeys and humans tested positive. Ovary connective tissue of the monkeys also tested positive.
- In mice and rats, neither lymph nodes nor spleen tissue tested positive. In rabbits, the lymph nodes, spleen, or tonsil tissue did not test positive.

According to the applicant, the expression of CTLA-4 protein on human placental fibroblasts was reported but its function has yet to be clarified (*Mol Hum Reprod.* 1999; 5: 84-7), and the effects of ipilimumab binding to placental connective tissue are unknown.

3.(iii).A.(7).3) *In vitro* study of cell proliferation and cytokine release using human peripheral blood mononuclear cells (reference data, non-GLP study)

PBMCs were incubated with ipilimumab alone (dry fixation assay, 0.016-50 μg/well; antibody binding assay, 0.08-250 μg/mL) or in combination with BMS-663513 (dry fixation assay, 0.016-50 μg/well, antibody binding assay, 0.08-250 μg/mL for both antibodies). After being incubated for 66 hours, the PBMCs were reacted with tritium-labeled thymidine to evaluate cell proliferation using liquid scintillation counter. Various cytokines (IFN-γ, TNF-α, interleukin [IL]-2, IL-4, IL-5, IL-6, IL-8, IL-12) produced by the PBMCs were also measured by bead based multiplex assay using the samples for antibody binding assay (ipilimumab 2 μg/mL) at 24 hours following the addition of ipilimumab alone or in combination with BMS-663513.

A slight proliferation of PBMCs was observed after the addition of ipilimumab alone at 0.4 μg/well by the dry fixation assay and 2.0 μg/mL by the antibody binding assay. The degree of proliferation of PBMCs incubated with BMS-665313 plus ipilimumab 0.4μg/well or 2.0 μg/mL (the doses that induced proliferative reactions) was comparable to or weaker than that of PBMCs incubated with ipilimumab alone. IL-2, IL-6, and IL-8 and TNF-α were slightly produced by PBMCs incubated with ipilimumab 2.0 μg/mL alone or in combination with BMS-663513 by the antibody binding assay. No effects on induction of cytokine release were observed following the incubation of ipilimumab and BMS-663513.

3.(iii).A.(7).4) Study of cytokine release using human peripheral blood cells (reference data, non-GLP study)

Ipilimumab (10 and 100 μg/mL) alone, nivolumab (10 and 100 μg/mL) alone, or ipilimumab and nivolumab (10 and 100 μg/mL of both antibodies) were added to human peripheral blood cells. Various cytokines (IFN-γ, TNF-α, IL-2, 4, 6, 10) produced by the cells were measured by the cytokine cytometry bead assay 4 and 24 hours after the addition. The production of these cytokines was not observed with ipilimumab alone, nivolumab alone, or with ipilimumab and nivolumab.

3.(iii).A.(7).5) A toxicity study of 1-month intermittent intravenous administration of ipilimumab and nivolumab in cynomolgus monkeys (reference data, GLP study)

Cynomolgus monkeys (5/sex/group) received ipilimumab and nivolumab (doses of ipilimumab/nivolumab: [a] 0/0 mg/kg [normal saline], [b] 3/10 mg/kg, and [c] 10/50 mg/kg) administered intravenously qw for 4 times. A 4-week recovery period was provided to 2 males and 2 females after the last dose. Peripheral blood lymphocyte phenotyping was performed and TDAR to KLH was measured.

No animals were sacrificed moribund or died for reasons associated with ipilimumab during the study period.

Changes observed in the 3/10 mg/kg and 10/50 mg/kg groups included liquid stool, increased weight of the spleen, decreased weight of the thymus, decreased albumin, increased globulin and neutrophil count, diffuse lymphoplasmacytic inflammation in lamina propria of the large intestine with distended pelvic lymph nodes, increased size and number of splenic lymph follicles, distended marginal zone of splenic lymph follicles, decreased size and number of cells of the germinal center of the spleen and lymph nodes, and enhanced ability to produce antibodies to KLH. Changes observed in the 10/50 mg/kg group were decreased food intake and body weight, degeneration and regeneration of mucosal epithelium of the large intestine, lymphocytic, histiocytic, and neutrophilic inflammation in submucosal tissue of the large intestine, breakdown of follicles, irregular mantle zone, maturation of lymphocytes throughout follicles, a decrease in centroblasts and lymphocytes in germinal center, and changes in lymphocyte subsets in lymphoid organs. All these changes tended to be reversible after the 4-week recovery period.

Based on increased gastrointestinal toxicity following the combination use of ipilimumab and nivolumab as compared with ipilimumab alone, the applicant explained that the combination of ipilimumab with nivolumab may enhance gastrointestinal toxicity [see “3.(iii).A.(2) Repeated-dose toxicity”].

3.(iii).A.(7).6) Toxicity study of 2-month intermittent repeated intravenous administration in monkeys (reference data, non-GLP study)

Cynomolgus monkeys (2/sex/group) received 10 mg/kg of respiratory syncytial virus (RSV)-specific human isotype-matched IgG antibody (negative control) or 10 mg/kg ipilimumab intravenously on Days 1 and 29, and vaccine antigen HBsAg with or without an immunostimulant CpG oligonucleotide intramuscularly on Days 2 and 30. The study also included TDAR test to HBsAg, peripheral blood lymphocyte phenotyping, and intracellular staining of cytokines (IFN-γ, TNF-α, IL-2) known to be produced *in vitro* by T cells of peripheral blood of monkeys in response to HBsAg.

No animals were sacrificed moribund or died during the study period.

The TDAR test showed increased capacity to produce antibodies to HBsAg in the group receiving ipilimumab plus vaccine without immunostimulant, the group receiving ipilimumab plus vaccine with immunostimulant, and the group receiving negative control antibody plus vaccine with immunostimulant. According to the applicant, similar TDAR reactions were observed in the groups receiving ipilimumab regardless of the immunostimulant, and neither additive nor synergistic effects was induced by the combination of ipilimumab and the immunostimulant. Antigen-specific cytokines (IFN-γ, TNF-α, IL-2) were produced in the group receiving ipilimumab plus vaccine without immunostimulant, the group receiving ipilimumab plus vaccine with immunostimulant, the group receiving negative control antibody plus vaccine without immunostimulant, and the group receiving negative control antibody plus vaccine with immunostimulant. The production of antigen-specific cytokines was seen more frequently in the group receiving ipilimumab or immunostimulant than the groups receiving negative control.

These findings suggested that the pharmacological actions of ipilimumab increased TDAR to HBsAg following ipilimumab administration and caused *ex vivo* antigen-specific T cell activation, which was similar to T cell activation induced by immunostimulants. There was no change suggestive of nonspecific activation of immune cells.

3.(iii).A.(7).7) Exploratory toxicity and biological activity study of 3-month intermittent repeated intravenous administration in monkeys (reference data, non-GLP study)

In the first stage of the study, normal saline or 10 mg/kg ipilimumab was administered intravenously q4w for 3 times to cynomolgus monkeys (3/sex/group). HBsAg was administered intramuscularly and SK-mel cells subcutaneously on Days 1, 29 and 57. Dinitrophenyl-ficoll (DNP-ficoll), a T cell-independent antigen, was intradermally administered on Days 1 and 29 prior to the DTH test.

In the second stage of the study, on Day 140, a single dose of 0 mg/kg normal saline or 10 mg/kg ipilimumab was intravenously re-administered to animals surviving the first stage. The following tests were performed in this study: the DTH test, and TDAR to vaccine antigens, peripheral blood lymphocyte phenotyping, tests of differential white blood count of epithelium of the spleen, inguinal lymph nodes,

and the (large) intestine, staining of peripheral leucocytes and splenocytes (CTLA-4 and FoxP3 [evaluation of regulatory T cells]), and intracellular staining of TNF-α and IFN-γ. All animals were autopsied on Day 154.

One of 6 animals treated with ipilimumab was sacrificed moribund due to worsening condition. The animal presented with a variety of changes including persistent diarrhoea, loss of appetite, weight loss, shallow agonal breathing, dehydration, decreases in blood pressure, heart rate, and body temperature, increased red blood cell count, decreased white blood cell count, azotemia, decreases in blood sodium, chloride, calcium, cholesterol, γ-glutamyl transpeptidase, total protein, globulin, and albumin, increases in aspartate aminotransferase, lactate dehydrogenase, urea nitrogen, inorganic phosphorus, and potassium, retention of green liquid stool in the large intestine, multifocal blackening of mucosa in the colon, dark-browning of the adrenal glands, reduction in size of the thymus and spleen, reddening of the lung, erythema of the administration site, acute or subacute inflammation from the colon to the rectum, abscess and erosion in the crypt, mixed cell infiltration in the renal glomerulus, and thickening of the glomerular mesangium. The applicant explained that inflammatory changes in the large intestine and renal glomerulus were also reported in the clinical studies of ipilimumab and that these changes were suggestive of a relationship to the pharmacological actions of ipilimumab [see "*4.(iii).A Summary of the submitted data, Reference data* (3).1) Foreign phase II study" and "4.(iii).B.(3).2) Diarrhea, colitis, gastrointestinal perforation"].

The surviving animals receiving ipilimumab showed increased DTH reaction to HBsAg and increased capacity to produce antibodies to SK-mel cells and HBsAg in the TDAR test in the first stage. These animals also showed an increase in CD4 central memory T cell subset in peripheral blood in the second stage.

3.(iii).A.(7).8) Toxicity study of 4-month intermittent repeated intravenous administration in monkeys (reference data, non-GLP study)

Cynomolgus monkeys (4 males and 2 females/group) received ipilimumab and BMS-663513 (dose of ipilimumab/BMS-663513, [a] 0/0 mg/kg [normal saline], [b] 0/10 mg/kg, [c] 10/0 mg/kg, and (d) 10/10 mg/kg) intravenously on Days 4, 9, 30, 32, 58, 60, 86, and 88. As the vaccine antigen, plasmid DNA expressing SIV-derived protein was intramuscularly administered on Days 1, 2, 29, 30, 57, 58, 85, and 86. Cynomolgus monkeys (3 males and 3 females) in the negative control group received normal saline intravenously and 0.25% aqueous solution of bupivacaine intramuscularly, according to the above-mentioned schedule.

No animals were sacrificed moribund or died during the study period. One of 6 animals receiving 10/0 mg/kg of ipilimumab/BMS-663513 showed cyanosis, thready pulse, and diminished cardiac sound following administration on Day 58. These symptoms were suspected to be infusion reactions. The shock symptoms were treated. Ipilimumab was re-administered to the animal while the infusion rate was

controlled on Day 211 (5 months after the onset of infusion reaction-like symptoms); no toxicologically significant change was observed.

One of 6 animals receiving 10/10 mg/kg of ipilimumab/BMS-663513 showed dermatitis in the groin, eruptions, swelling in the area around peripheral lymph nodes, perivascular edema in the lower area of dermis and thickening of epidermis with infiltration of lymphocytes, macrophage, and mast cells in the area of skin inflammation, and increased nuclear proliferation antigen Ki67-positive cells.

The applicant's explanation on (a) the infusion reaction-like symptoms observed in the group receiving 10/0 mg/kg of ipilimumab/BMS-663513 and (b) enhanced toxicity by the combination of ipilimumab and BMS-663513:
The infusion reaction-like symptoms (a) may be attributable to rapid infusion, and the binding of ipilimumab to CTLA-4 is unlikely to be the direct cause of the symptoms. Although the possibility of (b) cannot be excluded, there are no findings suggestive of (b) in this study or in a toxicity study of 1-month intermittent repeated intravenous administration in monkeys [see "3.(iii).A.(2).2) Toxicity study of 1-month intermittent repeated intravenous administration in monkeys"].

3.(iii).A.(7).9) Toxicity study of single intravenous administration of ipilimumab produced by Process B ([redacted]L) or Process C in monkeys (reference data, non-GLP study)
Female cynomolgus monkeys (4/group) received a single intravenous dose of 10 mg/kg ipilimumab produced by Process B ([redacted]L) or Process C. None of the animals in any treatment group died or were sacrificed moribund during the study period. No ipilimumab-related toxicity was found in any treatment group.

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

Based on the submitted data and the following discussion, PMDA concluded that there were no problems related to the clinical use of ipilimumab in the evaluation of nonclinical toxicity.

Administration of ipilimumab in pregnant women or in women who may be pregnant
The proposed package insert submitted in approval application has a precautionary statement that ipilimumab should be administered only if the expected therapeutic benefits outweigh the potential risks associated with the treatment. PMDA asked the applicant to explain the rationale for the precaution.

The applicant's response:
The possibility that ipilimumab may affect the maintenance of pregnancy and postnatal development cannot be excluded in the use of the drug in pregnant women or women who may be pregnant, based on the expression of the target molecule of ipilimumab in the placenta [see "3.(iii).A.(7).2) Tissue cross-reactivity study using normal tissues of mice, rats, rabbits, monkeys, and humans"]. The following published literature also supports the possibility:

- Regulatory T cells are involved in the maintenance of pregnancy and immunological tolerance of dams to alloantigen in concepti (*Mol Hum Reprod*. 2004; 10: 347-53).
- Fatal lymphoproliferative disorder was observed in CTLA-4-knockout mice (*Immunity.* 1995; 3: 541-7, *Science*. 1995; 270: 985-8).

However, ipilimumab may be used in this population if the therapeutic benefits outweigh the risks, provided that the package insert contains precautionary advice on the risks of ipilimumab for placental transfer [see "3.(iii).A.(5) Reproductive and developmental toxicity"], teratogenicity, miscarriage, and other events. The reasons are listed below:

- Malignant melanoma is of poor prognosis, and has extremely limited therapeutic options.
- In response to fetal deaths in the third trimester of gestation and early newborn deaths in the reproductive and developmental toxicity study [see "3.(iii).A.(5) Reproductive and developmental toxicity"], pathological examinations were performed on the placenta and umbilical cord of dams whose fetuses or offspring died, as well as on the aborted fetuses and the newborn offspring that died shortly after birth. The examinations did not yield findings related to the pharmacological actions of ipilimumab
- The reproductive and developmental toxicity study revealed unilateral defect of the left kidney and ureter, imperforate urethra, urinary tract obstruction, and subcutaneous edema of scrotum in offspring [see "3.(iii).A.(5) Reproductive and developmental toxicity"]. However, teratogenicity is unlikely to be related to ipilimumab for the following reasons:
  - There is no report suggesting the involvement of CTLA-4 in the organogenesis of mammals. Thus, exposure to ipilimumab is unlikely to directly affect the fetal organogenesis.
  - The teratogenicity reported from the reproductive and developmental toxicity study are known as infrequent spontaneous abnormality—unilateral defects of the kidneys in humans and imperforate urethra in cynomolgus monkeys.
  - There was no report on teratogenicity in CTLA-4-knockout mice (*Immunity.* 1995; 3: 541-7, *Science*. 1995; 270: 985-8).
  - Placental transfer of maternal IgG in pregnant women is mainly attributable to binding to the fetal Fc receptors. The placental transfer is minimal in the first trimester of pregnancy and increases significantly in the second and third trimesters (*Crit Rev Toxicol*. 2012; 42: 185-210). Therefore, the exposure of human fetuses to ipilimumab during the period of organogenesis is expected to be very low as compared with ipilimumab exposure of mothers.
  - The maximum ipilimumab exposure (AUC) in dams given 10 mg/kg dose, which did not induce teratogenicity, was 70.1 mg·h/mL in the reproductive and developmental toxicity study [see "3.(iii).A.(5) Reproductive and developmental toxicity"]. The ratio of the exposure in the dams to the clinical exposure[*1] was approximately 2.2, after adjustment for the difference

in the target binding affinity of ipilimumab in tissues between cynomolgus monkeys and humans [see "3.(i).A.(1).1) Binding properties to CTLA-4"].[*2]

- Although binding of CTLA-4 to ipilimumab was seen in the placenta of monkeys [see "3.(iii).A.(7).2) Tissue cross-reactivity study using normal tissues of mice, rats, rabbits, monkeys, and humans"], no ipilimumab-related toxicity findings were obtained from the pathological examinations of the placenta or umbilical cord of dams whose fetuses or offspring died [see "3.(iii).A.(5) Reproductive and developmental toxicity"].

[*1] The AUC (3 weeks) in 3 mg/kg ipilimumab-treated Japanese patients with malignant melanoma was estimated to be 17.5 mg·h/mL by population pharmacokinetic analysis.
[*2] When multiplied by the ratio of target binding affinity in cynomolgus monkeys to humans (0.55), the estimated maximum exposure (AUC) in dams is 38.6 mg·h/mL.

A total of 14 pregnant patients received ipilimumab in the post-marketing settings outside Japan or in the clinical studies of ipilimumab (as of February 13, 2015). The outcomes of their pregnancy were unknown in 7 patients, induced abortion in 4 patients, and death of a patient, delivery of a normal newborn, and a newborn with abnormal respiratory symptoms in 1 patient each. In the patient whose newborn showed abnormalities in respiratory symptoms, no abnormality was observed on Day 114 after birth.

PMDA's view:

The explanation of the applicant is basically acceptable. However, the applicant should take the following measures, considering the effects of ipilimumab on fetuses following administration to pregnant women or women who may be pregnant.

- To help healthcare professionals determine the clinical benefits and risks of ipilimumab, the results of embryo-fetal developmental studies of ipilimumab should be provided through information materials, etc. to healthcare professionals.
- Before the administration of ipilimumab to pregnant women or women who may be pregnant, alternative therapeutic options should be considered. At the same time, patients and healthcare professionals should be sufficiently informed of the risks of ipilimumab and cautioned about the risks. For example, the applicant should prepare appropriate information materials to ensure that patients or their family members are informed of the risks of ipilimumab including teratogenicity and abortion and that patients well understand the potential risks of ipilimumab before starting treatment.
- Information on the outcomes in pregnant women and newborns following the administration of ipilimumab to pregnant women should be collected through post-marketing surveillance, etc. and any new findings should be promptly provided to healthcare professionals.

4. Clinical data

4.(i) Summary of biopharmaceutical studies and associated analytical methods

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

4.(i).A.(1) Analytical methods

4.(i).A.(1).1) Measurement method of ipilimumab (genetic recombination)

[redacted]

4.(i).A.(1).2) Measurement method of anti-ipilimumab antibodies

Anti-ipilimumab antibodies (in [a] human plasma and [b] human serum) and anti-ipilimumab neutralizing antibodies (in [c] human serum) were quantified by the following methods. The applicant explained that no confirmatory assay was performed for quantification Method 1 and Method 2 for anti-ipilimumab antibodies in human plasma (a). Thus, false positive results are possible.

(a) Quantitation of anti-ipilimumab antibodies in human plasma:

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

(b) Quantitation of anti-ipilimumab antibodies in human serum

- [redacted]
- Method 2: ECL method (detection sensitivity, 62.5 ng/mL) in which the antibodies are measured by a method similar to Method 1 after separating ipilimumab and anti-ipilimumab antibodies in samples by pretreatment with solid-phase extraction or acid dissociation (measurement method number: [redacted])

(c) Quantitation of anti-ipilimumab neutralizing antibody in human serum

- [redacted]
- [redacted]

[redacted]

4.(i).A.(2) Changes in the manufacturing processes of the drug substance and drug product during product development

The manufacturing processes of the drug substance and drug product were modified during the development of Yervoy [see "2.A.(1).4) History of development of manufacturing process (comparability)"]. The formulations used in the clinical studies are listed below. The results of the studies were submitted in this approval application. The proposed manufacturing process is Process C.1.

Formulations used in clinical studies

Manucaturing process of drug substance	Study titles
A	Foreign phase I study (Study MDX010-15) and foreign phase II study (Study MDX010-08)
B[redacted]	Foreign phase I study (Study MDX010-15) and foreign phase III study (Study MDX010-20)
B[redacted]	Foreign phase I studies (Studies CA184078 and CA184087), foreign phase II studies (Studies CA184004, CA184007, CA184008, CA184022, and CA184041), foreign phase III studies (Studies MDX010-20 and CA184024)
C	Japanese phase I study (Study CA184113) and foreign phase I study (Study CA184087)
C.1	Japanese phase II study (Study CA184396) and Japanese phase II study (Study CA184202)

The applicant explained that the changes in manufacturing processes of the drug substance and drug product were not considered to affect the pharmacokinetics (PK) of ipilimumab for the following reasons.

- At each change from Process A through Process C.1, comparability in quality attributes was evaluated, and the drug substances before and after each change were considered comparable [see "2.A.(1).4) History of development of manufacturing process (comparability)"].
- Study CA184087 compared PK parameters of ipilimumab produced by Process B ([redacted]L) and ipilimumab produced by Process C. Geometric mean ratio of C_{max} and AUC_{21d} (Process C/Process B [[redacted]L]) met the bioequivalence criteria (0.80-1.25) [see "4.(i).A.(3) Foreign phase I study"].
- (a) PK parameters of 3.0 mg/kg ipilimumab produced by Process A was compared with those of 2.8 mg/kg ipilimumab produced by Process B ([redacted]L) in Study MDX010-15 [see "4.(ii).A.(2) Foreign phase I study"]. (b) PK parameters of 10 mg/kg ipilimumab produced by Process B ([redacted]L) in Study MDX010-15 was compared with those of 10 mg/kg ipilimumab produced by Process B ([redacted]L) in Study CA184008 [see "4.(ii).A.(2) Foreign phase I study" and "4.(ii).A.(3) Foreign phase II study"]. These comparisons (a) and (b) showed no clear difference in PK of ipilimumab between Process A and Process B ([redacted]L) or between Process B ([redacted]L) and Process B ([redacted]L).

4.(i).A.(3) Foreign phase I study (5.3.1.2.1: Study CA184087 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label randomized study was conducted in 99 patients with unresectable (Stage III or IV, the same applies hereinafter) malignant melanoma (75 included in PK analysis) to investigate the PK, etc. of ipilimumab produced by Process B ([redacted]L) and Process C. Ipilimumab produced by Process B ([redacted]L) or Process C was administered intravenously at 10 mg/kg every 3 weeks for 4 times, followed

by repeated intravenous administration every 12 weeks. Serum ipilimumab concentrations were then assessed (see the table below).

The geometric mean ratios of C_{max} and AUC_{21d} (Process C/Process B [L]) (90% confidence interval [CI]) following the initial dose of ipilimumab were 0.99 (0.90, 1.10) and 0.99 (0.88, 1.13), respectively. These values met the bioequivalence criteria (0.80-1.25).

Of 70 patients whose anti-ipilimumab antibodies were measured both at baseline and after the administration of ipilimumab, 2 patients (2.9%) tested positive for anti-ipilimumab antibodies after treatment. Neutralizing antibodies were not detected in the 2 patients.

PK parameters of ipilimumab produced by Process B (L) and Process C

Manufacturing process of drug substance	n	C_{max} (μg/mL)	T_{max}[*1] (h)	AUC_{21d} (μg·h/mL)	$T_{1/2}$[*2] (day)	CL[*2] (mL/h)	V_{ss}[*2] (L)
B	37	253[*3] (29)	2.0[*3] (1.4, 6.0)	40,374[*4] (25)	15.5 ± 6.9[*4]	13.6 ± 6.1[*4]	6.2 ± 1.3[*4]
C	38	251 (24)	2.5 (1.4, 6.0)	40,086[*5] (29)	15.2 ± 8.7[*5]	14.2 ± 7.6[*5]	6.3 ± 2.0[*5]

Geometric mean (coefficient of variation, %), [*1] median (range), [*2] arithmetic mean ± standard deviation, [*3] n = 36, [*4] n = 33, [*5] n = 36

4.(ii) Summary of clinical pharmacology studies

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

In patients with solid cancer, the PK of ipilimumab administered alone and in combination with other drugs was investigated.

4.(ii).A.(1) Japanese phase I study (5.3.5.2.2: Study CA184113 [20 to 20])

An open-label study was conducted in 15 patients with unresectable advanced non-small-cell lung cancer (12 patients included in the PK analysis) to investigate the PK, etc. of ipilimumab in combination with paclitaxel (PTX) and carboplatin (CBDCA and PTX/CBDCA). This study consisted of an induction period and a maintenance period. In the induction period (the first 24 weeks) with each cycle consisting of 3 weeks, PTX 175 mg/m^2 per dose and CBDCA (equivalent to AUC of 6 mg·min/mL) were intravenously administered on Day 1 of Cycles 1 to 6, and ipilimumab was intravenously administered at 3 or 10 mg/kg on Day 1 of Cycles 3 to 6. In the maintenance period (after Week 24), ipilimumab was intravenously administered at 3 or 10 mg/kg every 12 weeks. Serum ipilimumab concentrations were measured. The PK parameters of ipilimumab following the initial dose are shown in the following table. Serum ipilimumab concentration following the administration of ipilimumab 3 and 10 mg/kg increased in a dose dependent manner. V_{ss} of ipilimumab was slightly greater than the human plasma volume (approximately 3L) (*Pharm Res.* 1993; 10: 1093-5). The applicant explained that pharmacokinetic interaction between ipilimumab, PTX, and CBDCA is unlikely [see "4.(ii).A.(4) Drug interactions"].

In 12 patients whose anti-ipilimumab antibodies were measured, no expression of anti-ipilimumab antibodies was observed. Neutralizing antibodies were not measured.

PK parameters of ipilimumab following the initial dose

Dose (mg/kg)	C_{max} (μg/mL)	T_{max}[*1] (h)	AUC_{21d} (μg·h/mL)	$T_{1/2}$[*2] (day)	CL[*2] (mL/h)	V_{ss}[*2] (L)
3	72.8 (12)	2.8 (1.4, 4.1)	12,632 (12)	13.3 ± 3.6	12.1 ± 2.1	5.0 ± 0.9
10	201 (21)	4.0 (1.5, 23.8)	36,489 (21)	11.3 ± 2.8	14.8 ± 3.7	5.5 ± 1.2

Geometric mean (coefficient of variation, %); n = 6; [*1] median (range); [*2] arithmetic mean ± standard deviation

4.(ii).A.(2) Foreign phase I study (5.3.3.2.1: Study MDX010-15 [[redacted] to [redacted]])

An open-label study was conducted in 88 patients with unresectable malignant melanoma (78 included in PK analysis) to investigate the PK, etc. of ipilimumab. The dosage regimen was as follows: (a) intravenous ipilimumab produced by Process A at 3 mg/kg on Days 1, 57, and 85, (b) intravenous ipilimumab produced by Process B ([redacted]) at 2.8 or 5 mg/kg on Days 1, 57, and 85, (c) a single dose of intravenous ipilimumab produced by Process B ([redacted]) at 7.5, 10, 15, and 20 mg/kg, and (d) repeated intravenous ipilimumab produced by Process B ([redacted]) at 10 mg/kg every 3 weeks. Plasma ipilimumab concentrations were then assessed (see the table below).

Following the single-dose administration and the initial dose of repeated administration, C_{max} and AUC_{inf} of ipilimumab tended to show a less than dose-proportional increase within the investigated dose range (2.8-20 mg/kg). The applicant explained that the reason for this tendency was not clear. The accumulation indices of AUC_{21d} against the initial dose were 1.26 on Day 57 in the 2.8 mg/kg group, 1.49 on Day 57 in the 3 mg/kg group, 1.40 on Day 85 in the 5 mg/kg group, and 1.47 on Day 64 in the 10 mg/kg group.

PK parameters following a single dose of ipilimumab

Dose (mg/kg)	n	C_{max} (μg/mL)	T_{max}[*1] (h)	AUC_{21d} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$T_{1/2}$[*2] (day)	CL[*2] (mL/h)	V_{ss}[*2] (L)
7.5	6	292 (23.1)	2.0 (1.5, 2.5)	44,853 (22)	70,847 (19.4)	16.1 ± 6.7	8.9 ± 2.1	4.7 ± 1.1
10	7	300 (24.4)	2.0 (1.5, 7.0)	37,706 (24)	60,099 (43.0)	15.3 ± 8.3	15.7 ± 6.2	6.7 ± 2.3
15	6	440 (7.47)	3.3 (1.5, 22.0)	67,107 (11)	98,325 (22.8)	16.5 ± 6.0	13.6 ± 2.2	6.2 ± 1.9
20	11	533 (32.8)	3.0 (1.4, 5.5)	64,808 (23)	78,258 (46.4)	12.4 ± 8.3	21.9 ± 11.5	6.1 ± 1.8

Geometric mean (coefficient of variation, %), [*1] median (range), [*2] arithmetic mean ± standard deviation

PK parameters following repeated dosing of ipilimumab

Day of treatment	Dose (mg/kg)	n	C_{max} (μg/mL)	T_{max}[*1] (h)	AUC_{21d} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$T_{1/2}$[*2] (day)	CL[*2] (mL/h)	V_{ss}[*2] (L)
1	2.8	13	79.9 (23.6)	2.5 (1.5, 5.5)	12,081 (44)	19,583 (74.2)	16.0 ± 9.5	12.8 ± 6.8	5.5 ± 2.1
	3.0	12	84.5 (38.2)	1.75 (1.5, 4.0)	12,383 (32)	19,596 (67.7)	17.3 ± 11.0	13.8 ± 8.1	5.9 ± 1.6
	5.0	10	162 (27.9)	3.5 (1.5, 5.5)	26,875 (23)	42,337 (31.9)	16.0 ± 10.9	11.6 ± 5.2	5.4 ± 1.9
57	2.8	7	108 (38.3)	2.5 (1.3, 4.0)	15,206 (30)	–	11.3 ± 2.7[*3]	–	–
	3.0	5	103 (67.9)	3.0 (1.5, 24.0)	18,396 (33)	–	13.4 ± 9.4[*4]	–	–
	5.0	3	213 (59.9)	2.0 (1.7, 4.8)	32,136 (15)	–	11.8[*5]	–	–
64	10	13	441 (35.6)	2.5 (1.3, 48.0)	55,433 (36)	–	15.0 ± 9.4[*6]	–	–
85	2.8	4	257 (50.7)	2.3 (1.3, 4.0)	25,707 (42)	–	29.2, 19.8[*7]	–	–
	3.0	2	96.7, 184	2.5, 5.0	27,581[*5]	–	2.9, 18.6	–	–
	5.0	3	237 (32.0)	2.5 (1.6, 5.5)	37,670 (30)	–	17.6, 16.0[*7]	–	–

Geometric mean (coefficient of variation, %), - not calculated, [*1] median (range) (individual value when n = 1 or n = 2),
[*2] arithmetic mean ± standard deviation (individual value when n = 1 or n = 2), [*3] n = 6, [*4] n = 4, [*5] n = 1, [*6] n = 12, [*7] n = 2

4.(ii).A.(3) Foreign phase II study (5.3.3.2.3: Study CA184008 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 155 previously treated patients with unresectable malignant melanoma (5 included in PK analysis) to investigate the PK, etc. of ipilimumab. This study consisted of an induction period and a maintenance period. In the induction period, ipilimumab was intravenously administered at 10 mg/kg every 3 weeks. In the maintenance period, ipilimumab was intravenously administered at 10 mg/kg every 12 weeks. Serum ipilimumab concentrations were then assessed (see the table below).

The accumulation index of AUC_{21d} following the third dose against the initial dose was 1.46. Of 142 patients whose anti-ipilimumab antibodies were measured both at baseline and after administration, 1 patient (0.7%) tested positive for anti-ipilimumab antibodies after the administration of ipilimumab. All patients tested negative for neutralizing antibodies.

PK parameters of ipilimumab

Administration (n-th)	C_{max} (μg/mL)	T_{max}[*1] (h)	AUC_{21d} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$T_{1/2}$[*2] (day)	CL[*2] (mL/h)	V_{ss}[*2] (L)
1st	200 (16)	1.6 (1.6, 1.7)	36,110 (24)	45,547 (32)	8.9 ± 2.1	16.2 ± 3.1	5.0 ± 0.5
3rd	251 (24)	1.6 (1.5, 1.6)	52,713 (17)	–	16.9 ± 7.1	–	–

Geometric mean (coefficient of variation, %), n = 4, - not calculated, [*1] median (range),
[*2] arithmetic mean ± standard deviation

4.(ii).A.(4) Drug interactions

Foreign phase I study (5.3.4.2.3: Study CA184078 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label randomized study was conducted in 59 previously untreated patients with unresectable malignant melanoma (59 included in PK analysis) to investigate pharmacokinetic interactions between ipilimumab and PTX/CBDCA and between ipilimumab and dacarbazine (DTIC). The patients were treated in 3-week cycles with the following dosing regimen: (a) intravenous PTX 175 mg/m^2 and CBDCA (equivalent to AUC of 6 mg·min/mL) on Day 1 and ipilimumab 10 mg/kg on Day 3 of Cycle 1 and Day 1 of the subsequent cycles; (b) intravenous DTIC 850 mg/m^2 on Day 1 and ipilimumab 10 mg/kg on Day 3 of Cycle 1 and Day 1 of the subsequent cycles; and (c) intravenous ipilimumab 10 mg/kg on Day 1.

The following table shows the PK parameters of ipilimumab administered alone and in combination with other drugs. The geometric mean ratios (90% CI) of C_{max} and AUC_{21d} of ipilimumab plus PTX/CBDCA to those of ipilimumab alone were 0.93 (0.77, 1.14) and 0.87 (0.69, 1.09), respectively. The geometric mean ratios (90% CI) of C_{max} and AUC_{21d} of ipilimumab plus DTIC to those of ipilimumab alone were 0.98 (0.80, 1.21) and 0.92 (0.76, 1.11), respectively.

Anti-ipilimumab antibodies were measured in 56 patients (7.1%) at baseline and after the administration of ipilimumab. Of the 56 patients, 4 tested positive for anti-ipilimumab antibodies. All patients in whom neutralizing antibodies were measured tested negative for neutralizing antibodies.

PK parameters of ipilimumab

	n	C_{max} (μg/mL)	T_{max}[*1] (h)	AUC_{21d} (μg·h/mL)	$T_{1/2}$[*2] (day)	CL (mL/h)	V_{ss} (L)
Ipilimumab alone	12	251 (34)	1.6 (1.5, 4.0)	54,040 (28)	15.3 ± 4.6	10.2 (44)	5.1 (29)
Ipilimumab/PTX/CBDCA	14	235 (29)	1.5 (1.5, 24.0)	46,925 (36)	13.9 ± 7.5	11.6 (50)	5.1 (25)
Ipilimumab/DTIC	14	247 (35)	4.0 (1.5, 24.6)	49,569 (25)	13.4 ± 4.5	11.2 (34)	4.9 (21)

Geometric mean (coefficient of variation, %), [*1] median (range), [*2] mean ± standard deviation

The following table summarizes the PK parameters of PTX, DTIC, and the major metabolite of DTIC 5-aminoimidazole-4-carboxamide (AIC) following the administration of PTX or DTIC alone or in combination with ipilimumab. The kidneys are the main route of excretion of CBDCA (*Cancer Res*. 1984; 44: 1693-7, *Nagoya J Med Sci*. 2014; 76: 1-9) and ipilimumab is not expected to be excreted renally [see "4.(ii).A.(10) Effects of impaired renal function on the PK of ipilimumab"]. Based on these reports, the applicant considers that a pharmacokinetic interaction between ipilimumab and CBDCA is unlikely to occur, and therefore the PK of CBDCA was not investigated in the study.

The geometric mean ratios (90% CI) of C_{max} and AUC_{inf} of PTX in combination with ipilimumab to those of PTX in combination with CBDCA were 0.96 (0.79, 1.17) and 1.07 (0.95, 1.20), respectively. The geometric mean ratios (90% CI) of C_{max} and AUC_{inf} of DTIC in combination with ipilimumab to those of DTIC alone were 1.03 (0.85, 1.24) and 0.91 (0.76, 1.10), respectively. The geometric mean ratios (90% CI) of C_{max} and AUC_{inf} of AIC (following DTIC + ipilimumab) to those of AIC (following DTIC alone) were 1.06 (0.97, 1.15) and 0.97 (0.89, 1.06), respectively.

PK parameters of PTX, DTIC, and AIC

Substance	Measurement day (Day)	n	C_{max} (μg/mL)	T_{max}[*1] (h)	AUC_{inf} (μg·h/mL)	$T_{1/2}$[*2] (h)	CL (L/h)	V_{ss} (L)
PTX	1	20	3.4 (23)	3.0 (2.9, 4.3)	12.4 (24)	10.3 ± 1.6	27.9 (28)	–
	43[*3]	14	3.2 (26)	3.0 (1.5, 9.5)	13.4 (24)	10.4 ± 2.7	25.4 (26)	206 (31)
DTIC	1	19	18.2 (37)	1.0 (1.0, 2.8)[*4]	47.4 (68)	2.1 ± 0.9	34.3 (52)	–
	43[*3]	16	18.6 (30)	1.0 (1.0, 1.1)[*5]	41.1 (55)	2.1 ± 0.9	37.1 (49)	108 (31)
AIC	1	19	3.6 (36)	1.0 (1.0, 2.8)	17.7 (26)[*4]	2.2 ± 1.0[*4]	91.7 (28)	–
	43[*3]	17	4.0 (40)	1.0 (1.0, 2.5)[*6]	17.4 (36)[*6]	2.2 ± 0.8[*6]	88.8 (37)	343 (47)

Geometric mean (coefficient of variation, %); - not calculated, [*1] median (range), [*2] mean ± standard deviation,
[*3] concomitant use of ipilimumab, [*4] n = 18, [*5] n = 15, [*6] n = 16

The applicant explained that pharmacokinetic interactions between ipilimumab and PTX/CBDCA or DTIC is unlikely to occur.

4.(ii).A.(5) Relationship between ipilimumab exposure and changes in QT/QTc

A double-blind randomized study (Study CA184004) was conducted in 82 patients with unresectable malignant melanoma (79 included in PK analysis) to investigate the PK, etc. of ipilimumab. In the study, the effects of ipilimumab on QT/QTc intervals were assessed. Ipilimumab 3 or 10 mg/kg was intravenously administered every 3 weeks for 4 times in the induction period and every 12 weeks in the maintenance period.

The maximum change in QT interval corrected by Fridericia's formula (QTcF) from baseline (ΔQTcF) (90% CI) (msec) was 4.00 (- 4.12, 12.1) at 150 minutes postdose on Day 64 in the 3 mg/kg group and 4.68 (- 0.27, 9.64) at 90 minutes postdose in the 10 mg/kg group. QT intervals corrected by Bazett's formula (QTcB) showed prolongation exceeding 450 msec after the administration of ipilimumab in 2 of 34 patients in the 3 mg/kg group and 5 of 38 patients in the 10 mg/kg group, but the prolongation was Grade 1 in all patients. Of these 7 patients, only 1 patient in the 3 mg/kg group showed prolonged QTcF exceeding 450 msec following the administration of ipilimumab. None of the patients in the 3 mg/kg or 10 mg/kg group showed changes in QTcB from baseline exceeding 60 msec.

The applicant explained that intravenous administration of ipilimumab 3 or 10 mg/kg every 3 weeks should have no clinically problematic impact on QTc intervals.

4.(ii).A.(6) Population pharmacokinetic (PPK) analysis

A population pharmacokinetic (PPK) analysis using the nonlinear mixed-effects model (NONMEM ver. 7.1.2) was performed based on PK data of ipilimumab (785 subjects, 3,200 measurement time points) obtained from 6 studies: a foreign phase I study (Study CA184078), foreign phase II studies (Studies CA184004, CA184007, CA184008, and CA184022), and a foreign phase III study (Study CA184024). The PK of ipilimumab was described by a two-compartment model, including zero-order absorption and first-order elimination.

The following were considered as covariates for the clearance (CL) of ipilimumab: age, body weight, sex, lactate dehydrogenase (LDH), estimated glomerular filtration rate (eGFR), concomitant use of DTIC, the classification of hepatic function according to US National Cancer Institute Organ Dysfunction Working Group classification (NCI-ODWG), immunogenicity, Eastern Cooperative Oncology Group performance status (ECOG PS), and prior treatment with antineoplastic agents. Body weight and sex were considered as covariates for the distribution volume of the central compartment (VC). After all, sex, body weight, LDH, ECOG PS, and eGFR were selected as significant covariates for the CL of ipilimumab, and sex and body weight were selected as significant covariates for VC. The extent of the effects of these covariates on CL and VC of ipilimumab were investigated. The result suggested that body weight and LDH are clinically important predictors of CL and that body weight also serves as a clinically important predictor of VC.

The applicant's explanation on these analysis results:

- Because the CL and VC of ipilimumab were expected to increase with increasing body weight, it is considered appropriate to determine the dose of ipilimumab by body weight.
- In patients with LDH 5 times the upper limit of normal (ULN), the CL of ipilimumab was estimated to be 28.0% higher than that in patients with LDH within the range of historical data from the medical institution. Based on a finding on the relationship between ipilimumab exposure and overall survival (OS), when the increase rate of CL is estimated as 28% (corresponding to a decrease of approximately 6.5 μg/mL in $C_{min,ss}$ following ipilimumab 3 mg/kg therapy) [see "4.(ii).A.(8).1)

Relationship between exposure and efficacy"], the hazard ratio for OS would increase by approximately 0.067 with decreasing exposure to ipilimumab. However, when the range of hazard ratios (0.676-0.945) for OS calculated from $C_{min,ss}$ following ipilimumab 3 mg/kg therapy is considered, the increase in the hazard ratio is unlikely to pose any clinical issues.

The above PPK analysis also revealed dose proportionality in the PK of ipilimumab within the dose range from 0.3 to 10 mg/kg.

The applicant explained that, prior to the above PPK analysis, the effects of concomitant use of budesonide and human leukocyte antigen (HLA)-A2*0201 status on the PK of ipilimumab were assessed by another PPK analysis with PK data (498 subjects, 2,089 measurement time points) from 4 foreign phase II studies (Studies CA184004, CA184007, CA184008, and CA184022) using a nonlinear mixed-effects model (NONMEM ver. VI). Neither concomitant use of budesonide nor HLA-A2*0201 status were selected as significant covariates for the CL of ipilimumab.

4.(ii).A.(7) Pharmacodynamics

The effects of ipilimumab on T cell activation was investigated in Study CA184004. The proportion of activated T cells increased following the administration of ipilimumab in both the 3 and 10 mg/kg groups, with no clear difference between these groups. The effects of ipilimumab on T cell activation were also investigated by the presence or absence of prior treatment in patients in the 3 mg/kg group. The proportion of activated T cells increased following the administration of ipilimumab in both previously treated and previously untreated patients, with no clear difference between the two types of patients.

4.(ii).A.(8) Relationship between exposure and efficacy or safety

4.(ii).A.(8).1) Relationship between exposure and efficacy

The relationship between exposure to ipilimumab* ($C_{min,ss}$) and OS was evaluated based on the results of foreign phase II studies (Studies CA184004, CA184007, CA184008, and CA184022) and a foreign phase III study (Study CA184024). An association between the increase in $C_{min,ss}$ of ipilimumab and prolongation of OS was identified.

* The exposure was estimated from the final model of PPK analysis using the nonlinear mixed-effects model (NONMEM ver. 7.1.2) [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"].

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

The relationship between exposure to ipilimumab* ($C_{min,ss}$) and incidence of gastrointestinal, dermatological, and hepatobiliary immune-related adverse events ("irAEs" hereinafter) or incidence of all irAEs (gastrointestinal, dermatological, hepatobiliary, endocrine system, nervous system, or others) was evaluated based on the results of a foreign phase I study (Study CA184078), foreign phase II studies (Studies CA184004, CA184007, CA184008, and CA184022) and a foreign phase III study (Study CA184024). An association was identified between the increase in $C_{min,ss}$ of ipilimumab and the increase in incidence of Grades 2 to 3 and more severe irAEs.

* The exposure was estimated from the final model of PPK analysis using the nonlinear mixed-effects model (NONMEM ver. 7.1.2) [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"].

4.(ii).A.(9) Effects of impaired hepatic function on the PK of ipilimumab

No clinical study was conducted to investigate the PK of ipilimumab in patients with hepatic impairment.

The applicant explained that, based on the following viewpoints, impaired hepatic function was unlikely to affect the PK of ipilimumab.

- Because ipilimumab is expected to be eliminated through a pathway mediated by binding to the target antigen and a pathway independent of the target antigen, impaired hepatic function is unlikely to affect the elimination of ipilimumab.
- The effects of hepatic function[*1] on the PK of ipilimumab was assessed in the PPK analysis [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"]. The geometric means (90% CI) of CL (mL/h) of ipilimumab in 708 patients with normal hepatic function, 76 patients with mild hepatic impairment, and 1 patient with moderate hepatic impairment were 15.2 (15.1, 15.3), 17.3 (16.9, 17.8), and 20.7[*2], respectively. Because CL of ipilimumab in patients with mild hepatic impairment does not exhibit clear differences from CL in patients with normal hepatic function, mild hepatic impairment is unlikely to affect CL of ipilimumab. There was a difficulty evaluating patients with moderate hepatic impairment due to the limited number of such patients. Nevertheless, data from patients with mild hepatic impairment suggest that moderate hepatic impairment is also unlikely to affect the CL of ipilimumab.
- In the PPK analysis, hepatic function (classification of hepatic function by NCI-ODWG) was not selected as a covariate for PK parameters of ipilimumab [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"].

[*1] Hepatic function was classified into normal hepatic function (total bilirubin [TBI] ≤ ULN and aspartate aminotransferase [AST] ≤ ULN), mild hepatic impairment (ULN < TBI ≤ 1.5 × ULN or AST > ULN), moderate hepatic impairment (1.5 × ULN < TBI ≤ 3 × ULN), and severe hepatic impairment (3 × ULN < TBI).

[*2] Individual values

The applicant explained that ipilimumab must be carefully administered to patients with severe hepatic impairment[*] for reasons, including the following: (a) no clinical study results have been obtained for patients with severe hepatic impairment[*]; (b) hepatic disorders may be induced by ipilimumab. The applicant also explained that hepatic impairment is unlikely to be exacerbated by ipilimumab administration in patients with severe hepatic impairment based on the following result: Of 6 patients with moderate hepatic impairment enrolled in a foreign phase III study (Study MDX010-20), none experienced exacerbation of hepatic impairment following the administration of ipilimumab.

[*] Patients with AST ≥ 5 × ULN or alanine aminotransferase (ALT) ≥ 5 × ULN and TBI ≥ 3 × ULN at baseline

4.(ii).A.(10) Effects of impaired renal function on the PK of ipilimumab

No clinical study has examined the PK of ipilimumab in patients with impaired renal function.

The applicant explains that, because of the following discussion, the PK of ipilimumab is unlikely to be affected by impaired renal function.

- Because ipilimumab is expected to be eliminated through a pathway mediated by binding to the target antigen and a pathway independent of the target antigen, impaired renal function is unlikely to affect the elimination of ipilimumab.
- Ipilimumab is a polymer (molecular weight, approximately 150,000) and is considered not to be renally excreted.
- The effects of renal function* on the PK of ipilimumab were assessed in the PPK analysis [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"]. The geometric means (90% CI) of CL (mL/h) of ipilimumab in 350 patients with normal renal function, 349 patients with mild renal impairment, 82 patients with moderate renal impairment, and 4 patients with severe renal impairment were 16.3 (16.1, 16.6), 14.7 (14.6, 14.9), 14.4 (14.1, 14.8), and 14.2 (13.3, 15.2), respectively. Because CL of ipilimumab in patients with mild and moderate renal impairment is comparable to CL in patients with normal renal function, mild and moderate renal impairment is unlikely to affect CL of ipilimumab. There was a difficulty evaluating patients with severe renal impairment due to the limited number of such patients. Nevertheless, data from patients with mild and moderate renal impairment suggest that severe renal impairment is also unlikely to affect CL of ipilimumab.

  * Renal function was classified into normal renal function (eGFR $\geq$ 90 mL/min/1.73 m^2), mild renal impairment (60 $\leq$ eGFR < 90 mL/min/1.73 m^2), moderate renal impairment (30 $\leq$ eGFR < 60 mL/min/1.73 m^2), and severe renal impairment (15 $\leq$ eGFR < 30 mL/min/1.73 m^2).

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

4.(ii).B.(1) Difference in PK of ipilimumab between the Japanese and non-Japanese populations

The applicant's explanation on the differences in the PK of ipilimumab between the Japanese and non-Japanese populations:

The following table shows serum ipilimumab concentrations after the first and third dose of ipilimumab in a Japanese phase II study (Study CA184396) and in foreign phase II studies (Studies CA184004 and CA184022). In these studies, ipilimumab 3 mg/kg was repeatedly administered intravenously to patients with malignant melanoma. No clear difference was observed in serum ipilimumab concentrations between Japanese and non-Japanese patients.

Serum ipilimumab concentrations in repeated dosing of ipilimumab 3 mg/kg (μg/mL)

	First dose					Third dose		
	n	1.5 hours postdose	n	Before the second dose	n	1.5 hours postdose	n	Before the fourth dose
Japanese	20	62.4 ± 22.5	14	16.9 ± 4.3	16	81.5 ± 21.8	14	18.4 ± 5.6
Non-Japanese	80	61.4 ± 15.3	32	15.6 ± 9.1	26	71.2 ± 16.2	30	15.8 ± 9.2

Arithmetic mean ± standard deviation

A PPK analysis was performed using the model that was originally obtained from the PPK analysis based on the PK data of non-Japanese patients with malignant melanoma [see "4.(ii).A.(6) Population pharmacokinetic [PPK] analysis"] and was updated after being combined with the PK data (223 subjects, 1601 measurement time points) from a Japanese phase I study (Study CA184113), a Japanese phase II study (Study CA184396), and a foreign phase II study (Study CA184041). As a result, race was not selected as a significant covariate for CL and VC of ipilimumab. The following table shows PK

parameters following repeated intravenous administration of ipilimumab 3 mg/kg in Japanese and non-Japanese patients estimated using the final model. There is no clear difference in the PK of ipilimumab between Japanese and non-Japanese patients.

Estimated PK parameters following repeated dosing of ipilimumab 3 mg/kg

	n	$C_{max,ss}$ (μg/mL)	$C_{min,ss}$ (μg/mL)	$C_{avg,ss}$[*1] (μg/mL)	$A_{1/2}$[*2] (h)	$B_{1/2}$[*3] (day)	AUC_{ss} (mg·h/mL)	CL (L/h/kg)	V_{ss} (mL/kg)
Japanese	20	80.5 ± 19.8	21.4 ± 11.6	34.8 ± 13.0	27.8 ± 2.7	19.0 ± 6.8	17.5 ± 6.6	150 ± 50	82.0 ± 8.3
Non-Japanese	101	76.9 ± 20.2	19.4 ± 14.1	33.3 ± 16.0	31.4 ± 2.6	16.3 ± 6.1	16.8 ± 8.1	210 ± 90	94.3 ± 9.9

Arithmetic mean ± standard deviation, [*1] mean blood concentration in steady state, [*2] elimination half-life in distribution phase, [*3] elimination half-life in elimination phase

The PK of ipilimumab appears not to differ between the Japanese and non-Japanese populations.

PMDA's view:

The PK of ipilimumab administered at the proposed dosing regimen (3 mg/kg every 3 weeks for a total of 4 times) was compared only in terms of serum ipilimumab concentrations at 1.5 hours after the start of administration and serum trough concentrations. This precludes rigorous evaluation of differences in the PK of ipilimumab between the Japanese and non-Japanese populations. Nevertheless, the submitted data did not reveal the trend toward clear differences in the PK of ipilimumab between Japanese and non-Japanese patients.

4.(ii).B.(2) Effects of anti-ipilimumab antibodies on the PK and safety of ipilimumab

The percentage of patients who tested negative for anti-ipilimumab antibodies at baseline but tested positive following ipilimumab therapy was as follows: (a) 0% (0 of 511 patients) in the foreign phase III study (Study MDX010-20) by [redacted] assay; (b) 2.3% (19 of 830 patients) in foreign phase I studies (Studies CA184078 and CA184087), foreign phase II studies (Studies CA184004, CA184007, CA184008, and CA184022), and the foreign phase III study (Study CA184024) by [redacted] assay; and (c) 6.3% (2 of 32 patients) in the Japanese phase I study (Study CA184113) and the Japanese phase II study (Study CA184396) by [redacted] assay.

The applicant's explanation on the potential effects of ipilimumab in samples on measurements of anti-ipilimumab antibodies:

- [redacted] revealed that the upper limit of ipilimumab concentrations in samples that did not affect the measurement of anti-ipilimumab antibodies was 10 μg/mL. In foreign clinical studies, [redacted] showed that the median C_{min} in the induction period (ipilimumab 10 mg/kg therapy) was 50.2 μg/mL, which is higher than the said upper limit of 10 μg/mL. This does not exclude the possibility that ipilimumab in the samples may have affected the measurement of anti-ipilimumab antibodies.
- [redacted] revealed that the upper limit of ipilimumab concentrations in samples that did not affect the measurement of anti-ipilimumab antibodies was 75 μg/mL. In Japanese clinical studies, [redacted] showed that the maximum C_{min} in the induction period (ipilimumab 10 mg/kg therapy) was 50.0 μg/mL, which is lower than the said upper limit of 75 μg/mL. Therefore,

ipilimumab in the samples was unlikely to have affected the measurement of anti-ipilimumab antibodies.

The applicant also explained that anti-ipilimumab antibodies are unlikely to clearly affect the PK of ipilimumab based on the following findings:

- In Study CA184396, 2 patients* tested positive for anti-ipilimumab antibodies; serum ipilimumab concentrations at detection of anti-ipilimumab antibodies were 14.0 μg/mL (Day 43) and 13.9 μg/mL (Day 64) in one patient and 12.1 μg/mL (Day 22) in the other patient. In patients testing negative for anti-ipilimumab antibodies, the geometric means (coefficient of variation, %) of serum ipilimumab concentrations were 13.2 μg/mL (27%) on Day 22 (15 patients), 16.3 μg/mL (26%) on Day 43 (12 patients), and 17.9 μg/mL (32%) on Day 64 (12 patients). Thus, there were no clear differences in serum ipilimumab concentrations between patients positive and negative for anti-ipilimumab antibodies.
- The PPK analysis [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"] showed that the CL of ipilimumab in patients positive for anti-ipilimumab antibodies was 14% higher than that in patients negative for the antibodies. However, the difference was not statistically significant.

* The patients testing positive for anti-ipilimumab antibodies by the [redacted] assay were found only in Study CA184396.

The applicant's explanation:
Anti-ipilimumab antibodies are not considered to affect the safety of ipilimumab because the safety profiles did not differ substantially between the patients positive and negative for anti-ipilimumab antibodies, although the number of patients positive for the antibodies was limited in the clinical studies.

PMDA's view:
It is difficult to draw a conclusion regarding the effects of anti-ipilimumab antibodies on the PK and safety of ipilimumab based on the submitted clinical study results, due to the small number of patients testing positive for anti-ipilimumab antibodies. Information on the effects of anti-ipilimumab antibodies on the PK and safety of ipilimumab should be further collected, and any new findings should be appropriately provided to healthcare professionals.

4.(iii) Summary of clinical efficacy and safety

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

The applicant submitted evaluation data regarding the efficacy and safety (data from 6 studies: 1 Japanese phase I study, 1 Japanese phase II study, 3 foreign phase II studies, and 1 foreign phase III study) and reference data (data from 1 Japanese phase II study, 3 foreign phase I studies, 3 foreign phase II studies, 1 foreign phase III study, and 2 foreign observation studies).

List of clinical studies on efficacy and safety

Data category	Study region	Study title	Phase	Subjects	No. of enrolled subjects	Summary of dosing regimen	Main evaluation items
Evaluation	Japan	CA184113	I	Patients with advanced non-small-cell lung cancer	15	Induction period (the first 24 weeks): intravenous PTX 175 mg/m^2 + intravenous CBDCA at a dose corresponding to AUC of 6 mg·min/mL (Cycles 1-6) + ipilimumab 3 or 10 mg/kg (Cycles 3-6) on Day 1 of each 3-week cycle Maintenance period (after Week 24): intravenous ipilimumab 3 or 10 mg/kg on Day 1 of each 12-week cycle	Safety
	Japan	CA184396	II	Patients with unresectable malignant melanoma	26	Intravenous ipilimumab 3 mg/kg on Day 1 of each 3-week cycle (Cycles 1-4)	Efficacy Safety
	Foreign	CA184022	II	Previously treated patients with unresectable malignant melanoma	217[*1] (a) 73 (b) 72 (c) 72	Induction period (the first 24 weeks): intravenous ipilimumab (a) 0.3 mg/kg, (b) 3 mg/kg, or (c) 10 mg/kg on Day 1 of each 3-week cycle (Cycles 1-4) Maintenance period (after Week 24): intravenous ipilimumab (a) 0.3 mg/kg, (b) 3 mg/kg, or (c) 10 mg/kg on Day 1 of each 12-week cycle,	Efficacy Safety PK
	Foreign	CA184004	II	Patients with unresectable malignant melanoma	82[*1] (a) 40 (b) 42	Induction period (the first 24 weeks): intravenous ipilimumab (a) 3 mg/kg or (b) 10 mg/kg on Day 1 of each 3-week cycle (Cycles 1-4) Maintenance period (after Week 24): intravenous ipilimumab (a) 3 mg/kg or (b) 10 mg/kg on Day 1 of each 12-week cycle	Efficacy Safety
	Foreign	MDX010-08	II	Previously untreated patients with unresectable malignant melanoma	76[*1] (a) 40 (b) 36	In each 4-week cycle, intravenous administration of (a) ipilimumab 3 mg/kg on Day 1 (Cycles 1-4) or (b) ipilimumab 3 mg/kg on Day 1 (Cycles 1-4) + DTIC 250 mg/m^2 on Days 1 to 5 (Cycles 1-6)	Efficacy Safety
	Foreign	MDX010-20	III	Previously treated patients with unresectable malignant melanoma	676[*1] (a) 403 (b) 137 (c) 136	Ipilimumab, gp100[*2], or placebo at the following doses on Day 1 of each 3-week cycle (Cycles 1-4) (a) intravenous ipilimumab 3 mg/kg + subcutaneous gp100; (b) intravenous ipilimumab 3 mg/kg + subcutaneous placebo; or (c) intravenous placebo + subcutaneous gp100	Efficacy Safety
Reference	Japan	CA184202	II	Previously untreated patients with unresectable malignant melanoma	21	Induction period (the first 24 weeks): intravenous administratino of ipilimumab 10 mg/kg (Cycles 1-4) + DTIC 850 mg/m^2 (Cycles 1-8) on Day 1 of each 3-week cycle Maintenance period (after Week 24): intravenous ipilimumab 10 mg/kg on Day 1 of each 12-week cycle	Efficacy Safety
	Foreign	CA184087	I	Patients with unresectable malignant melanoma	99	Induction period (the first 12 weeks): intravenous ipilimumab 10 mg/kg (produced by Process B [[redacted]L] or Process C) on Day 1 of each 3-week cycle (Cycles 1-4) Maintenance period (after Week 12): intravenous ipilimumab 10 mg/kg (produced by Process B [[redacted]L] or Process C) on Day 1 of each 12-week cycle,	Safety PK
	Foreign	MDX010-15	I	Patients with unresectable malignant melanoma	90	(a) Intravenous ipilimumab 3 mg/kg (produced by Process A) or ipilimumab 2.8 or 5 mg/kg (produced by Process B) on Days 1, 57, and 85 (b) Single-dose intravenous ipilimumab 7.5, 10, 15, or 20 mg/kg (produced by Process B [[redacted]L]) (c) Intravenous ipilimumab 10 mg/kg (produced by Process B [[redacted]L]) on Day 1 of each 3-week cycle (Cycles 1-4)	Safety PK
	Foreign	CA184078	I	Previously untreated patients with unresectable malignant melanoma	72	Induction period (the first 24 weeks): in each 3-week cycle, intravenous PTX 175 mg/m^2 + intravenous CBDCA at a dose corresponding to AUC of 6 mg·min/mL on Day 1 (Cycles 1-8) + intravenous ipilimumab 10 mg/kg on Day 3 (Cycles 1-4) Maintenance period (after Week 24): intravenous ipilimumab 10 mg/kg on Day 1 of each 12-week cycle	Safety PK
	Foreign	CA184007	II	Patients with unresectable malignant melanoma	115[*1] (a) 58 (b) 57	Induction period (the first 24 weeks): intravenous ipilimumab 10 mg/kg (Cycles 1-4) + (a) oral budesonide or (b) oral placebo on Day 1 of each 3-week cycle Maintenance period (after Week 24): intravenous ipilimumab 10 mg/kg on Day 1 of each 12-week cycle	Efficacy Safety PK

Data category	Study region	Study title	Phase	Subjects	No. of enrolled subjects	Summary of dosing regimen	Main evaluation items
	Foreign	CA184008	II	Previously treated patients with unresectable malignant melanoma	226	Induction period (the first 24 weeks): intravenous ipilimumab 10 mg/kg on Day 1 of each 3-week cycle (Cycles 1-4) Maintenance period (after Week 24): intravenous ipilimumab 10 mg/kg on Day 1 of each 12-week cycle	Efficacy Safety PK
	Foreign	CA184041	II	Previously untreated patients with advanced lung cancer	334[*1] (a) 113 (b) 110 (c) 111	In each 3-week cycle, intravenous administration of (a), (b), or (c): (a) Ipilimumab 10 mg/kg (placebo from Cycle 4 onward) + PTX + CBDCA (Cycles 1-6) (b) Ipilimumab 10 mg/kg (placebo in Cycles 1-2) + PTX + CBDCA (Cycles 1-6) (c) Placebo + PTX + CBDCA (Cycles 1-6)	Efficacy Safety PK
	Foreign	CA184024	III	Previously untreated patients with unresectable malignant melanoma	502[*1] (a) 250 (b) 252	Induction period (the first 24 weeks): intravenous administration of DTIC 850 mg/m^2 (Cycles 1-8) + (a) ipilimumab 10 mg/kg (Cycles 1-4) or (b) placebo on Day 1 of each 3-week cycle Maintenance period (after Week 24): intravenous (a) ipilimumab 10 mg/kg or (b) placebo on Day 1 of each 12-week cycle	Efficacy Safety PK

PTX, paclitaxel; CBDCA, carboplatin; PK, pharmacokinetics; DTIC, dacarbazine; [*1] number of randomized patients; [*2] antigen peptide derived from malignant melanoma (not approved)

The clinical studies are summarized below.

Major adverse events other than death observed in the clinical studies are described in "4.(iv).A Adverse events, etc. observed in clinical studies." The results of studies related to PK, etc. are described in "4.(i) Summary of biopharmaceutical studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

4.(iii).A-1 Evaluation data

4.(iii).A-1.(1) Japanese clinical studies

4.(iii).A-1.(1).1) Japanese phase I study (5.3.5.2-2: Study CA184113 [[redacted] to [redacted]])

An open-label uncontrolled study was conducted in patients with advanced non-small cell lung cancer (target sample size, 3 to 6 patients per dose group) at 1 study site in Japan, to assess the safety, etc. of ipilimumab plus PTX/CBDCA.

On Day 1 of each 3-week cycle, PTX 175 mg/m^2 and CBDCA at a dose corresponding to AUC of 6 mg·min/kg (Cycles 1-6) were administered intravenously, and ipilimumab 3 or 10 mg/kg was administered intravenously over a period of 90 minutes (from Cycle 3 to 6) (the induction period, the first 24 weeks). After Week 24, on Day 1 of each 12-week cycle, ipilimumab was administered intravenously at the same dose as used in the induction period over a period of 90 minutes (the maintenance period).

All 15 enrolled patients were treated with the investigational products and included in the safety analysis.

No deaths were observed during the study period.

4.(iii).A-1.(1).2) Japanese phase II study (5.3.5.2-1: Study CA184396. ongoing since [redacted] 20[redacted], [data cutoff date, [redacted], 20[redacted]])

An open-label uncontrolled study was conducted in patients with unresectable malignant melanoma (target sample size, 18) at 6 study sites in Japan to assess the efficacy and safety of ipilimumab.

On Day 1 of each 3-week cycle, ipilimumab 3 mg/kg was administered over a period of 90 minutes (Cycles 1-4).

Of 26 patients enrolled in this study, 20 treated with ipilimumab were included in the Full Analysis Set (FAS) and subjected to the efficacy and safety analyses.

Some subjects were classified as responders by investigators according to the modified WHO criteria.*

A total of 5 subjects died during the treatment period or within 90 days after the last dose. The cause of death was disease progression in all patients.

* Criteria established by the applicant by modifying the WHO criteria (*Cancer.* 1981; 47: 207-14)

Definition

Measurable lesions	Lesions accurately measurable at 2 mutually orthogonal diameters. At least one diameter is ≥20 mm and the other ≥10 mm (or 10 mm × 10 mm by 5 mm-sclice thickness spiral CT). The lesion area is equal to maximum diameter multiplied by its orthogonal diameter.
Non-measurable lesions	Lesions accurately measurable in one dimension or small lesions (at least one diameter is <20 mm [or not 10 mm by spiral CT]), lesions developing at previously irradiated sites (excluding new lesions identified after the completion of radiation therapy), bone lesions, lesions in pia mater and meninges, ascites, pleural effusion, pericardial effusion, skin/pulmonary lymphangitis, histologically or cytologically uncofirmed abdominal mass being followed up by imaging, and cystic lesions
Target lesions	Of all measurable lesions, up to 5 lesions per organ, 10 lesions in total, are considered target lesions at screening. Up to 5 skin lesions are also considered target lesions. The sum of the product of diameters (SPD) of the target lesions, calculated at screening, is the baseline value.
Efficacy criteria	<u>Target lesions</u> CR: Complete elimination of all target lesions PR: ≥50% decrease in SPD from baseline SD: Other than CR, PR, and PD PD: ≥25% increase in SPD from the minimum measuremnt after baseline Unknown: Unmeasurable (including patients without measurable lesions) <u>Non-target lesions</u> CR: Complete elimination of all non-target lesions IR/PR: No change or changes with ≥ 1 remaining non-target lesion PD: Obviously exacerbated non-target lesions (excluding benign lesions due to a cause that has been identified radiographically and lesions with effusion that contains no malignant cells histologically) Unknown: Unmeasurable (due to unclear images, etc.)
New lesions	<u>New lesions</u> Absent: No clear new lesions developed. Present: At least 1 clear new lesion developed. Unknown: Unmeasurable (due to unclear images, etc.)
Overall response	Evaluated comprehensively based on target lesions, non-target lesions, and new lesions

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; IR, incomplete response

Evaluation of best overall response

Overall response before Week 12	Overall response at Week 12	Overall response after Week 12	Best overall response
CR†	Not considered	Not considered	CR
PR†	Other than CR†	Other than CR†	PR
	PR†	CR†	CR

	CR†	Not considered	CR
PD, SD, PR,†† CR,††or no data	CR†	Not considered	CR
	PR†	Other than CR†	PR
		CR†	CR
	SD, CR,†† or PR††	CR†	CR
		PR†	PR
		PD, SD, PR,†† CR,†† or no data	SD
SD, PR,†† CR,†† or no data	PD	Not considered	PD
PD	PD or no data	Not considered	PD

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
† PR or CR confirmed at the second tumor evaluation at ≥4 weeks after the first confirmation of CR or PR
†† PR or CR not confirmed at the second tumor evaluation at ≥4 weeks after the first confirmation of CR or PR

4.(iii).A-1.(2) Foreign clinical studies

4.(iii).A-1.(2).1) Foreign phase II study (5.3.3.2-4: Study CA184022 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, comparative study in previously treated patients with unresectable malignant melanoma (target sample size, 210) was conducted at 66 foreign study sites to assess the safety, etc. of ipilimumab.

On Day 1 of each 3-week cycle, ipilimumab was administered intravenously at 0.3, 3, or 10 mg/kg over a period of 90 minutes (Cycles 1-4) (the induction period, the first 24 weeks). After Week 24, on Day 1 of each 12-week cycle, ipilimumab was administered intravenously over a period of 90 minutes at the same dose as used during the induction period (the maintenance period).

In this study, 217 randomized patients (73 in the 0.3 mg/kg group, 72 in the 3 mg/kg group, and 72 in the 10 mg/kg group) were included in the intent-to-treat (ITT) population. Of the patients in the ITT population, 214 patients treated with ipilimumab (72 in the 0.3 mg/kg group, 71 in the 3 mg/kg group, and 71 in the 10 mg/kg group) were included in the safety analysis.

In total, 18 subjects in the 0.3 mg/kg group, 18 subjects in the 3 mg/kg group, and 19 subjects in the 10 mg/kg group died during the treatment period or within 70 days after the last dose. The primary cause of death was disease progression (in 16 subjects in the 0.3 mg/kg group, 15 subjects in the 3 mg/kg group, and 18 subjects in the 10 mg/kg group). Other causes of death were pulmonary embolism and unknown cause in 1 subject each in the 0.3 mg/kg group; acute myocardial infarction, respiratory tract infection, and unknown cause in 1 subject each in the 3 mg/kg group; and multiple organ failure in 1 subject in the 10 mg/kg group. A causal relationship to ipilimumab could not be ruled out for respiratory tract infection* in the 3 mg/kg group.

* A man aged 6[redacted] years: The patient experienced respiratory tract infection (Grade 3) on Day 42 after the start of treatment with ipilimumab (the last dose of ipilimumab was administered on Day 25) and was hospitalized. No neutropenia was observed. Despite antibiotic therapy, the patient died on Day 51 due to respiratory tract infection.

4.(iii).A-1.(2).2) Foreign phase II study (5.3.4.2-1: Study CA184004 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, comparative study in patients with unresectable malignant melanoma (target sample size, 80) was conducted at 14 study sites overseas to assess the safety, etc. of ipilimumab.

In each 3-week cycle, ipilimumab was administered intravenously at 3 or 10 mg/kg over a period of 90 minutes (Cycles 1-4) (the induction period, the first 24 weeks). After Week 24, on Day 1 of each 12-week cycle, ipilimumab was administered intravenously over a period of 90 minutes at the same dose as used during the induction period (the maintenance period).

In this study, all 82 randomized patients (40 in the 3 mg/kg group and 42 in the 10 mg/kg group) were treated with ipilimumab and included in the safety analysis.

Eight of 40 patients in the 3 mg/kg group and 8 of 42 patients in the 10 mg/kg group died during the treatment period or within 70 days after the last dose. The primary cause of death was disease progression (in 7 patients in the 3 mg/kg group and 6 patients in the 10 mg/kg group). Other causes of death were large intestine perforation in 1 patient in the 3 mg/kg group and sudden death and dyspnea in 1 patient in the 10 mg/kg group. A causal relationship to ipilimumab could not be ruled out for large intestine perforation* in 1 patient in the 3 mg/kg group.

* A man aged 6[redacted] years: The patient experienced diarrhoea (Grade 3) on Day 42 after the start of treatment with ipilimumab (the last dose of ipilimumab was administered on Day 21) and was hospitalized. The administration of steroids and fluid replacement, etc. were performed. Nonspecific colitis was observed in colonoscopy on Day 50. On Day 58, abdominal x-ray revealed perforation and a surgery was performed. The patient was given diagnoses of ulcerative/necrotizing pancolitis with large intestine perforation, fecal peritonitis, megacolon, and septic shock. The patient died due to intestinal perforation on Day 59.

4.(iii).A-1.(2).3) Foreign phase II study (5.3.5.1-2: Study MDX010-08 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, comparative study was conducted in previously untreated patients with unresectable malignant melanoma (target sample size, 46) at 12 institutions overseas to assess the safety, etc. of ipilimumab plus DTIC (ipilimumab/DTIC).

Each cycle consisted of 4 weeks. In the ipilimumab/DTIC group, ipilimumab was administered intravenously at 3 mg/kg over a period of 90 minutes on Day 1 (Cycles 1-4), and DTIC was administered intravenously at 250 mg/m^2 from Day 1 to Day 5 (Cycles 1-6). In the ipilimumab group, ipilimumab was administered intravenously at 3 mg/kg over a period of 90 minutes on Day 1 (Cycles 1-4).

In this study, 74 patients (35 in the ipilimumab/DTIC group and 39 in the ipilimumab group) were included in the safety analysis. This patient population consisted of 72 patients treated with ipilimumab (35 in the ipilimumab/DTIC group and 37 in the ipilimumab group) out of 76 randomized patients (36 in the ipilimumab/DTIC group and 40 in the ipilimumab group), and 2 patients who were not randomized due to ineligibility for the study but treated with ipilimumab in the compassionate use program.

Two subjects in the ipilimumab/DTIC group and 3 subjects in the ipilimumab group died during the treatment period or within 70 days after the last dose. The primary cause of death was disease progression (in 1 subject in the ipilimumab/DTIC group and 2 subjects in the ipilimumab group). Other causes of death were multiple organ failure*1 in 1 subject in the ipilimumab/DTIC group and pulmonary

embolism/sepsis[*2] in 1 subject in the ipilimumab group. For all these events, a causal relationship to the investigational products could not be ruled out.

[*1] A man aged 6[redacted] years: The patient experienced light-headedness, lethargy, and hypotension on Day 57 after the start of treatment with ipilimumab (the last dose of ipilimumab was administered on Day 57) and was hospitalized. Hepatic enzyme increased (a marked increase) and renal dysfunction were observed. Despite therapies with antibiotics, vasopressors, and other drugs, the patient died of multiple organ failure on Day 58.

[*2] A man aged 6[redacted] years: The patient experienced swelling of the both malleoli (Grade 2), hemoptysis (Grade 1), left chest pain and chest pressure (Grade 2) at 30 days after the start of treatment with ipilimumab (the last dose of ipilimumab was administered on Day 85) and was hospitalized. The patient had a diagnosis of pulmonary embolism after a detailed examination and was treated with anticoagulants and other drugs. He was found lying at home on Day 108 and eventually died of pulmonary embolism or sepsis.

4.(iii).A-1.(2).4) Foreign phase III study (5.3.5.1-1: Study MDX010-20 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, comparative study was conducted in previously treated[*1] patients with unresectable malignant melanoma[*2] (target sample size, 750) at 125 study sites overseas, to compare the efficacy and safety of ipilimumab plus gp100[*3] (the ipilimumab/gp100 group) versus placebo plus gp100 (the gp100 group).

In each 3-week cycles, ipilimumab 3 mg/kg or placebo was administered intravenously over a period of 90 minutes, followed immediately by subcutaneous gp100 or placebo.[*4] The treatment was continued for 4 cycles (the induction period). Patients who responded to the treatment in the induction period[*5] and tolerated the treatment were allowed to receive the same investigational products as used in the induction period to treat increased tumors (re-treatment).

In this study, 676 randomized patients (403 in the ipilimumab/gp100 group, 137 in the ipilimumab/placebo group [ipilimumab group], and 136 in the gp100 group) were included in the ITT population and subjected to the efficacy analysis. Of the patients in the ITT population, 643 patients treated with the investigational products (380 in the ipilimumab/gp100 group,[*6] 131 in the ipilimumab group, and 132 in the gp100 group[*6]) were included in the safety analysis.

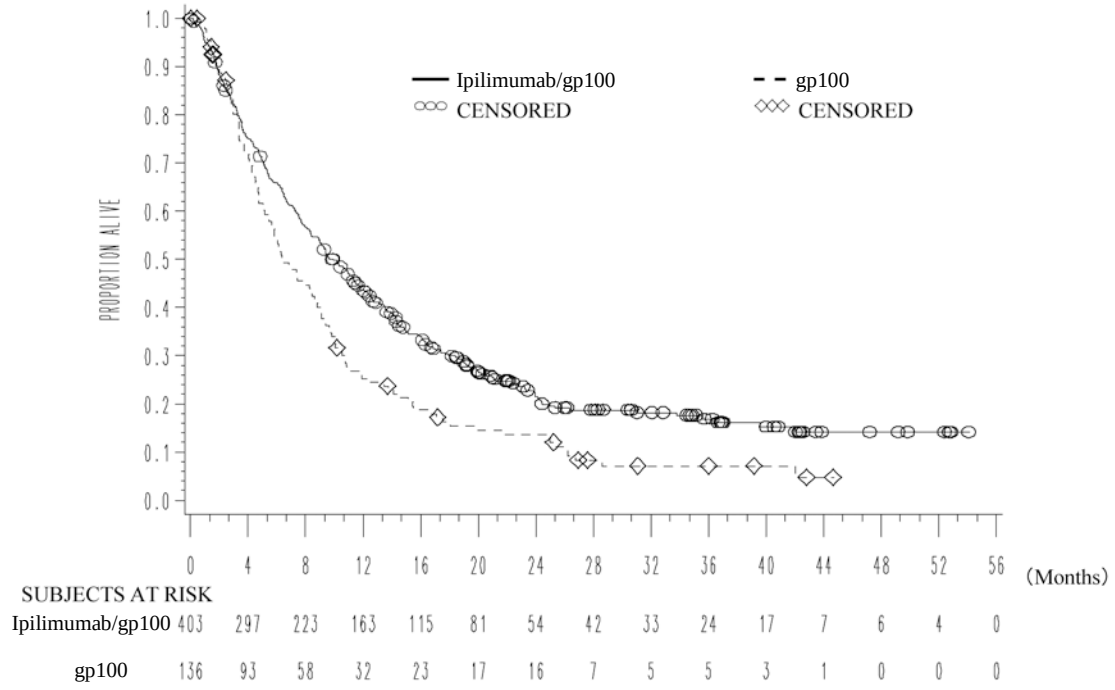
The response rate according to the modified WHO criteria (assessed by investigators) was defined as the primary endpoint at the beginning of the study. The primary endpoint, however, was later changed to OS, mainly because (a) the European Medicines Agency (EMA) advised the sponsor to do so, and (b) ipilimumab showed limited therapeutic effects (based on the response rates following the administration of ipilimumab) in the ongoing foreign phase II studies (Studies CA184004, CA184022, etc.). At the beginning of this study, the primary analyses were defined as (i) the verification of the superiority of the ipilimumab/gp100 group to the gp100 group, and (ii) the verification of the superiority of the ipilimumab/gp100 group to the ipilimumab group (performed only when the superiority in the verification (i) had been demonstrated). Subsequently, however, the verification (ii) was changed from a primary analysis to the secondary analysis, so that the primary analysis included the verification (i) alone. In order to change the primary endpoint from response rate to OS, the protocol was revised on [redacted], 20[redacted] before unblinding and database lock.

The following table and figure show OS and Kaplan-Meier curves for efficacy.

OS (ITT population, data cut off on [redacted], 20[redacted]

	Ipilimumab/gp100	gp100
Number of subjects	403	136
Number of deaths (%)	306 (76.0)	119 (87.5)
Median [95%CI] (months)	9.95 [8.48, 11.50]	6.44 [5.49, 8.71]
Hazard ratio [95%CI][*1]	0.68 [0.55, 0.85]	
p value (two-sided)[*2]	0.0004	

CI, confidence interval; [*1] Cox proportional hazards model adjusted for stratification factors (M classification, the presence or absence of previous treatment with IL-2); [*2] stratified log-rank test (stratified by M classification and the presence or absence of previous treatment with IL-2), two-sided significance level, 0.05



Kaplan-Meier OS curves (ITT population, data cutoff date, [redacted], 20[redacted])

In total, 83 subjects in the ipilimumab/gp100 group, 27 subjects in the ipilimumab group, and 36 subjects in the gp100 group died during the treatment period or within 70 days after the last dose. The primary cause of death was disease progression (in 76 subjects in the ipilimumab/gp100 group, 22 subjects in the ipilimumab group, and 34 subjects in the gp100 group). Other causes of death were sepsis, gastrointestinal perforation/colitis/septic shock, respiratory failure, acute respiratory distress syndrome, cardiopulmonary failure, diarrhoea/multiple organ failure/peritonitis, and Guillain-Barre syndrome in 1 subject each in the ipilimumab/gp100 group; liver failure, coronary artery disease, sepsis, angiopathy and unknown cause in 1 subject each in the ipilimumab group; and pleural effusion and septic shock in 1 subject each in the gp100 group. A causal relationship to the investigational products could not be ruled out for sepsis,[*7] gastrointestinal perforation/colitis/septic shock, acute respiratory distress syndrome, diarrhoea/multiple organ failure/peritonitis, and Guillain-Barre syndrome in 1 subject each in the ipilimumab/gp100 group; for liver failure and angiopathy[*8] in 1 subject each in the ipilimumab group; and for septic shock in 1 subject in the gp100 group.

[*1] Treatment including IL-2, DTIC, temozolomide, fotemustine (not approved in Japan), or CBDCA.
[*2] Only HLA-A2*0201-positive patients were included.

*3 gp100, antigen peptides derived from malignant melanoma, consists of (a) peptide 209-217 (201M) with a threonine-to-methionine substitution at the second residue of amino acid residues 209 to 217 and (b) peptide 280-288 (288V) with an alanine-to-valine substitution at the ninth residue of amino acid residues 280 to 288. gp100 has not been approved.

*4 Patients treated with intravenous ipilimumab received subcutaneous gp100 or placebo. Patients who received intravenous placebo was treated with subcutaneous gp100.

*5 Rated as SD (stable period, ≥3 months from Week 12) or PR or CR in tumor evaluation in the induction period

*6 One patient assigned to the ipilimumab/gp100 group actually received gp100 alone. This patient was included in the gp100 group for safety analysis.

*7 A man aged 4[redacted] years: The patient experienced bronchitis (Grade 3) on Day 19 after the start of treatment with ipilimumab and gp100 and was treated with antibiotics. Dyspnea, tachypnea, sweating, confusion, and metabolic acidosis (Grade 4) were observed on Day 21, and the patient was treated with intravenous fluid and oxygen. A blood culture was positive for methicillin-resistant *Staphylococcus aureus*. The patient had a diagnosis of pneumonia (Grade 3) accompanied by sepsis (Grade 5), and died on Day 22.

*8 A man aged 5[redacted] years: The patient experienced exacerbated dyspnea (Grade 3) and exacerbated oedema (Grade 3) on Day 7 after the start of treatment with ipilimumab and was hospitalized. A CT scan performed on the same day showed bilateral pleural effusion and pericardial effusion. The patient was given a diagnosis of vascular leak syndrome. Despite treatment with diuretics and other drugs, exacerbated dyspnea (Grade 4) was observed on Day 19, and the patient died of angiopathy on Day 20.

4.(iii).A-2. Reference data

4.(iii).A-2.(1) Clinical pharmacology studies

4.(iii).A-2.(1).1) Foreign phase I study (5.3.1.2-1: Study CA184087 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, comparative study was conducted in patients with unresectable malignant melanoma (target sample size, 62) at 7 study sites overseas to investigate the PK and safety, etc. of ipilimumab.

Of the 99 patients enrolled in this study, 75 were treated with ipilimumab and included in the safety analysis.

In total, 12 patients died during the treatment period or within 70 days after the last dose. The causes of the deaths were disease progression in 10 patients, respiratory failure in 1 patient, and respiratory failure/pneumonia in 1 patient. A causal relationship to ipilimumab was ruled out for all these causative events.

4.(iii).A-2.(1).2) Foreign phase I study (5.3.3.2-1: Study MDX010-15 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in patients with unresectable malignant melanoma (target sample size, 90) at 5 study sites overseas to investigate the PK and safety, etc. of ipilimumab.

Of the 90 patients enrolled in this study, 88 were treated with ipilimumab and included in the safety analysis.

Four patients died during the study period or within 70 days after the last dose. The causes of the deaths were disease progression in 3 patients and cardiac arrest in 1 patient. In all patients, a causal relationship to ipilimumab was ruled out.

4.(iii).A-2.(1).3) Foreign phase I study (5.3.4.2-3: Study CA184078 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized open-label study was conducted in previously untreated patients with unresectable malignant melanoma (target sample size, 48) at 4 study sites overseas to investigate the pharmacokinetic interactions, etc. of ipilimumab with PTX/CBDCA or DTIC.

Of the 72 patients enrolled in this study, 59 (20 in the ipilimumab/PTX/CBDCA group, 19 in the ipilimumab/DTIC group, and 20 in the ipilimumab group) were treated with the investigational products and included in the safety analysis.

Four patients in the ipilimumab/PTX/CBDCA group died during the study period or within 70 days after the last dose. The causes of deaths were disease progression in 3 patients and cardiac arrest/progression of malignant neoplasm in 1 patient. In all patients, a causal relationship to the investigational products was ruled out.

4.(iii).A-2.(1).4) Foreign phase II study (5.3.3.2-2: Study CA184007 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, comparative study was conducted in patients with unresectable malignant melanoma (target sample size, 100) at 11 study sites overseas to compare the safety, etc. of ipilimumab plus budesonide versus ipilimumab monotherapy.

In this study, all 115 randomized patients (58 in the ipilimumab/budesonide group and 57 in the ipilimumab/placebo group) were treated with the investigational products and included in the safety analysis.

Eight patients in the ipilimumab/budesonide group and 11 patients in the ipilimumab/placebo group died during the study period or within 70 days after the last dose. The primary cause of death was disease progression (in 6 patients in the ipilimumab/budesonide group and 9 patients in the ipilimumab/placebo group). Other causes of death were arrhythmia and lobar pneumonia in 1 patient each in the ipilimumab/budesonide group and cardiac arrest and pneumonia aspiration in 1 patient each in the ipilimumab/placebo group. In all patients, a causal relationship to ipilimumab was ruled out.

4.(iii).A-2.(2) Japanese clinical studies

Japanese phase II study (5.3.5.2-3: Study CA184202 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in previously untreated patients with unresectable malignant melanoma (target sample size, 26) at 6 study sites in Japan to investigate the efficacy and safety of ipilimumab 10 mg/kg plus DTIC.

Of the 21 patients enrolled in this study, 15 were treated with the investigational products and included in the safety analysis.

No deaths were reported during the study period or within 90 days after the last dose.

AST increased and ALT increased (Grade ≥3) were observed in 10 of 15 patients treated with the investigational products. The combination therapy was therefore not considered tolerable and the study was discontinued.

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

4.(iii).A-2.(3).1) Foreign phase II study (5.3.3.2-3: Study CA184008 [[redacted] to [redacted]])

An open-label uncontrolled study was conducted in previously treated* patients with unresectable malignant melanoma (target sample size, 150) at 50 study sites overseas to assess the safety and other aspects of ipilimumab.

Of 226 patients enrolled in this study, 155 were treated with ipilimumab and included in the safety analysis.

In total, 33 of 155 patients died during the treatment period or within 70 days after the last dose. The causes of deaths were disease progression in 28 patients, and acute glomerulonephritis, abnormal hepatic function, cerebral ischemia, left ventricular dysfunction, and unknown cause in 1 patient each. A causal relationship to the investigational product could not be ruled out for acute glomerulonephritis and abnormal hepatic function in 1 patient each.

* Treatment including IL-2, DTIC, temozolomide, fotemustine (not approved in Japan), CBDCA, or PTX

4.(iii).A-2.(3).2) Foreign phase II study (5.3.5.4-1: Study CA184041 [[redacted] to [redacted]])

A randomized, double-blind, comparative study was conducted in patients with unresectable lung cancer (target sample size, 330) at 61 study sites overseas to compare the safety and efficacy of the combination of ipilimumab, PTX, and CBDCA versus the combination of PTX and CBDCA.

In this study, 334 patients were randomized (113 in the group treated with 4 doses of ipilimumab, PTX, and CBDCA followed by 2 doses of placebo, PTX, and CBDCA [the simultaneous treatment group], 110 in the group treated with 2 doses of placebo, PTX, and CBDCA followed by 4 doses of ipilimumab, PTX, and CBDCA [the sequential treatment group], and 111 in the group treated with 6 doses of placebo, PTX, and CBDCA [the control group]). In total, 331 patients treated with the investigational products (113 in the simultaneous treatment group, 109 in the sequential treatment group, and 109 in the control group) were included in the safety analysis.

In total, 34 patients in the simultaneous treatment group, 23 patients in the sequential treatment group, and 26 patients in the control group died during the treatment period or within 70 days after the last dose. The primary cause of death was disease progression (in 25 in the simultaneous treatment group, 17* in the sequential treatment group, and 23 in the control group). Other causes of death were drowning, septic shock/chronic obstructive lung disease/progression of malignant neoplasm/acidosis, cerebral haemorrhage, ileal perforation, septic shock/toxic epidermal necrolysis, haemoptysis, pulmonary haemorrhage, cardiac failure/hepatotoxicity, and unknown cause in 1 patient each in the simultaneous

treatment group; unknown cause in 2 patients and cardiopulmonary arrest, cardiopulmonary arrest/erysipelas, respiratory tract infection,* cardiogenic shock, and cachexia/malignant neoplasm of the lung in 1 patient each in the sequential treatment group; and pulmonary haemorrhage, febrile neutropenia/hyponatraemia/hypotension, and unknown cause in 1 patient each in the control group. A causal relationship to the investigational products could not be ruled out for septic shock/toxic epidermal necrolysis, and hepatotoxicity in 1 patient each in the simultaneous treatment group, erysipelas in 1 patient in the sequential treatment group, and pulmonary haemorrhage and febrile neutropenia/hypotension in 1 patient each in the control group.

* The causes of death of 1 patient were disease progression and respiratory tract infection.

4.(iii).A-2.(3).3) Foreign phase III study (5.3.5.1-5: Study CA184024 [20 to 20])

A randomized, double-blind, comparative study was conducted in previously untreated patients with unresectable malignant melanoma (target sample size, 500) at 111 study sites overseas to compare the safety, etc. of ipilimumab plus DTIC versus DTIC monotherapy.

In this study, 502 patients were randomized (250 in the ipilimumab/DTIC group and 252 in the DTIC group), and 498 patients treated with the investigational products (247 in the ipilimumab/DTIC group and 251 in the DTIC group) were included in the safety analysis.

In total, 40 patients in the ipilimumab/DTIC group and 62 patients in the DTIC group died during the treatment period or within 70 days after the last dose. The primary cause of death was disease progression (36 in the ipilimumab/DTIC group and 56 in the DTIC group). Other causes of death were acute myocardial infarction, septic shock/pneumonia/metastatic malignant melanoma/systemic inflammatory response syndrome, coronary arteriosclerosis, and respiratory failure in 1 patient each in the ipilimumab/DTIC group and suicide, pulmonary embolism, cerebral ischaemia, cardiopulmonary arrest/progression of malignant neoplasm, cardiopulmonary failure, and gastrointestinal haemorrhage in 1 patient each in the DTIC group. A causal relationship to the investigational products could not be ruled out for systemic inflammatory response syndrome in the ipilimumab/DTIC group and gastrointestinal haemorrhage in the DTIC group.

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

4.(iii).B.(1) Review policy

PMDA considers that the foreign phase III study (Study MDX010-20) is the most important data among the submitted evaluation data for evaluating the efficacy and safety of ipilimumab in previously treated patients with unresectable malignant melanoma. PMDA therefore decided to primarily evaluate this study.

PMDA also decided to evaluate the efficacy and safety of ipilimumab in the Japanese population primarily focusing on the Japanese phase II study (Study CA184396) involving patients with unresectable malignant melanoma.

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

As a result of the following investigation, PMDA concluded that ipilimumab had demonstrated a certain level of efficacy in previously treated patients with unresectable malignant melanoma.

4.(iii).B.(2).1) Design of Study MDX010-20

PMDA considers that OS is the appropriate primary efficacy endpoint of Study MDX010-20.

PMDA asked the applicant the reasons for using gp100 (not approved) as control and for planning the verification of superiority of ipilimumab/gp100 over gp100 alone in Study MDX010-20.

The applicant's response:

As of 2004, when Study MDX010-20 started, no standard therapy had been established for previously treated unresectable malignant melanoma. Because of extremely poor prognosis of the disease, treatment with the investigational product was considered a therapeutic option.

The applicant expected that gp100 would induce antitumor immune response and ipilimumab administered in combination with gp100 would inhibit CTLA-4, resulting in the activation of T cells, which are suppressed by CTLA-4. This mechanism of action would allow clinically adequate antitumor immune response. The reasons are presented below:

- Gp100 (not approved), an antigen peptide derived from malignant melanoma, has been reported to increase T progenitor cells, induce effector T cell reactions, and cause other changes (*J Immunol.* 1999; 163: 6292-300, *J Clin Oncol. 2003.* 21: 1562-73, etc.).
- Ipilimumab is expected to inhibit the binding of CTLA-4 on T cells to B7.1 and B7.2 on antigen presenting cells and thereby promote antitumor T cell immune responses, resulting in the inhibition of tumor growth [see "*3.(i).B Outline of the review by PMDA*, Efficacy of ipilimumab against malignant melanoma"].
- The response rate calculated from the results of clinical studies (in a total of 381 patients) of various antigen peptides (including gp100) conducted by the US National Cancer Institute was 2.9%. The response rate in 100 patients treated with gp100 was 2.0%. It was concluded that antigen peptides exhibit immunogenicity, but the clinical effects of gp100 monotherapy are inadequate, requiring other concomitant immunotherapies (*Nat Med.* 2004; 10: 909-15, etc.).
- The response rate in patients treated with ipilimumab/gp100 in a foreign phase II study (Study MDX010-05) was 12.5% (7 or 56 patients) (*J Clin Oncol.* 2005; 23: 6043-53).

Thus, Study MDX010-20 was planned to evaluate the superiority of ipilimumab/gp100 (i.e. gp100 plus ipilimumab, a drug inducing T cell activation) to gp100, an active control agent expected to induce antitumor immune responses but with inadequate clinical efficacy in monotherapy.

PMDA's view:

In Study MDX010-20, the primary analysis demonstrated that ipilimumab/gp100 was superior in OS to gp100. However, gp100 is yet to be approved for previously treated unresectable malignant melanoma, and its clinical positioning is unclear. Study MDX010-20 thus provides only limited data for evaluating the efficacy of ipilimumab monotherapy, the proposed dosing regimen [see "4.(iii).B.(5) Dosage and administration"].

In addition, multiplicity adjustment was not performed in the comparison between the ipilimumab group and the gp100 group [see "4.(iii).B.(2).2) Results of efficacy evaluation"]. Therefore, the results of Study MDX010-20 alone are not sufficient to demonstrate the superiority of ipilimumab to gp100.

Despite these issues, PMDA decided to comprehensively evaluate the efficacy of ipilimumab monotherapy based mainly on the results of Study MDX010-20, considering the rationale for selecting gp100 as control and the fact that Study MDX010-20 was a randomized comparative study with the primary endpoint of OS. Further, the effect of gp100 on the survival of patients with unresectable malignant melanoma and the OS results in each treatment group of Study MDX010-20 are to be examined.

4.(iii).B.(2).2) Results of efficacy evaluation

The applicant's explanation on the efficacy of ipilimumab based on data including the results of Study MDX010-20:

Study MDX010-20 showed that ipilimumab/gp100 was superior to gp100 in OS, the primary endpoint [see "4.(iii).A-1.(2).4) Foreign phase III study"]. The following tables and figure show the results of OS and the Kaplan-Meier curves in secondary analysis, demonstrating the superiority of ipilimumab to gp100. No clear differences were observed between the ipilimumab group and the ipilimumab/gp100 group. Thus, ipilimumab monotherapy can be expected to prolong OS.

OS results in secondary analysis (ipilimumab versus gp100)
(ITT population, data cutoff on [redacted])

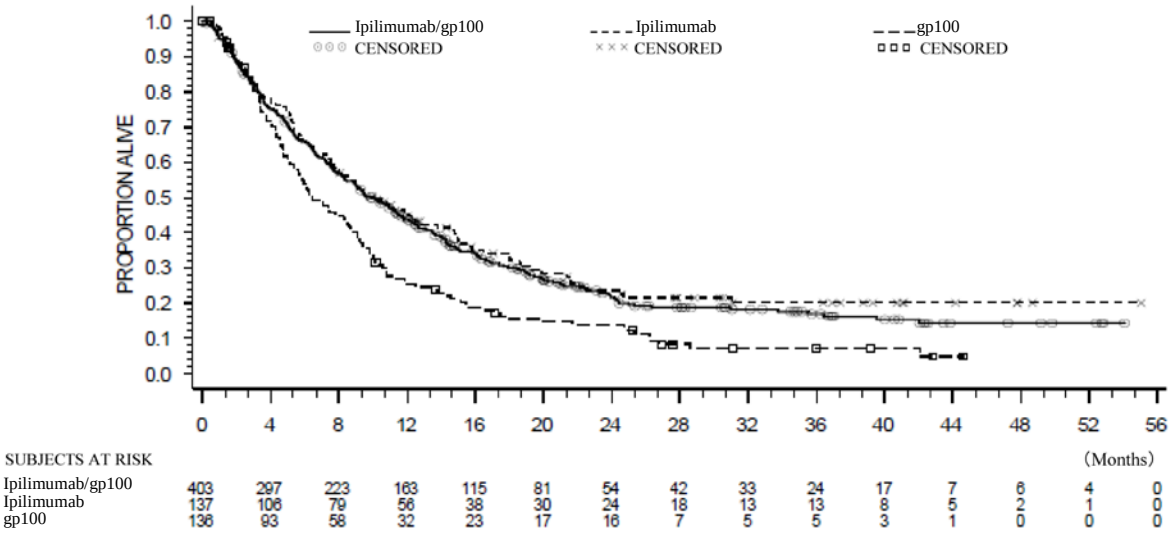
	Ipilimumab	gp100
Number of subjects	137	136
Number of deaths (%)	100 (73.0)	119 (87.5)
Median [95%CI] (months)	10.12 [8.02, 13.80]	6.44 [5.49, 8.71]
Hazard ratio [95%CI][*1]	0.66 [0.51, 0.87]	
p value (two-sided)[*2]	0.0026	

CI, confidence interval; [*1] Cox proportional hazards model adjusted for stratification factors (M classification, presence or absence of previous treatment with IL-2); [*2] stratified log-rank test (stratified by M classification and presence or absence of previous treatment with IL-2)

OS results in secondary analysis (ipilimumab/gp100 versus ipilimumab)
(ITT population, data cutoff on [redacted], 20[redacted])

	Ipilimumab/gp100	Ipilimumab
Number of subjects	403	137
Number of deaths (%)	306 (75.9)	100 (73.0)
Median [95%CI] (months)	9.95 [8.48, 11.50]	10.12 [8.02, 13.80]
Hazard ratio [95%CI][*1]	1.04 [0.83, 1.30]	
p value (two-sided)[*2]	0.7575	

CI, confidence interval; [*1] Cox proportional hazards model adjusted for stratification factors (M classification, presence or absence of previous treatment with IL-2); [*2] stratified log-rank test (stratified by M classification and presence or absence of previous treatment with IL-2)



Kaplan-Meier OS curves in secondary analysis (ITT population, data cutoff on [redacted], 20[redacted])

Furthermore, the effect of gp100 on OS in patients with unresectable malignant melanoma was investigated using a predictive model of OS (*J Clin Oncol.* 2008; 26: 527-34), proposed based on data from individual patients in 42 phase II studies of antineoplastic agents conducted from 1975 to 2005 in patients with unresectable malignant melanoma. The results of OS estimated from data for individual patients in the gp100 group of Study MDX010-20 were similar to results observed in the actual clinical studies. To confirm the usability of the predictive model of OS, the model was applied to published data from a pooled analysis of 7 randomized comparative studies in patients with unresectable malignant melanoma for efficacy evaluations of DTIC, etc. and 8 phase II studies of IL-2. (These data were not used to build the model.) These studies were conducted from 1985 to 2006. The results showed that the predicted survival curve did not differ significantly from the survival curves observed in individual studies. This suggests that the administration of gp100 is unlikely to adversely affect OS in patients with unresectable malignant melanoma. The median OS (95%CI) based on a meta-analysis of 42 studies was 6.2 (5.9, 6.5) months.

PMDA's view:

PMDA does not consider that Study MDX010-20 has demonstrated the superiority of ipilimumab to gp100 in OS, for reasons including that the comparison between the ipilimumab and gp100 groups was

not adjusted for multiplicity. However, PMDA considers ipilimumab monotherapy has demonstrated a certain efficacy in patients with previously treated unresectable malignant melanoma, for the following reasons:

- The ipilimumab/gp100 group was shown to be superior to the gp100 group in OS.
- The ipilimumab group tended to exhibit longer OS than the gp100 group.
- No clear difference was observed in OS between the ipilimumab/gp100 group and ipilimumab groups.
- Given the discussion, etc. based on the results of past clinical studies conducted by the applicant, gp100 is unlikely to adversely affect OS in patients with unresectable malignant melanoma.

4.(iii).B.(2).3) Efficacy in Japanese patients

The table below presents response rates assessed by investigators according to the modified WHO criteria in Studies CA184396 and MDX010-20.

Best overall response and response rate by modified WHO criteria (ITT population, data cutoff on [redacted])

Best overall response	Study CA184396[*1]		Study MDX010-20[*2]
	Ipilimumab 20 subjects	Ipilimumab/gp100 403 subjects	Ipilimumab 137 subjects
Complete response (CR)	0	1 (0.2)	2 (1.5)
Partial response (PR)	2 (10.0)	22 (5.5)	13 (9.5)
Stable disease (SD)	2 (10.0)	58 (14.4)	24 (17.5)
Progressive disease (PD)	13 (65.0)	239 (59.3)	70 (51.1)
Unknown	3 (15.0)	83 (20.6)	28 (20.4)
Response rate (CR + PR) [95%CI] (%)	10.0 [1.2, 31.7]	5.7 [3.7, 8.4]	10.9 [6.3, 17.4]

CI, confidence interval; *[1] assessment by investigators, FAS, data cutoff on [redacted]; *[2] assessment by investigators

PMDA's view:

Response rates in the Japanese population have not been fully evaluated because of the small number of Japanese patients examined in the clinical studies. Nevertheless, ipilimumab can be expected to be effective in the Japanese population, because some Japanese patients responded to ipilimumab in the clinical studies and for other reasons.

4.(iii).B.(3) Safety [for adverse events, see "4.(iv).A Adverse events, etc. observed in clinical studies"]

Based on the investigations summarized in 4.(iii).B.(3).1) to 10) sections, PMDA considers attention should be paid to the following adverse events during treatment with ipilimumab: diarrhoea, colitis, gastrointestinal perforation, skin disorders, hepatic disorders, hypophysitis, hypopituitarism, hypothyroidism, adrenal insufficiency, peripheral neuropathy, renal disorders, interstitial lung disease (ILD), infusion reactions. Patients should be monitored for these events during treatment with ipilimumab.

However, PMDA considers that the use of ipilimumab is allowed as long as appropriate actions (e.g., monitoring and management of adverse events, the suspension of ipilimumab therapy) are taken by a

physician with expertise and experience in cancer chemotherapy. Because of extremely limited experience in the use of ipilimumab in Japanese patients, further information should be gathered in the post-marketing settings, and new findings on safety should be provided to healthcare professionals in an appropriate manner.

4.(iii).B.(3).1) Safety profile of ipilimumab

The applicant's explanation on the safety profile of ipilimumab:

The following table summarizes the safety issues in Studies MDX010-20 and CA184396.

Summary of safety

	Number of subjects (%)			
	Study CA184396	Study MDX010-20		
	20 subjects	Ipilimumab/gp100 380 subjects	Ipilimumab 131 subjects	gp100 132 subjects
All adverse events	20 (100)	374 (98.4)	127 (96.9)	128 (97.0)
Grade ≥3 adverse events	11 (55.0)	193 (50.8)	72 (55.0)	69 (52.3)
Deaths due to causes other than disease progression	0	7 (1.8)	4 (3.1)	2 (1.5)
Serious adverse events	11 (55.0)	155 (40.8)	55 (42.0)	52 (39.4)
Adverse events leading to the discontinuation of administration	1 (5.0)	34 (8.9)	17 (13.0)	5 (3.8)
Adverse events leading to the suspension of administration*	4 (20.0)	18 (4.7)	7 (5.3)	9 (6.8)

* No data on adverse events leading to the suspension of administration were obtained from Study MDX010-20.

The following table summarizes adverse events with an incidence of ≥10% in any group of Study MDX010-20.

Adverse events occurring with an incidence of ≥10% in any group (Study MDX010-20)

Preferred term MedDRA ver.12.1	Number of subjects (%)					
	Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	374 (98.4)	193 (50.8)	127 (96.9)	72 (55.0)	128 (97.0)	69 (52.3)
Anaemia	41 (10.8)	11 (2.9)	15 (11.5)	4 (3.1)	23 (17.4)	11 (8.3)
Abdominal pain	67 (17.6)	6 (1.6)	20 (15.3)	2 (1.5)	22 (16.7)	7 (5.3)
Constipation	81 (21.3)	3 (0.8)	27 (20.6)	3 (2.3)	34 (25.8)	1 (0.8)
Diarrhoea	146 (38.4)	17 (4.5)	43 (32.8)	7 (5.3)	26 (19.7)	1 (0.8)
Nausea	129 (33.9)	6 (1.6)	46 (35.1)	3 (2.3)	52 (39.4)	3 (2.3)
Vomiting	75 (19.7)	7 (1.8)	31 (23.7)	3 (2.3)	29 (22.0)	3 (2.3)
Asthenia	39 (10.3)	7 (1.8)	8 (6.1)	4 (3.1)	18 (13.6)	7 (5.3)
Fatigue	137 (36.1)	19 (5.0)	55 (42.0)	9 (6.9)	41 (31.1)	4 (3.0)
Injection site reaction	110 (28.9)	7 (1.8)	2 (1.5)	0	26 (19.7)	0
Peripheral oedema	48 (12.6)	4 (1.1)	13 (9.9)	1 (0.8)	22 (16.7)	1 (0.8)
Pain	25 (6.6)	7 (1.8)	7 (5.3)	1 (0.8)	15 (11.4)	1 (0.8)
Pyrexia	78 (20.5)	2 (0.5)	16 (12.2)	0	23 (17.4)	2 (1.5)
Decreased appetite	88 (23.2)	6 (1.6)	35 (26.7)	2 (1.5)	29 (22.0)	4 (3.0)
Arthralgia	31 (8.2)	2 (0.5)	12 (9.2)	1 (0.8)	15 (11.4)	1 (0.8)
Back pain	34 (8.9)	6 (1.6)	9 (6.9)	2 (1.5)	17 (12.9)	3 (2.3)
Pain in extremity	53 (13.9)	5 (1.3)	9 (6.9)	0	20 (15.2)	2 (1.5)
Dizziness	27 (7.1)	0	5 (3.8)	0	14 (10.6)	2 (1.5)
Headache	65 (17.1)	4 (1.1)	19 (14.5)	3 (2.3)	19 (14.4)	3 (2.3)
Insomnia	33 (8.7)	1 (0.3)	16 (12.2)	0	15 (11.4)	0
Cough	55 (14.5)	1 (0.3)	21 (16.0)	0	18 (13.6)	0
Dyspnea	46 (12.1)	14 (3.7)	19 (14.5)	6 (4.6)	25 (18.9)	6 (4.5)
Pruritus	79 (20.8)	1 (0.3)	39 (29.8)	0	14 (10.6)	0
Rash	79 (20.8)	5 (1.3)	29 (22.1)	2 (1.5)	9 (6.8)	0

Serious adverse events with an incidence of ≥3% in the ipilimumab/gp100 group or the ipilimumab group in Study MDX010-20 were colitis (14 subjects [3.7%] in the ipilimumab/gp100 group, 7 subjects [5.3%] in the ipilimumab group, 0 subject in the gp100 group; the same applies hereinafter), diarrhoea (16 subjects [4.2%], 6 subjects [4.6%], 0 subject), and anaemia (5 subjects [1.3%], 4 subjects [3.1%], 5 subjects [3.8%]). The adverse events occurring in ≥ 2 subjects in the ipilimumab/gp100 group or the ipilimumab group that led to the discontinuation of administration of the investigational products were colitis (10 subjects [2.6%], 3 subjects [2.3%], 0 subject), diarrhoea (10 subject [2.6%], 2 subjects [1.5%], 0 subject), sepsis (1 subject [0.3%], 2 subjects [1.5%], 0 subject), and uveitis (0 subject, 2 subjects [1.5%], 0 subject).

The applicant's explanation on the difference in the safety of ipilimumab between the Japanese and non-Japanese populations:

The following table summarizes adverse events in ipilimumab-treated patients with a ≥10% difference in incidence between Studies CA184396 and MDX010-20.

Adverse events in ipilimumab-treated patients with a ≥10% difference in incidence between Studies CA184396 and MDX010-20

Preferred term*	Number of subjects (%)			
	Japanese		Non-Japanese	
	Study CA184396		Study MDX010-20 (the ipilimumab group)	
	20 subjects		131 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	20 (100)	11 (55.0)	127 (96.9)	72 (55.0)
Anaemia	0	0	15 (11.5)	4 (3.1)
Diarrhoea	4 (20.0)	0	43 (32.8)	7 (5.3)
Nausea	1 (5.0)	0	46 (35.1)	3 (2.3)
Vomiting	2 (10.0)	0	31 (23.7)	3 (2.3)
Fatigue	1 (5.0)	0	55 (42.0)	9 (6.9)
Malaise	3 (15.0)	1 (5.0)	1 (0.8)	0
Mucosal inflammation	2 (10.0)	0	0	0
Pyrexia	6 (30.0)	1 (5.0)	16 (12.2)	0
ALT increased	4 (20.0)	1 (5.0)	2 (1.5)	0
AST increased	4 (20.0)	2 (10.0)	1 (0.8)	0
Malignant neoplasm progression	2 (10.0)	2 (10.0)	0	0
Cough	0	0	21 (16.0)	0
Alopecia	3 (15.0)	0	3 (2.3)	0
Pruritus	2 (10.0)	0	39 (29.8)	0
Rash	8 (40.0)	0	29 (22.1)	2 (1.5)
Deep vein thrombosis	3 (15.0)	1 (5.0)	2 (1.5)	2 (1.5)

* ver. 12.1 for Study MDX010-20 and ver. 17.0 for Study CA184396
ALT, alanine aminotransferase; AST, aspartate aminotransferase

The incidences of the following serious adverse events were ≥10% higher in Japanese patients than in non-Japanese patients: ALT increased, AST increased, and malignant neoplasm progression. None of these adverse events led to the discontinuation of treatment.

The following adverse events were not reported from non-Japanese patients (the ipilimumab/gp100 group and the ipilimumab group in Study MDX010-20) but were observed in Japanese patients: eye movement disorder, cerebral infarction, metastases to meninges, hyperlipidemia, toxic skin eruption, disseminated intravascular coagulation, conjunctivitis allergic, asteatotic eczema, emphysema, pneumocystis jiroveci pneumonia, erysipelas, acne, and anaphylactic shock in 1 patient each. A causal relationship to ipilimumab was ruled out for all these events.

PMDA's view:

Adverse events with a high incidence in the ipilimumab group require attention during treatment with ipilimumab. Information on the occurrence of these events should be provided to healthcare professionals. Extremely limited experience in treatment with ipilimumab in Japanese patients precludes the determination of whether the safety profiles of ipilimumab differ between the Japanese and non-Japanese populations. Thus, post-marketing safety data on ipilimumab in Japanese patients should be promptly collected. When ipilimumab is used in Japanese patients, special attention should be paid to adverse events occurring more frequently in Japanese patients than in non-Japanese patients in Study CA184396. The occurrence of these events should therefore be communicated to healthcare professionals in an appropriate manner via the package insert, etc.

Some serious adverse events occurred after the completion of treatment with ipilimumab. PMDA is inquiring the applicant about the timing of onset of these events. This matter will be reported in Review Report (2).

The following sections summarize PMDA's discussion on the adverse events that led to death following treatment with ipilimumab [see "4.(iii).A-1.(2).4) Foreign phase III study"] and serious adverse events occurring more frequently in Japanese patients than in non-Japanese patients in Study MDX010-20.

4.(iii).B.(3).2) Diarrhea, colitis, gastrointestinal perforation

The applicant's explanation on the diarrhoea, colitis, and gastrointestinal perforation observed following treatment with ipilimumab:

In Studies MDX010-20 and CA184396, symptomatic treatment, oral or intravenous corticosteroids, and as-needed administration of immunosuppressants were recommended for the treatment of diarrhoea or colitis, depending on the severity and duration of the symptoms.

Preferred terms (PTs) of gastrointestinal tract disorders under the MedDRA system organ class (SOC) of "gastrointestinal disorders" were summarized.

The following table shows gastrointestinal disorders with an incidence of ≥5% in any group treated with ipilimumab in Studies MDX010-20 and CA184396.

Gastrointestinal disorders with an incidence ≥5% in any group treated with ipilimumab (Studies CA184396 and MDX010-20)

Preferred term[*]	Number of subjects (%)							
	Study CA184396		Study MDX010-20					
	20 subjects		Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	13 (65.0)	2 (10.0)	274 (72.1)	56 (14.7)	90 (68.4)	21 (16.0)	93 (70.5)	15 (11.4)
Nausea	1 (5.0)	0	129 (33.9)	6 (1.6)	46 (35.1)	3 (2.3)	52 (39.4)	3 (2.3)
Diarrhoea	4 (20.0)	0	146 (38.4)	17 (4.5)	43 (32.8)	7 (5.3)	26 (19.7)	1 (0.8)
Constipation	3 (15.0)	0	81 (21.3)	3 (0.8)	27 (20.6)	3 (2.3)	34 (25.8)	1 (0.8)
Vomiting	2 (10.0)	0	75 (19.7)	7 (1.8)	31 (23.7)	3 (2.3)	29 (22.0)	3 (2.3)
Abdominal pain	2 (10.0)	0	67 (17.6)	6 (1.6)	20 (15.3)	2 (1.5)	22 (16.7)	7 (5.3)
Abdominal pain upper	2 (10.0)	0	18 (4.7)	0	7 (5.3)	0	11 (8.3)	2 (1.5)
Colitis	0	0	21 (5.5)	13 (3.4)	10 (7.6)	7 (5.3)	2 (1.5)	0
Dry mouth	1 (5.0)	0	8 (2.1)	1 (0.3)	4 (3.1)	0	5 (3.8)	0
Ascites	1 (5.0)	1 (5.0)	4 (1.1)	2 (0.5)	2 (1.5)	2 (1.5)	5 (3.8)	2 (1.5)
Haemorrhoids	1 (5.0)	0	6 (1.6)	1 (0.3)	1 (0.8)	0	1 (0.8)	0
Ileus	1 (5.0)	1 (5.0)	3 (0.8)	3 (0.8)	0	0	1 (0.8)	0

[*] Ver. 12.1 for Study MDX010-20 and ver. 17.0 for Study CA184396

In Study MDX010-20, gastrointestinal disorders resulted in death in 2 of 380 subjects in the ipilimumab/gp100 group (colitis/gastrointestinal perforation[*1] and diarrhoea/peritonitis[*2] in 1 subject each).[*3] For all these disorders, a causal relationship to the investigational products could not be ruled out. Serious gastrointestinal disorders other than death were observed in 56 of 380 subjects (14.7%) in

the ipilimumab/gp100 group, 18 of 131 subjects (13.7%) in the ipilimumab group, and 12 of 132 subjects (9.1%) in the gp100 group (see the table below). A causal relationship to the investigational products could not be ruled out for 25 subjects in the ipilimumab/gp100 group (diarrhoea in 9 subjects, colitis in 7 subjects, colitis/diarrhoea in 4 subjects, intestinal perforation in 2 subjects, and large intestine perforation, colitis/haematochezia, and colitis/large intestine perforation in 1 subject each), 10 subjects in the ipilimumab group (colitis in 4 subjects, colitis/diarrhoea in 2 subjects, diarrhoea in 2 subjects, colitis/proctalgia in 1 subject, and abdominal pain/diarrhoea/vomiting in 1 subject), and 2 subjects in the gp100 group (nausea and vomiting in 1 subject each). Gastrointestinal disorders led to the discontinuation of administration in 19 of 380 subjects (5.0%) in the ipilimumab/gp100 group (diarrhoea and colitis in 8 subjects each, colitis/diarrhoea in 2 subjects, and intestinal perforation in 1 subject), 5 of 131 subjects (3.8%) in the ipilimumab group (colitis in 3 subjects and diarrhoea in 2 subjects), and 1 of 132 subjects (0.8%) in the gp100 group (vomiting). Excluding colitis, intestinal perforation, and diarrhoea in 1 subject each who died of gastrointestinal disorders or disease progression, these events resolved with fluid replacement or administration of antidiarrhoeal agents, corticosteroids, or immunosuppressants.

[*1] A woman aged 5[redacted] years: Rectal hemorrhage and hypotension developed on Day 83 after the start of treatment with ipilimumab (the last dose of ipilimumab was administered on Day 64). Ischemic colitis was diagnosed by colonoscopy. On Day 88, a surgery was performed due to perforation suspected at CT scan on the same day. Gastrointestinal perforation accompanied by acute pancolitis and acute peritonitis was diagnosed. Following the onset of septic shock, the patient was treated with antibiotics but died on Day 91.

[*2] A man aged 7[redacted] years: He experienced diarrhoea (Grade 3) on Day 64 after the start of treatment with ipilimumab (the last dose of ipilimumab was administered on Day 43) and was hospitalized. Due to intestinal perforation suspected at CT scan performed on the same day, a surgery was performed. Sigmoid colon perforation and peritonitis were diagnosed. Cardiopulmonary insufficiency and multi-organ failure were observed following the surgery. The patient died on Day 66.

[*3] A subject in the ipilimumab group experienced large intestine perforation on Day 191 after the start of treatment with ipilimumab (the last dose of ipilimumab was administered on Day 44). On Day 193, the subject died of sepsis probably attributable to the large intestine perforation. A causal relationship between the large intestine perforation and the investigational products could not be ruled out. The event was not included in adverse events resulting in death, because it was observed later than 70 days after the last dosing.

Serious gastrointestinal disorders other than death (Study MDX010-20)

Ipilimumab/gp100	Diarrhoea in 9 subjects; colitis in 7 subjects; colitis/diarrhoea in 4 subjects; vomiting and constipation in 3 subjects each; nausea, abdominal pain upper, abdominal pain/nausea/vomiting, intestinal perforation, and gastrointestinal haemorrhage in 2 subjects each, haematochezia, abdominal wall mass, ascites/ileus, colitis/haematochezia, ileus, gastritis/nausea/vomiting, nausea/vomiting, diarrhoea/intestinal obstruction, intestinal haemorrhage, upper gastrointestinal haemorrhage, colitis/large intestine perforation, abdominal pain/intestinal perforation, abdominal distension, diarrhoea/ileus, large intestine perforation, rectal stenosis, haemorrhoids, intestinal obstruction, gastritis, and abdominal pain in 1 subject each
Ipilimumab	Colitis in 4 subjects; diarrhoea in 3 subjects; colitis/diarrhoea in 2 subjects; abdominal distension, dysphagia, colitis/protodynia, nausea, vomiting, abdominal pain/diarrhoea/vomiting/large intestinal obstruction, nausea/vomiting, ascites, and abdominal pain in 1 subject each
gp100	Abdominal pain in 4 subjects; nausea in 2 subjects; abdominal pain/constipation, dysphagia/nausea/vomiting, nausea/vomiting, vomiting, intussusception, and intussusception/small intestinal obstruction in 1 subject each

In Study CA184396, no gastrointestinal disorders resulted in death or the discontinuation of administration. A serious gastrointestinal disorder (ileus) was observed in 1 of 20 subjects (5.0%), and a causal relationship to ipilimumab was ruled out for the event. A gastrointestinal disorder (diarrhoea) led to the suspension of administration in 1 of 20 subjects (5.0%). The diarrhoea resolved after the administration of corticosteroids.

PMDA's view:

In Study MDX010-20, serious diarrhoea, colitis, and gastrointestinal perforation were observed following treatment with ipilimumab. Some events resulted in death, and gastrointestinal perforation led to sepsis in some patients. Thus, attention should be paid to the potential occurrence of these events during treatment with ipilimumab. Healthcare professionals should be informed that serious diarrhoea, colitis, and gastrointestinal perforation occurred in the clinical studies, with fatal outcomes in some patients, and that these events occurred after the completion of treatment with ipilimumab, and should be advised to carefully monitor patients treated with ipilimumab and take appropriate actions in case of colitis, diarrhoea, etc., through the package insert etc. Healthcare professionals should also be appropriately informed of recommended actions for these events through information materials, etc.

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

The applicant's explanation on skin disorders associated with ipilimumab treatment:

In Study MDX010-20, symptomatic treatment, oral or intravenous corticosteroids, or immunosuppressants were considered, depending on the severity etc., for the treatment of skin disorders for which a causal relationship to ipilimumab could not be ruled out after a detailed investigation of the cause. In Study CA184396, symptomatic treatment or oral or intravenous corticosteroids were recommended for the treatment of skin disorders.

PTs of skin disorder under the MedDRA SOC "Skin and subcutaneous tissue disorders" were counted.

The following table shows skin disorders with an incidence of ≥5% in any group treated with ipilimumab in Studies MDX010-20 and CA184396:

Skin disorders with an incidence ≥5% in any group treated with ipilimumab (Studies MDX010-20 and CA184396)

Preferred term[*1]	Number of subjects (%)							
	Study CA184396[*2]		Study MDX010-20					
	20 subjects		Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
All adverse events	12 (60.0)	1 (5.0)	221 (58.2)	14 (3.7)	74 (56.5)	3 (2.3)	46 (34.8)	0
Pruritus	2 (10.0)	0	79 (20.8)	1 (0.3)	39 (29.8)	0	14 (10.6)	0
Rash	8 (40.0)	0	79 (20.8)	5 (1.3)	29 (22.1)	2 (1.5)	9 (6.8)	0
Erythema	0	0	26 (6.8)	1 (0.3)	10 (7.6)	0	7 (5.3)	0
Alopecia	3 (15.0)	0	10 (2.6)	0	3 (2.3)	0	2 (1.5)	0
Dry skin	1 (5.0)	0	10 (2.6)	0	3 (2.3)	0	2 (1.5)	0
Acne	1 (5.0)	0	0	0	0	0	1 (0.8)	0
Asteatotic eczema	1 (5.0)	0	0	0	0	0	0	0
Toxic skin eruption	1 (5.0)	1 (5.0)	0	0	0	0	0	0

[*1] MedDRA ver. 12.1 for Study MDX010-20 and MedDRA ver. 17.0 for Study CA184396

[*2] Adverse events occurring within 90 days after ipilimumab treatment were counted in Study CA184396. Vitiligo was observed in 1 subject at least 91 days after the completion of ipilimumab treatment.

No skin disorders resulted in death in Study MDX010-20. Serious skin disorders were observed in 6 of 380 subjects (1.6%) in the ipilimumab/gp100 group (rash in 2 subjects and toxic epidermal

necrolysis/leukocytoclastic vasculitis,* leukocytoclastic vasculitis, rash generalized, and rash pruritic in 1 subject each). Except for rash in 1 subject, a causal relationship to the investigational products could not be ruled out for these events. An adverse event (rash erythematous) led to the discontinuation of administration in 1 of 131 subjects (0.8%) in the ipilimumab group.

* A man aged 4[redacted] years. He was hospitalized due to convulsion, pyrexia, and productive cough developing on Day 12 after the start of ipilimumab treatment. Severe brain oedema was observed at head CT. On Day 14, leukocytoclastic vasculitis (Grade 1) and respiratory distress developed. On Day 15 toxic epidermal necrolysis (TEN) and acute respiratory distress syndrome (Grade 3) developed. Despite treatment with corticosteroids, etc., the patient entered a confusional state and coma on the same day. He died of acute respiratory distress syndrome on Day 18.

In Study CA184396, no serious skin disorders occurred, and no skin disorders led to the discontinuation or suspension of treatment.

PMDA's view:
Serious skin disorders associated with ipilimumab occurred in several studies including Study MDX010-20. Therefore, attention should be paid to potential skin disorders during ipilimumab therapy. Through the package insert, etc., healthcare professionals should be informed of the occurrence of skin disorders and advised to adequately monitor the patient's condition during ipilimumab therapy and appropriately response to these events. Healthcare professionals should also be appropriately informed of recommended actions for skin disorders through information materials, etc.

4.(iii).B.(3).4) Hepatic disorders

The applicant's explanation on hepatic disorders associated with ipilimumab treatment:
In Studies MDX010-20 and CA184396, patients with liver function test abnormal were monitored more frequently and recommended to receive oral or intravenous of corticosteroids, depending on the severity of the abnormality, etc. Immunosuppressant therapy was considered as necessary.

Compiled hepatic disorders were the PTs under the MedDRA SOC "Hepatobiliary disorders" and other PTs including "blood alkaline phosphatase increased," "aspartate aminotransferase increased," "alanine aminotransferase increased," "blood bilirubin increased," "hepatic enzyme increased," and "liver function test abnormal."

The following table summarizes hepatic disorders with an incidence of ≥1% in any group treated with ipilimumab in Studies MDX010-20 and CA184396:

Hepatic disorders with an incidence ≥1% in any group treated with ipilimumab (Studies CA184396 and MDX010-20)

Preferred term*	Number of subjects (%)							
	Study CA184396		Study MDX010-20					
	20 subjects		Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (20.0)	3 (15.0)	23 (6.1)	11 (2.9)	13 (9.9)	7 (5.3)	6 (4.5)	3 (2.3)
Hepatomegaly	0	0	2 (0.5)	0	2 (1.5)	1 (0.8)	0	0
Blood ALP increased	1 (5.0)	1 (5.0)	8 (2.1)	2 (0.5)	4 (3.1)	2 (1.5)	4 (3.0)	1 (0.8)
AST increased	4 (20.0)	2 (10.0)	6 (1.6)	2 (0.5)	1 (0.8)	0	3 (2.3)	1 (0.8)
ALT increased	4 (20.0)	1 (5.0)	4 (1.1)	3 (0.8)	2 (1.5)	0	3 (2.3)	0
Blood bilirubin increased	1 (5.0)	0	0	0	2 (1.5)	0	2 (1.5)	1 (0.8)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase
* MedDRA ver. 12.1 for Study MDX010-20 and MedDRA ver. 17.0 for Study CA184396

In Study MDX010-20, a hepatic disorder (hepatic failure) resulted in death in 1 of 131 subjects (0.8%) in the ipilimumab group. A causal relationship to ipilimumab could not be ruled out for the event. Serious hepatic disorders other than death were observed in 5 of 380 subjects (1.3%) in the ipilimumab/gp100 group (hyperbilirubinaemia, hepatic failure, jaundice, hepatitis, and bile duct obstruction/cholestatic jaundice in 1 subject each); 2 of 131 subjects (0.8%) in the ipilimumab group (acute hepatic failure and cholecystitis in 1 subject each); and 1 of 132 subjects (0.8%) in the gp100 group (AST increased). A causal relationship to the investigational products could not be ruled out for hepatitis in 1 subject in the ipilimumab/gp100 group. A hepatic disorder led to the discontinuation of investigational products in 1 of 380 subjects (0.3%) in the ipilimumab/gp100 group (hepatitis) and 2 of 131 subjects (1.5%) in the ipilimumab group (cholecystitis and hepatic failure in 1 subject each).

In Study CA184396, no hepatic disorders resulted in death or the discontinuation of treatment. Serious hepatic disorders were observed in 2 of 20 subjects (10%, AST increased/ALT increased in both subjects). A causal relationship to ipilimumab could not be ruled out for either event. Hepatic disorders led to the suspension of treatment in 1 of 20 subjects (5%, AST increased/ALT increased).

The following table summarizes the details of patients in Studies MDX010-20 and CA184396 who experienced serious hepatic disorders.

List of patients who experienced serious hepatic disorders (Studies MDX010-20 and CA184396)

Treatment	Age	Sex	MedDRA preferred term[*1]	Grade	No. of days to onset	Duration (days)	Actions taken	Causal relationship	Outcome
Study MDX010-20									
Ipilimumab/gp 100	5[redacted]	Male	Hyperbilirubinaemia	3	19	–	Percutaneous biliary stent placement	Unrelated	Not resolved
Ipilimumab/gp 100	5[redacted]	Male	Hepatic failure	2	22	1	Unknown	Unrelated	Resolved
Ipilimumab/gp 100	7[redacted]	Male	Jaundice	3	86	10	Unknown	Unrelated	Resolved
Ipilimumab/gp 100	4[redacted]	Male	Cholestatic jaundice	3	299	53	None	Unrelated	Resolved
			Bile duct obstruction	1	538	6	None	Unrelated	Resolved
Ipilimumab/gp 100	6[redacted]	Male	Hepatitis	3	48	11	Discontinuation of investigational produts, administration of corticosteroids	Related	Resolved
Ipilimumab	6[redacted]	Male	Hepatic failure	5	24	2	Discontinuation of ipilimumab, administration of antibiotics	Related	Death
Ipilimumab	7[redacted]	Male	Acute hepatic failure	5	33	1	None	Unrelated	Death[*2]
Ipilimumab	5[redacted]	Female	Cholecystitis	3	51	14	Discontinuation of ipilimumab	Unrelated	Resolved
Study CA184396									
Ipilimumab	2[redacted]	Female	AST increased	1	9	2	Administration of corticosteroids, antibiotics, and other drugs	Related	Resolved
			ALT increased	2	9	2	Administration of corticosteroids, antibiotics, and other drugs	Related	Resolved
			CRP increased	2	9	23	Administration of corticosteroids, antibiotics, and other drugs	Related	Resolved
			AST increased	2	10	4	Administration of corticosteroids, antibiotics, and other drugs	Related	Resolved
			ALT increased	3	10	4	Administration of corticosteroids, antibiotics, and other drugs	Related	Resolved
			ALT increased	1	13	10	Administration of corticosteroids and other drugs	Related	Resolved
			AST increased	1	15	3	Administration of corticosteroids and other drugs	Related	Resolved
Ipilimumab	7[redacted]	Male	AST increased	2	58	4	Administration of corticosteroids and other drugs	Related	Resolved
			ALT increased	2	58	4	Administration of corticosteroids and other drugs	Related	Resolved
			AST increased	1	61	–	Suspension of ipilimumab, administration of corticosteroids	Related	Not resolved
			ALT increased	1	61	–	Suspension of ipilimumab, administration of corticosteroids	Related	Not resolved

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein
[*1] MedDRA ver. 12.1 for Study MDX010-20 and MedDRA ver. 17.0 for Study CA184396; [*2] Death due to disease progression

In Studies MDX010-20 and CA184396, no patients experienced hepatic dysfunction meeting Hy's law (defined based on "Guidance for Industry. Drug-induced Liver Injury: Premarketing Clinical Evaluation," US Department of Health and Human Services, Food and Drug Administration, July 2009).

PMDA's view:

The findings listed below suggest that attention should be paid to potential hepatic disorders during ipilimumab therapy. Through the package insert, etc., healthcare professionals should be informed of the occurrence of hepatic disorders, including serious hepatic disorders resulting in death, and advised to monitor liver function test results regularly during treatment and to appropriately response to abnormality. Healthcare professionals should also be appropriately informed of recommended actions for hepatic disorders through information materials, etc.

- Serious hepatic dysfunction, including hepatic failure, were observed during treatment with ipilimumab, and one fatal case was reported.
- The incidences of hepatic dysfunction tended to be higher in Japanese patients than in non-Japanese patients.
- The Japanese phase II study (Study CA184202) in Japanese patients designed to assess the efficacy and safety of 10 mg/kg ipilimumab plus DTIC was discontinued because of serious hepatic dysfunction, although its dosing regimen was different from the proposed dosage and administration [see "4.(iii).B.(5).3) Concomitant use of other antineoplastic agents"].

4.(iii).B.(3).5) Hypophysitis, hypopituitarism, hypothyroidism, adrenal insufficiency

The applicant's explanation on hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency in ipilimumab administration:

In Study CA184396, thyroid-stimulating hormone was measured before the administration of ipilimumab. Free T3, free T4, cortisol, and early morning adrenocorticotropic hormone were measured when clinically necessary. In Studies MDX010-20 and CA184396, intravenous steroids with mineralocorticoid activity was considered for the treatment of suspected adrenal crisis without sepsis. In Study MDX010-20, pituitary gland imaging was considered for suspected endocrine disorder without adrenal crisis. In Study CA184396, pituitary gland imaging was considered for a confirmed symptomatic endocrine disorder. In Studies MDX010-20 and CA184396, hormone therapy and corticosteroid therapy were recommended for any abnormality detected by pituitary gland imaging or laboratory tests.

The following table summarizes hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency reported in Studies MDX010-20 and CA184396.

Incidences of hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency (Studies MDX010-20 and CA184396)

Preferred term[*1]	Number of subjects (%)							
	Study CA184396[*2]		Study MDX010-20					
	20 subjects		Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypophysitis	0	0	2 (0.5)	2 (0.5)	2 (1.5)	2 (1.5)	0	0
Hypopituitarism	0	0	3 (0.8)	2 (0.5)	3 (2.3)	2 (1.5)	0	0
Hypothyroidism	0	0	7 (1.8)	1 (0.3)	5 (3.8)	0	2 (1.5)	0
Adrenal insufficiency	0	0	3 (0.8)	2 (0.5)	2 (1.5)	0	0	0

[*1] Ver. 12.1 for Study MDX010-20 and ver. 17.0 for Study CA184396

[*2] In Study CA184396, adverse events occurring within 90 days after ipilimumab treatment was counted. Hypopituitarism and hypothyroidism were observed in 1 subject each at least 91 days after the completion of ipilimumab treatment.

In Study MDX010-20, no hypophysitis, hypopituitarism, hypothyroidism, or adrenal insufficiency resulted in death. Serious hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency were observed in 4 of 380 subjects (1.1%) in the ipilimumab/gp100 group (hypopituitarism in 2 subjects, and adrenal insufficiency/hypopituitarism/hypothyroidism,[*] and hypophysitis in 1 subject each) and 5 of 131 subjects (3.8%) in the ipilimumab group (hypophysitis and hypopituitarism in 2 subjects each, and adrenal insufficiency in 1 subject). A causal relationship to the investigational products could not be ruled out for all these events. Treatment was discontinued due to hypopituitarism in 1 of 131 subjects (0.8%) in the ipilimumab group. The following table summarizes the details of patients who experienced

serious hypophysitis, hypopituitarism, hypothyroidism, or adrenal insufficiency. Some patients failed to recover and required long-term treatment with hormone replacement therapy, etc.

* Hypogonadism was also observed on the same day when adrenal insufficiency and hypopituitarism occurred.

List of patients experiencing serious hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency (Study MDX010-20)

Treatment	Age	Sex	MedDRA preferred term (ver.12.1)	Grade	No. of days to onset	Duration (days)	Treatment for adverse events	Causal relation-ship	Outcome
Ipilimumab/gp100	5[redacted]	Female	Hypopituitarism	2	122	–	Administration of corticosteroids	Related	Not resolved
Ipilimumab/gp100	7[redacted]	Male	Adrenal insufficiency	3	85	–	Administration of corticosteroids	Related	Not resolved
			Hypopituitarism	3	85	–	Administration of corticosteroids	Related	Not resolved
			Hypothyroidism	3	81	–	Administration of corticosteroids and thyroid hormone	Related	Not resolved
Ipilimumab/gp100	4[redacted]	Female	Hypophysitis	3	39	4	Administration of corticosteroids	Related	Resolved
Ipilimumab/gp100	4[redacted]	Female	Hypopituitarism	3	79	169	Administration of corticosteroids and thyroid hormone	Related	Resolved
Ipilimumab	4[redacted]	Male	Adrenal insufficiency	2	135	–	Administration of corticosteroids	Related	Not resolved
Ipilimumab	6[redacted]	Male	Hypopituitarism	3	50	–	Discontination of ipilimumab, administration of corticosteroids and thyroid hormone	Related	Not resolved
Ipilimumab	6[redacted]	Male	Hypophysitis	3	118	–	Administration of corticosteroids	Related	Not resolved
Ipilimumab	5[redacted]	Female	Hypophysitis	3	81	–	Administration of corticosteroids and thyroid hormone	Related	Resolved
Ipilimumab	5[redacted]	Male	Hypopituitarism	4	100	14	Administration of corticosteroids	Related	Resolved

No hypophysitis, hypopituitarism, hypothyroidism, or adrenal insufficiency resulted in death in patients treated with ipilimumab in the Japanese phase II study (Study CA184113), the Japanese phase II study (Study CA184202), the foreign phase I studies (Studies MDX010-15, CA184078, and CA184087), the foreign phase II studies (Studies MDX010-08, CA184004, CA184007, CA184008, CA184022, and CA184041), or the foreign phase III study (Study CA184024). Serious hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency other than those resulting in deaths were observed in 26 subjects (hypopituitarism in 12 subjects, hypophysitis in 7 subjects, adrenal insufficiency in 3 subjects, hypothyroidism in 2 subjects, hypophysitis/hypopituitarism in 1 subject and hypopituitarism/adrenal insufficiency in 1 subject). A causal relationship to ipilimumab could not be ruled out for all these events, except for adrenal insufficiency in 1 subject.

PMDA's view:

Serious hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency were observed following treatment with ipilimumab, and some patients required long-term care. These events therefore requires attention during treatment. Through the package insert etc., healthcare professionals should be informed of the occurrence of these events (including the fact that some events occurred after the completion of treatment) and advised to monitor the endocrine function of patients during treatment and appropriately respond to abnormal changes. Recommended response for hypophysitis, hypopituitarism, hypothyroidism, or adrenal insufficiency should also be communicated to healthcare professionals through information materials, etc.

4.(iii).B.(3).6) Peripheral neuropathy

The applicant's explanation on peripheral neuropathy associated ipilimumab:

In Study CA184396, when peripheral neuropathy was found and a causal relationship to ipilimumab could not be ruled out for the event, the use of intravenous corticosteroids was recommended depending on the severity of the event. Treatment with intravenous immunoglobulin or other immunosuppressants was considered for Grade ≥3 motor neuropathy failing to respond to high-dose intravenous corticosteroids.

PTs of peripheral neuropathy-related events under the standardised MedDRA query of "peripheral neuropathy" were counted.

The following table summarizes peripheral neuropathy-related events with an incidence of ≥1% in any group treated with ipilimumab in Studies MDX010-20 and CA184396.

Peripheral neuropathy-related events with an incidence of ≥1% in any group treated with ipilimumab (Studies MDX010-20 and CA184396)

Preferred term*	Number of subjects (%)							
	Study CA184396		Study MDX010-20					
	20 subjects		Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (15.0)	0	41 (10.8)	7 (1.8)	12 (9.2)	2 (1.5)	16 (12.1)	3 (2.3)
Muscular weakness	2 (10.0)	0	12 (3.2)	2 (0.5)	3 (2.3)	0	5 (3.8)	1 (0.8)
Peripheral sensory neuropathy	1 (5.0)	0	4 (1.1)	0	0	0	3 (2.3)	1 (0.8)
Hypoaesthesia	0	0	8 (2.1)	1 (0.3)	4 (3.1)	0	1 (0.8)	0
Paraesthesia	0	0	6 (1.6)	0	3 (2.3)	0	4 (3.0)	0
Peripheral neuropathy	0	0	5 (1.3)	0	1 (0.8)	0	1 (0.8)	0

* MedDRA ver. 12.1 for Study MDX010-20 and MedDRA ver. 17.0 for Study CA184396

In Study MDX010-20, a peripheral neuropathy-related event resulted in death in 1 of 380 subjects (0.3%) in the ipilimumab/gp100 group (Guillain-Barre syndrome*). A causal relationship to the investigational products could not be ruled out. A serious peripheral neuropathy-related event other than death was observed in 1 of 380 subjects (0.3%) in the ipilimumab/gp100 group (hypoaesthesia). A causal relationship to the investigational products was ruled out. No peripheral neuropathy-related event led to the discontinuation of treatment.

* A man aged 6[redacted] years. The patient experienced paraesthesia of the hands and feet on Day 89 after the start of ipilimumab treatment (the last dose of ipilimumab was administered on Day 64) and movement disorders on Day 92. He was hospitalized on Day 94. Dyspnoea (Grade 1) developed on Day 98. Electromyography on the same day (Day 98) showed distal and proximal axonopathy. Guillain-Barre syndrome was diagnosed. The patient transiently responded to an immunoglobulin preparation, but his condition declined again. The patient died of respiratory failure on Day 102.

In Study CA184396, no peripheral neuropathy-related events resulted in death or the discontinuation or suspension of treatment, or no serious peripheral neuropathy-related events were observed.

No peripheral neuropathy-related events resulted in death in subjects treated with ipilimumab in the Japanese phase I study (Study CA184113), Japanese phase II study (Study CA184202), foreign phase I

studies (Studies MDX010-15, CA184078, and CA184087), foreign phase II studies (Studies MDX010-08, CA184004, CA184007, CA184008, CA184022, and CA184041), or foreign phase III study (Study CA184024). Serious peripheral neuropathy-related events were observed in 15 subjects (muscular weakness in 5 subjects, Guillain-Barre syndrome, peripheral sensory neuropathy, peripheral motor neuropathy, and peripheral sensory neuropathy/peripheral motor neuropathy in 2 subjects each, and peripheral sensorimotor neuropathy and peripheral neuropathy in 1 subject each). A causal relationship to ipilimumab could not be ruled out for muscular weakness, Guillain-Barre syndrome, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, or peripheral neuropathy in 1 subject each.

PMDA's view:

Serious peripheral neuropathy-related events were observed following treatment with ipilimumab and one of the events resulted in death. Therefore, treatment with ipilimumab requires attention to potential peripheral neuropathy. Through the package insert, etc., healthcare professionals should be appropriately informed of the occurrence of peripheral neuropathy in the clinical studies, including the fact that a patient died due to a serious peripheral neuropathy-related event and that a serious peripheral neuropathy-related event occurred after the completion of ipilimumab therapy in the clinical studies. Through the package insert, etc., healthcare professionals should be advised to monitor patients' condition during treatment and appropriately respond to these events. They should also be informed about recommended actions for peripheral neuropathy through information materials, etc.

4.(iii).B.(3).7) Renal disorders

The applicant's explanation on renal disorders associated with ipilimumab:

PTs of adverse events under the MedDRA SOC, "renal and urinary disorders," and other PTs, "blood creatinine increased" and "creatinine renal clearance decreased," were counted.

The following table summarizes renal disorders with an incidence of ≥1% in any group treated with ipilimumab in Studies MDX010-20 and CA184396.

Renal disorders with an incidence of ≥1% in any group treated with ipilimumab (Studies MDX010-20 and CA184396)

Preferred term*	Number of subjects (%)							
	Study CA184396		Study MDX010-20					
	20 subjects		Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	1 (5.0)	1 (5.0)	30 (7.9)	10 (2.6)	14 (10.7)	4 (3.1)	13 (9.8)	4 (3.0)
Renal failure	0	0	4 (1.1)	3 (0.8)	4 (3.1)	3 (2.3)	2 (1.5)	1 (0.8)
Pollakiuria	0	0	7 (1.8)	0	2 (1.5)	0	0	0
Haematuria	0	0	3 (0.8)	0	2 (1.5)	0	2 (1.5)	0
Urinary retention	1 (5.0)	1 (5.0)	4 (1.1)	1 (0.3)	0	0	1 (0.8)	1 (0.8)
Blood creatinine increased	0	0	4 (1.1)	0	5 (3.8)	0	2 (1.5)	0

* MedDRA ver. 12.1 for Study MDX010-20 and MedDRA ver. 17.0 for Study CA184396

In Study MDX010-20, a renal disorder resulted in death in 1 of 131 subjects (0.8%) in the ipilimumab group (renal failure*). A causal relationship to ipilimumab could not be ruled out for the event. Serious renal disorders other than death were observed in 10 of 380 subjects (2.6%) in the ipilimumab/gp100 group (renal failure in 3 subjects, urinary retention in 2 subjects, and atonic urinary bladder/bladder pain, hydronephrosis, renal tubular necrosis, ureteric obstruction, and urinary incontinence in 1 subject each), 3 of 131 subjects (2.3%) in the ipilimumab group (renal failure in 2 subjects and glomerulonephritis in 1 subject), and 2 of 132 subjects (1.5%) in the gp100 group (acute renal failure and urinary incontinence in 1 subject each). A causal relationship to ipilimumab could not be ruled out for renal failure and glomerulonephritis in 1 subject each in the ipilimumab group. Renal disorders led to the discontinuation of treatment in 1 of 380 subjects (0.3%) in the ipilimumab/gp100 group (blood creatinine increased) and 3 of 131 subjects (2.3%) in the ipilimumab group (renal failure, blood creatinine increased, and glomerulonephritis in 1 subject each). The glomerulonephritis proved reversible.

* A woman aged 6[redacted] years: The patient was hospitalized due to vomiting on Day 58 after the start of ipilimumab treatment. On the same day, infection and blood creatinine increased were reported, and ipilimumab was discontinued. Renal failure was observed on Day 64 and septic shock on Day 65. On Day 123, renal failure, infection, and septic shock led to multi-organ failure, and the patient died.

In Study CA184396, no renal disorders resulted in death or the discontinuation or suspension of treatment. No serious renal disorders other than death were observed.

Renal disorders resulted in death in 4 subjects (haematuria, renal failure, acute renal failure, and acute glomerulonephritis in 1 subject each) among those treated with ipilimumab in the Japanese phase I study (Study CA184113), Japanese phase II study (Study CA184202), foreign phase I studies (Studies MDX010-15, CA184078, and CA184087), foreign phase II studies (Studies MDX010-08, CA184004, CA184007, CA184008, CA184022, and CA184041), and foreign phase III study (Study CA184024). A causal relationship to ipilimumab could not be ruled out for acute glomerulonephritis. Serious renal disorders other than death were observed in 25 subjects (renal failure in 7 subjects, acute renal failure in 5 subjects, urinary retention in 4 subjects, and haematuria, acute prerenal failure, blood creatinine increased, proteinuria/haematuria, haemorrhage urinary tract, oliguria, hydronephrosis/acute renal failure/urinary retention, and dysuria in 1 subject each). A causal relationship to ipilimumab could not be ruled out for acute renal failure and haematuria in 2 subjects each or for haematuria, renal failure, blood creatinine increased, proteinuria/haematuria, and dysuria in 1 subject each.

PMDA's view:

Serious renal disorders, including a fatal event, occurred following treatment with ipilimumab. Therefore, attention must be paid to renal disorders during treatment with ipilimumab. Healthcare professionals should be informed of the occurrence of these events, including the fatal event of a serious renal disorder in a clinical study through the package insert, etc. They should also be advised to adequately monitor patients' condition and to appropriately response to renal disorders through the package insert, etc. Healthcare professionals should also be informed about recommended actions for renal disorders through information materials, etc.

4.(iii).B.(3).8) ILD

The applicant's explanation on ILD associated with ipilimumab:

MedDRA PTs of "acute respiratory distress syndrome," "acute respiratory failure," "interstitial lung disease," "lung infiltration," and "pneumonitis," were counted as ILD-related events.

The following table presents details of patients who experienced ILD-related events in Study MDX010-20.

List of patients experiencing ILD-related events (Study MDX010-20)

Treatment	Age	Sex	MedDRA preferred term (ver.12.1)	Grade	No. of days to onset	Duration (days)	Treatment for adverse event	Causal relation-ship	Serious/ non-serious	Outcome
Ipilimumab/gp100	3[redacted]	Female	Pneumonitis	3	35	15	Discontinued treatment, oxygen inhalation, administration of corticosteroids, antibiotics, etc.	Related	Serious	Resolved
Ipilimumab/gp100	4[redacted]	Male	Acute respiratory distress syndrome	5	16	3	Oxygen inhalation, administration of diuretics, antibiotics, etc.	Related	Serious	Death
Ipilimumab/gp100	3[redacted]	Male	Pneumonitis	3	15	39	Oxygen inhalation, administration of antibiotics, etc.	Unrelated	Non-serious	Resolved

No ILD-related events were observed in Study CA184396.

No ILD-related events resulted in death in patients treated with ipilimumab in the Japanese phase I study (Study CA184113), Japanese phase II study (Study CA184202), foreign phase I studies (Studies MDX010-15, CA184078, and CA184087), foreign phase II studies (Studies MDX010-08, CA184004, CA184007, CA184008, CA184022, and CA184041), or foreign phase III study (Study CA184024). Serious ILD-related events were observed in 9 subjects (pneumonitis in 8 subjects and acute respiratory failure in 1 subject). A causal relationship to ipilimumab could not be ruled out for pneumonitis in 5 subjects.

PMDA's view:

ILD-related events, including a fatal event, occurred following treatment with ipilimumab. Therefore, attention must be paid to ILD-related events during treatment with ipilimumab. Healthcare professionals should be informed of the occurrence of these events, including the fatal ILD-related event in a clinical study, advised to adequately monitor the condition of patients during treatment and to appropriately response to these events, through the package insert, etc. They should also be informed about recommended actions for ILD-related events through information materials, etc.

4.(iii).B.(3).9) Infusion reaction

The applicant's explanation on infusion reaction to the ipilimumab:

The following MedDRA PTs of infusion reaction-related events were counted: "anaphylactic reaction," "anaphylactic shock," "anaphylactoid reaction," "anaphylactoid shock," "anaphylactic infusion reaction," "anaphylactoid syndrome of pregnancy," "first use syndrome," "angioedema," "reversible airways obstruction," "epiglottic oedema," "laryngeal oedema," "laryngospasm," "laryngotracheal

oedema," "pharyngeal oedema," "infusion related reaction," "bronchial obstruction," "bronchial oedema," "bronchospasm," "laryngeal obstruction," "hypersensitivity," and "drug hypersensitivity."

The following table summarized infusion reaction-related events in Studies MDX010-20 and CA184396.

Infusion reaction-related events (Studies MDX010-20 and CA184396)

Preferred term*	Number of subjects (%)							
	Study CA184396		Study MDX010-20					
	20 subjects		Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	2 (10.0)	1 (5.0)	7 (1.8)	1 (0.3)	1 (0.8)	0	3 (2.3)	1 (0.8)
Hypersensitivity	1 (5.0)	0	2 (0.5)	0	0	0	1 (0.8)	0
Anaphylactic shock	1 (5.0)	1 (5.0)	0	0	0	0	0	0
Drug hypersensitivity	0	0	1 (0.3)	0	0	0	0	0
Infusion related reaction	0	0	2 (0.5)	1 (0.3)	1 (0.8)	0	1 (0.8)	0
Bronchial obstruction	0	0	2 (0.5)	0	0	0	0	0
Bronchospasm	0	0	0	0	0	0	1 (0.8)	1 (0.8)

* MedDRA ver. 12.1 for Study MDX010-20 and MedDRA ver. 17.0 for Study CA184396

In Study MDX010-20, no infusion reaction-related events resulted in death or the discontinuation of treatment. Serious infusion reaction-related events were observed in 2 of 380 subjects in the ipilimumab/gp100 group (0.5%; bronchial obstruction and infusion related reaction in 1 subject each). A causal relationship to the investigational products could not be ruled out for infusion related reaction in 1 subject.

In Study CA184396, no infusion reaction-related events resulted in death or the discontinuation or suspension of treatment. Although a serious infusion reaction-related event (anaphylactic shock) was observed in 1 of 20 subjects (5%), it was considered to be due to contrast medium and its causal relationship to ipilimumab was ruled out.

No infusion reaction-related events resulted in death in patients treated with ipilimumab in the Japanese phase I study (Study CA184113), Japanese phase II study (Study CA184202), foreign phase I studies (Studies MDX010-15, CA184078, and CA184087), foreign phase II studies (Studies MDX010-08, CA184004, CA184007, CA184008, CA184022, and CA184041), and foreign phase III study (Study CA184024). Serious infusion reaction-related events were observed in 10 subjects (hypersensitivity in 5 subjects, infusion related reaction in 3 subjects, and bronchospasm and anaphylactic reaction in 1 subject each) and a causal relationship with ipilimumab could not be ruled out for all these events.

PMDA's view:
Serious infusion reactions occurred following treatment with ipilimumab. Therefore attention must be paid to potential infusion reactions during treatment. Healthcare professionals should be informed of the occurrence of these events and advised to adequately monitor the condition of patients during treatment and to appropriately respond to these events, through the package insert, etc.

4.(iii).B.(3).10) Other

(a) Eye disorders

The applicant's explanation on eye disorders associated with ipilimumab:

In Study MDX010-20, the instillation of corticosteroids was recommended for the treatment of uveitis or episcleritis for which a causal relationship could not be ruled out. The protocol of Study CA184396 required the discontinuation of ipilimumab if Grade ≥2 eye pain and reduced visual acuity do not respond to local treatment and fail to improve to Grade 1 within 2 weeks from the start of treatment or if the said events require systemic treatment.

PTs of eye disorders under the MedDRA SOC "eye disorders," were counted.

In Study MDX010-20, eye disorders were observed in 49 of 380 subjects (12.9%) in the ipilimumab/gp100 group, 14 of 131 subjects (10.7%) in the ipilimumab group, and 16 of 132 subjects (12.1%) in the gp100 group. Eye disorders with an incidence of ≥1% in any group treated with ipilimumab were vision blurred (14 of 380 subjects [3.7%] in the ipilimumab/gp100 group, 5 of 131 subjects [3.8%] in the ipilimumab group, and 5 of 132 subjects [3.8% in the gp100 group]; the same applies hereinafter), conjunctivitis (7 of 380 subjects [1.8%], 1 of 131 subjects [0.8%], and 1 of 132 subjects [0.8%]), eye pain (4 of 380 subjects [1.1%], 1 of 131 subjects [0.8%], and 1 of 132 subjects [0.8%]), and uveitis (1 of 380 subjects [0.3%], 2 of 131 subjects [1.5%], and 1 of 132 subjects [0.8%]). A Grade ≥3 eye disorder was vision blurred (1 of 380 subjects [0.3%], 0 subjects, and 1 of 132 subjects [0.8%]). Serious eye disorder (iridocyclitis) was observed in 1 subject (0.3%) in the ipilimumab/gp100 group, and a causal relationship to the investigational products could not be ruled out for the event. In 2 subjects (1.5%) in the ipilimumab group, an eye disorder (uveitis) led to the discontinuation of treatment, but resolved with topical corticosteroids.

In Study CA184396, eye disorders were observed in 2 of 20 subjects (10.0%; conjunctivitis allergic and eye movement disorder in 1 subject each); both were non-serious.

Serious eye disorders (uveitis and retinal detachment in 2 subjects each and eye oedema, scleritis, vitreous haemorrhage, diplopia, macular cyst, and optic ischaemic neuropathy in 1 subject each) were observed in 10 subjects treated with ipilimumab in the Japanese phase I study (Study CA184113), Japanese phase II study (Study CA184202), foreign phase I studies (Studies MDX010-15, CA184078, and CA184087), foreign phase II studies (Studies MDX010-08, CA184004, CA184007, CA184008, CA184022, and CA184041), and foreign phase III study (Studies CA184024). A causal relationship to ipilimumab could not be ruled out for uveitis in 2 subjects and eye oedema, scleritis, diplopia, and optic ischaemic neuropathy in 1 subject each.

PMDA's view:

The incidence of serious eye disorders associated with ipilimumab has been low to date, but 2 patients discontinued treatment due to eye disorder. Thus, information on eye disorders following treatment with

ipilimumab should be further collected via post-marketing surveillance, etc., and the need for precautionary advice about potential eye disorders should be determined based on the results of the surveillance, etc.

(b) Excessive immune response

The applicant's explanation on potential irAEs based on the mechanism of action of ipilimumab:
Inflammatory adverse events for which a causal relationship cannot be ruled out were counted as irAEs. The events include diarrhoea, colitis, gastrointestinal perforation, skin disorders, hepatic disorders, peripheral neuropathy, hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency, renal disorders, ILD, and eye disorders.

In Study MDX010-20, irAEs were observed in 216 of 380 subjects (56.8%) in the ipilimumab/gp100 group, 78 of 131 subjects (59.5%) in the ipilimumab group, and 42 of 132 subjects (31.8%) in the gp100 group. In Study CA184396, irAEs were observed in 12 of 20 subjects (60.0%).

In Study MDX010-20, irAEs with an incidence of ≥1% in the ipilimumab/gp100 group or the ipilimumab group were as follows (other than diarrhoea, colitis, gastrointestinal perforation; skin disorders; hepatic disorders; peripheral neuropathy; hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency; renal disorders; ILD; and eye disorders): Haematochezia (4 of 380 subjects [1.1%] in the ipilimumab/gp100 group, 1 of 131 subjects [0.8%] in the ipilimumab group, and 0 subject in the gp100 group; the same applies hereinafter), lipase increased (4 of 380 subjects [1.1%], 1 of 131 subjects [0.8%], and 0 subject), hyperthyroidism (2 of 380 subjects [0.5%], 2 of 131 subjects [1.5%], and 0 subject), blood corticotrophin decreased (0 subject, 2 of 131 subjects [1.5%], and 0 subject), and eosinophilia (1 of 380 subjects [0.3%], 2 of 131 subjects [1.5%], and 0 subject).

In Study MDX010-20, irAEs (other than diarrhoea, colitis, gastrointestinal perforation; skin disorders; hepatic dysfunction; peripheral neuropathy; hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency; renal disorders; ILD; and eye disorders) resulted in death in 1 of 380 subjects (0.3%) in the ipilimumab/gp100 group (multi-organ failure), serious irAEs other than death were observed in 4 of 380 subjects (1.1%) in the ipilimumab/gp100 group (haematochezia, hypogonadism, haemolytic anaemia, and meningitis in 1 subject each) and 1 of 131 subjects (0.8%) in the ipilimumab group (blood corticotrophin decreased), and an irAE led to the discontinuation of treatment in 1 of 380 subjects (0.3%) in the ipilimumab/gp100 group (haemolytic anaemia).

In Study CA184396, irAEs (other than diarrhoea, colitis, gastrointestinal perforation; skin disorders; hepatic dysfunction; peripheral neuropathy; hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency; renal disorders; ILD; and eye disorders) were observed in 2 or 20 subjects (10.0%; hypersensitivity and diabetes mellitus in 1 subject each). Diabetes mellitus was serious.

In the foreign phase I study (Study CA184087), serious myasthenia gravis for which a causal relationship to ipilimumab could not be ruled out was observed in 1 subject treated with ipilimumab (Process B ([redacted]L)). This subject tested positive for antiacetylcholine receptor antibodies (unknown at baseline).

As described above, immune-related adverse events occurred following treatment with ipilimumab in the Japanese and foreign clinical studies, and therefore patients treated with ipilimumab should be monitored for these events after treatment. Using the package insert, the applicant should advise healthcare professionals not to administer ipilimumab to patients with severe active autoimmune disease.

PMDA's view:
Using information materials, etc., the applicant should advise healthcare professionals to carefully determine the eligibility of patients for ipilimumab, to monitor patients for immune-related symptoms following ipilimumab therapy, and to provide appropriate treatment for patients presenting with symptoms suggestive of excessive immune response, because of the following reasons:

- The pharmacological action of ipilimumab indicated the possibility of an adverse event caused by immune response to the drug.
- Some patients experienced adverse events suspected to be due to immune response.
- The Japanese and foreign clinical studies excluded patients with autoimmune diseases or a history of autoimmune disease.

4.(iii).B.(4) Clinical positioning and indications
The proposed indication of ipilimumab was "unresectable or metastatic malignant melanoma."

Based on the findings in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety" and the discussion presented in 4.(iii).B.(4).1) to 3) sections, PMDA considers that the indication of "unresectable malignant melanoma" is appropriate, provided that the "Clinical Studies" section of the package insert mentions previous treatment, etc. of patients enrolled in Study MDX010-20 and the "Precautions for Indications" section includes the following precautionary statements:

- Eligibility of patients for treatment with ipilimumab should be determined based on a good understanding of the "Clinical Studies" section of the package insert and the efficacy and safety of ipilimumab. In particular for previously untreated patients, other therapeutic options should also be carefully considered.
- The efficacy and safety of ipilimumab in postoperative adjuvant chemotherapy have not been established.

4.(iii).B.(4).1) Clinical positioning, target patient populations (in terms of previous treatment), and indication of ipilimumab
PMDA acknowledged that ipilimumab for the treatment of unresectable malignant melanoma is explained in foreign practice guidelines and textbooks of clinical oncology as summarized below. No explanation on ipilimumab was found in "Clinical practice guidelines for malignant skin tumors, Version

1" (edited by the Japanese Skin Cancer Society, published by Kanehara, 2007) or textbooks of clinical oncology.

Clinical practice guidelines

- The US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Melanoma (NCCN guidelines) (v.2.2015): Ipilimumab is strongly recommended for the treatment of unresectable malignant melanoma (Category 1[*]).

  [*] Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- The ESMO Clinical Practice Guidelines of the European Society for Medical Oncology (ESMO guidelines) (*Ann Oncol.* 2012; 23 Suppl 7: vii86-91): Ipilimumab is recommended as first-line or second-line therapy unresectable malignant melanoma.
- The US National Cancer Institute Physician Data Query (NCI-PDQ) (version dated November 7, 2014): The utility of ipilimumab was supported by Study CA184024 in previously untreated patients with malignant melanoma and Study MDX010-20 in previously treated patients with malignant melanoma.

Textbooks

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (Lippincott Williams & Wilkins 2014, PA, US): The efficacy data from Study MDX010-20 demonstrated prolonged OS in patients with unresectable malignant melanoma treated with ipilimumab.

PMDA asked the applicant to explain the clinical positioning of ipilimumab in the treatment of unresectable malignant melanoma, target patient populations for ipilimumab (in terms of previous treatment), and indication of ipilimumab.

The applicant's response:
In Study MDX010-20 in previously treated patients with unresectable malignant melanoma, ipilimumab demonstrated tolerability and a certain level of efficacy. Ipilimumab is therefore recommended for this patient population.

At the same time, the use of ipilimumab is also recommended for previously untreated patients based on the following findings:

- In foreign practice guidelines, ipilimumab is recommended for patients with unresectable malignant melanoma, regardless of previous treatment.
- Pooled analyses of OS data from Study MDX010-20 and foreign phase II studies (the 3 mg/kg groups in Studies CA184004, CA184022, and MDX010-08) revealed the median OS (95% CI) of 13.47 (8.77, 15.47) months in previously untreated patients and 9.72 (8.34, 12.1) months in previously treated patients, showing no clear difference between the two patient population.
- In Study CA184396, 1 of 4 previously untreated patients responded to the treatment. Ipilimumab was tolerated by this patient.

- In previously untreated patients with unresectable malignant melanoma, OS and 1-year survival rate[*1] in patients treated with ipilimumab tended to be better than OS and 1-year survival rate[*2] in patients treated with DTIC.

[*1] Results in previously untreated patients from the pooled data from foreign phase II studies (the 3 mg/kg groups in Studies CA184004, CA184022, and MDX010-08) and the results of 2 foreign observation studies in previously untreated patients with advanced malignant melanoma in the post-marketing phase (Observation studies CA184338 and CA184332)

[*2] Results of the administration of DTIC in Study CA184024 and published papers (*N Engl J Med.* 1992; 327: 516-23, *J Clin Oncol.* 1998; 16: 1743-51, *J Clin Oncol.* 1999; 17: 2745-51)

Accordingly, ipilimumab is considered a therapeutic option for unresectable malignant melanoma, regardless of previous treatment. The indication of ipilimumab was proposed to be "unresectable or metastatic malignant melanoma."

PMDA's view:

Ipilimumab is recommended for previously treated patients with unresectable malignant melanoma, the patient population enrolled in Study MDX010-20. Ipilimumab is therefore considered a therapeutic option for previously treated patients with unresectable malignant melanoma.

Furthermore, the following findings indicate little necessity to exclude previously untreated patients from the target population for ipilimumab.

- Malignant melanoma is of poor prognosis, and therapeutic options for previously untreated patients with unresectable malignant melanoma are extremely limited. DTIC and vemurafenib are available as approved antineoplastic agents for previously untreated patients in Japan. Nevertheless, treatment with ipilimumab in these patients is of a certain clinical significance because:
  - No study results have shown DTIC to prolong OS.
  - Vemurafenib is indicated only for "patients with unresectable malignant melanoma with mutation in *BRAF* gene."

Accordingly, the proposed indication should be changed to "unresectable malignant melanoma." In addition, the package insert should appropriately provide information on previous treatment, etc. of patients enrolled in the clinical studies in the "Clinical Studies" section, and the following precautionary advice in the "Precautions for Indications" section.

- Eligibility of patients for treatment with ipilimumab should be determined based on a good understanding of the "Clinical Studies" section of the package insert and the efficacy and safety of ipilimumab. In particular for previously untreated patients, other therapeutic options should also be carefully considered.

4.(iii).B.(4).2) Expression of HLA-A2*0201

Study MDX010-20 was conducted in HLA-A2*0201-positive patients [see "4.(iii).A-1.(2).4) Foreign phase III study"]. The applicant discussed whether patients should be screened for HLA-A2*0201 expression before starting treatment with ipilimumab.

The applicant's explanation:

Gp100, used as a control in Study MDX010-20, is an antigen peptide that activates T cells of HLA-A2*0201-positive patients with malignant melanoma. Therefore HLA-A2*0201-positive patients alone were eligible for Study MDX010-20. However, ipilimumab is expected to inhibit tumor growth by blocking interactions between the CTLA-4 expressed on activated T cells and B7 molecules expressed on antigen-presenting cells [see "3.(i).B *Outline of the review by PMDA*, Efficacy of ipilimumab against malignant melanoma"]. Thus, ipilimumab is expected to exhibit efficacy regardless of HLA-A2*0201. In fact, HLA-A2*0201-negative patients were enrolled in foreign phase II studies (Studies CA184004 and CA184022), and the following results were obtained. Thus, the efficacy of ipilimumab is expected also in HLA-A2*0201-negative patients with unresectable malignant melanoma and screening for HLA-A2*0201 expression need not be performed before starting ipilimumab therapy.

- The analyses of pooled data from Study MDX010-20 and foreign phase II studies (the 3 mg/kg groups in Studies CA184004 and CA184022) revealed that the survival curves were similar for HLA-A2*0201-positive patients and HLA-A2*0201-negative patients.
- In foreign phase II studies (Studies CA184004 and CA184022), 3 of 46 HLA-A2*0201-negative patients in the 3 mg/kg groups responded to ipilimumab treatment.

PMDA accepted this explanation by the applicant.

4.(iii).B.(4).3) Efficacy and safety of ipilimumab as postoperative adjuvant chemotherapy

No clinical study results have been obtained regarding the efficacy and safety of ipilimumab in postoperative adjuvant chemotherapy, and the use of ipilimumab is therefore not recommended for postoperative adjuvant chemotherapy. The applicant mentioned that this will be highlighted to healthcare professionals.

PMDA accepted the explanation provided by the applicant.

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

The proposed dosage and administration was that "the usual adult dosage is 3 mg/kg of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 times." The "Precautions of Dosage and Administration" section explained the following:

- Preparation methods of injection solution and infusion time
- New lesions may develop or existing lesions may grow during treatment with ipilimumab. However, consider continuing treatment if ipilimumab is well tolerated by the patient without rapid exacerbation of the condition.
- Criteria for the suspension or discontinuation of ipilimumab

As a result of the discussion given in 4.(iii).B.(5).1) to 3) sections, PMDA has concluded that dosage and administration should be that "the usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 times." Meanwhile,

precautionary advice on the following should be included in the "Precautions of Dosage and Administration" section of the package insert:

- Criteria for the suspension or discontinuation of ipilimumab
- Preparation methods of injection solution and infusion time
- Prohibition of the concomitant use of other antineoplastic agents

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

The applicant's explanation on the rationale for the proposed dosage and administration of ipilimumab:
The proposed dosage and administration was based on the dosage regimen used in Studies MDX010-20 and CA184396.

The dosage regimen of study MDX010-20, 3 mg/kg every 3 weeks for 4 times, was determined after discussion (presented below) based on the results of foreign phase II studies (Studies MDX010-05 and MDX010-08) in patients with unresectable malignant melanoma. (The results of Studies MDX010-05 and MDX010-08 were available before the start of Study MDX010-20.) In Study MDX010-20, re-treatment was allowed [see "4.(iii).A-1.(2).4) Foreign phase III study"]. Of 40 of 676 subjects who received re-treatment (29 in the ipilimumab/gp100 group, 9 in the ipilimumab group, and 2 in the gp100 group), 6 subjects responded (3 in the ipilimumab/gp100 group and 3 in the ipilimumab group). However, since the analysis was intended to evaluate the efficacy, and the re-treatment of treatment was not defined in the proposed dosage and administration.

- In Study MDX010-05, ipilimumab in combination with gp100 demonstrated higher disease control rates* in (a) the group treated with ipilimumab 3 mg/kg every 3 weeks than in (b) the group treated with ipilimumab at the first dose of 3 mg/kg and subsequent doses of 1 mg/kg every 3 weeks. Thus, greater therapeutic effects were expected with ipilimumab at 3 mg/kg than at 1 mg/kg.
- The efficacy and safety of ipilimumab in Studies MDX010-05 and MDX010-08 (ipilimumab 3 mg/kg every 3 weeks) was compared with those in Study MDX010-08 (ipilimumab 3 mg/kg every 4 weeks for 4 times). The results showed that 4 doses every 3 weeks would enhance the therapeutic effects of ipilimumab and reduce adverse events due to the mechanism of action of ipilimumab.

* Disease control was defined as SD (stable duration, ≥3 months from Week 12) or PR or CR in the tumor evaluation in the induction period

The dosage regimen in Study CA184396 was determined based on the dosage regimen in Study MDX010-20, but re-treatment was not performed in Study CA184396.

Since a certain time may require for ipilimumab to show its effect, treatment should not be discontinued too early. In Study MDX010-20, patients meeting the following criteria continued to receive ipilimumab at the discretion of the investigators even if disease progression was evident before diagnostic imaging scheduled at Week 12.

- No rapid disease progression or symptoms associated with disease progression
- Stable performance status

A total of 5 subjects in the ipilimumab/gp100 or ipilimumab group received ipilimumab on the day of confirmation of PD or later. Thus, the "Precautions of Dosage and Administration" section of the package insert should include the following statement: "New lesions may develop or existing lesions may grow during treatment with ipilimumab. However, consider continuing treatment if ipilimumab is well tolerated by the patient without rapid exacerbation of the condition." A foreign phase III study (Study CA184169) in patients with unresectable malignant melanoma is currently underway to compare the efficacy and safety of ipilimumab 3 mg/kg with those of ipilimumab 10 mg/kg.

PMDA's view:
The dosage regimen of Study MDX010-20 was determined without detailed discussion, and Study CA184169 (which compares the efficacy and safety between ipilimumab 3 and 10 mg/kg) is still underway. For these reasons, whether 3 mg/kg is the most appropriate dose is unknown at present. However, in light of the clinical utility of ipilimumab shown in Study MDX010-20 and other studies [see "4.(iii).B.(2) Efficacy"], defining the dosage and administration of ipilimumab based on the dosage regimen of Study MDX010-20 is acceptable.

PMDA accepted the applicant's explanation that "re-treatment" would not be included in the dosage and administration.

Furthermore, a precautionary statement about the decision on the continuation of treatment following the development of new lesions or growth of existing lesions during treatment period need not be added to the "Precautions of Dosage and Administration" section, because (a) only a small number of patients were treated with ipilimumab on the day of confirmation of PD or later in Study MDX010-20, and the clinical significance of ipilimumab administered to these patients after confirmation of PD is unclear, and because (b) there were no criteria for the continuation of ipilimumab after disease progression in Study CA184396.

The results of ongoing Study CA184169 are expected to clarify the positioning of 3 and 10 mg/kg doses of ipilimumab.

4.(iii).B.(5).2) Suspension or discontinuation of ipilimumab
The applicant's explanation on the rationale for the criteria for suspension or discontinuation of ipilimumab therapy:
The protocol of Study MDX010-20 specified tests and treatment recommended in case of irAEs (of the gastrointestinal tract, liver, skin, eye, endocrine, and pancreas) and the criteria for the suspension or discontinuation of ipilimumab. Ipilimumab was tolerable in the study.

- Treatment with ipilimumab is suspended in case of the following adverse events: (1) Grade 2 skin-related irAEs or Grade 3 skin disorders for which a causal relationship to ipilimumab cannot be ruled out; or (2) Non-skin-related adverse events of Grade 2 or acceptable Grade 3 irAEs for which

a causal relationship to ipilimumab cannot be ruled out. The suspension of treatment should be continued until the events improve to Grade ≤1 or the baseline level.

- The investigational products are discontinued in case of Grade 3 adverse events other than skin disorders for which a causal relationship to investigational product cannot be ruled out (excluding treatable inflammation regarded as a manifestation of local response to an antitumor therapy and endocrine disorder that can be controlled by hormone replacement therapy) or Grade 4 adverse events for which a causal relationship to investigational product cannot be ruled out.

Based on safety information of ipilimumab accumulated since the start of Study MDX010-20, the actions to be taken for the irAEs in Study MDX010-20 were revised, and a management algorithm for irAEs was created. In Study CA184396, recommended actions were taken for irAEs based on the management algorithm, and ipilimumab was tolerable.

Accordingly, the following criteria were defined for the suspension or discontinuation of ipilimumab in case of irAEs based on the management algorithm for irAEs. These criteria should be included in the "Precautions of Dosage and Administration "section in the package insert.

- The administration of ipilimumab should be suspended in case of Grade 2 adverse events (excluding endocrine or skin disorders), Grade 3 skin disorders, or symptomatic endocrine disorders.
- The administration of ipilimumab should be discontinued in case of Grade ≥2 eye disorders failing to respond to a local immunosuppressive therapy, Grade ≥3 events (excluding endocrine and skin disorders), or Grade 4 skin disorders.

PMDA accepted this explanation by the applicant.

4.(iii).B.(5).3) Concomitant use of other antineoplastic agents

The applicant's explanation on the need for precautionary advice on the combination of ipilimumab with other antineoplastic agents:

The efficacy and safety of ipilimumab in combination with other antineoplastic agents have yet to be established, and therefore concomitant use of other antineoplastic agents is not recommended. The package insert will give precautionary advice on the combination of ipilimumab and DTIC or vemurafenib, in consideration of the following:

- In the Japanese phase II study (Study CA184202) in previously untreated patients with unresectable malignant melanoma, 10 of 15 subjects exhibited a Grade ≥3 AST increased/ALT increased following the administration of ipilimumab 10 mg/kg with DTIC 850 mg/m^2, and the enrollment of patients in this study was discontinued. The events of AST increased/ALT increased were treated with corticosteroids or immunosuppressants, and some patients needed several months to recover.
- In a foreign phase I study (Study CA194161) in patients with metastatic malignant melanoma who had a *BRAF* gene mutation, hepatic dysfunction due to dose-limiting toxicity were observed in 6 of

10 patients following the administration of ipilimumab 3 mg/kg with vemurafenib 720 or 960 mg twice a day. This study was discontinued.

PMDA's view:
PMDA basically accepted the applicant's explanation. However, the package insert should properly advise against using ipilimumab with other antineoplastic agents in the "Precautions of Dosage and Administration" section.

4.(iii).B.(6) Post-marketing investigations
The applicant plans to undertake a post-marketing surveillance (the surveillance) that covers all patients with malignant melanoma treated with ipilimumab based on the all-case surveillance method, to examine the safety, etc. of ipilimumab in post-marketing clinical use.

The applicant's explanation on the surveillance plan:
The priority investigation items are immune-related adverse reactions (irARs) considered characteristic of ipilimumab (gastrointestinal, hepatic, dermatological, neurological, and endocrine irARs and other irARs).

The target sample size is 100, based on the incidence of irARs in Study MDX010-20. This sample size will allow for a certain level of precision in identifying each irAR (excluding neurological irARs).

The observation period was determined to be 12 months after the start of ipilimumab for the following reasons:

- In Studies MDX010-20 and CA184396, many adverse events were observed within 6 months after the start of ipilimumab. No adverse events tended to increase in incidence at >6 months. However, safety information should be further collected from 6 to 12 months after the start of ipilimumab because:
  - In the ipilimumab groups of Study MDX010-20, large intestine perforation, rash, vitiligo, and hypothyroidism, all characteristic of ipilimumab, were observed in 1 patient each at >6 months. Hypothyroidism was the latest event observed on Day 317.
  - In Study CA184396, vitiligo, hypopituitarism, and hypothyroidism, all characteristic of ipilimumab, were observed in 1 patient each at >6 months. Hypothyroidism was the latest event observed on Day 197.

PMDA's view:
Because of extremely limited information on the safety of ipilimumab in Japanese patients with malignant melanoma, relevant safety information should be collected promptly in an impartial manner. Therefore, the surveillance should cover all patients treated with ipilimumab over a certain period of time, based on the estimated number of patients to be treated with ipilimumab, in view of the feasibility. Obtained safety information must be promptly provided to healthcare professionals.

Priority investigation items of surveillance should be (a) diarrhoea, colitis, gastrointestinal perforation, (b) skin disorders, (c) hepatic disorders, (d) hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency, (e) peripheral neuropathy, (f) renal disorders, (g) ILD, and (h) infusion reaction. Attention should be paid to these adverse events during treatment with ipilimumab [see "4.(iii).B.(3) Safety"].

The observation period can be defined as 6 months after the start of ipilimumab, because i) most adverse events, including those requiring attention during treatment with ipilimumab, were observed within 6 months after the start of ipilimumab, and ii) no adverse events tended to increase in incidence >6 months after the start of ipilimumab.

4.(iv).A Summary of the submitted data

4.(iv).A Adverse events, etc. observed in clinical studies

This section explains major adverse events other than death based on the submitted clinical study results. Death is reported in "4.(iii) Summary of clinical efficacy and safety."

4.(iv).A.(1) Japanese phase I study (Study CA184113)

Adverse events were observed in 8 of 8 subjects (100%) in the 3 mg/kg group and 7 of 7 subjects (100%) in the 10 mg/kg group. Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 8 of 8 subjects (100%) in the 3 mg/kg group and in 7 of 7 subjects (100%) in the 10 mg/kg group. The following table lists adverse events occurring in ≥3 subjects in either group.

Adverse events occurring in ≥3 subjects in either group

System organ class Preferred term (MedDRA/J ver.16.0)	Number of subjects (%)			
	3 mg/kg 8 subjects		10 mg/kg 7 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	8 (100)	8 (100)	7 (100)	7 (100)
Blood and lymphatic system disorders				
Leukopenia	4 (50.0)	4 (50.0)	2 (28.6)	2 (28.6)
Neutropenia	7 (87.5)	7 (87.5)	7 (100)	7 (100)
Gastrointestinal disorders				
Constipation	4 (50.0)	0	5 (71.4)	0
Diarrhoea	3 (37.5)	0	2 (28.6)	0
Nausea	5 (62.5)	0	4 (57.1)	0
General disorders and administration site conditions				
Fatigue	2 (25.0)	0	5 (71.4)	0
Pyrexia	3 (37.5)	0	3 (42.9)	0
Laboratory tests				
Electrocardiogram QT prolonged	4 (50.0)	0	2 (28.6)	0
Haemoglobin decreased	0	0	4 (57.1)	4 (57.1)
Weight decreased	4 (50.0)	0	3 (42.9)	0
Metabolism and nutrition disorders				
Decreased appetite	7 (87.5)	0	6 (85.7)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	8 (100)	0	6 (85.7)	0
Myalgia	5 (62.5)	0	2 (28.6)	0
Nervous system disorders				
Hypoaesthesia	3 (37.5)	0	0	0
Peripheral sensory neuropathy	7 (87.5)	0	6 (85.7)	0
Skin and subcutaneous tissue disorders				
Alopecia	6 (75.0)	0	7 (100)	0
Pruritus	1 (12.5)	0	4 (57.1)	0
Rash	6 (75.0)	1 (12.5)	5 (71.4)	0

Serious adverse events were observed in 3 of 8 subjects (37.5%) in the 3 mg/kg group and in 1 of 7 subjects (14.3%) in the 10 mg/kg group. These events consisted of adrenal insufficiency, hypoparathyroidism, hyponatraemia, and dyspnoea exertional in 1 subject (12.5%) each in the 3 mg/kg group and pneumonitis in 1 subject (14.3%) in the 10 mg/kg group. For all these events, a causal relationship to the investigational products could not be ruled out.

Adverse events led to the discontinuation of treatment with the investigational products in 6 of 8 subjects (75.0%) in the 3 mg/kg group and in 3 of 7 subjects (42.9%) in the 10 mg/kg group. These events consisted of adrenal insufficiency, hypoparathyroidism, thrombocytopenia, retinal haemorrhage, amylase increased, hypocalcaemia, and rash in 1 subject (12.5%) each in the 3 mg/kg group and neutropenia, diarrhoea, pyrexia, and pneumonitis in 1 subject (14.3%) each in the 10 mg/kg group. For all these events, a causal relationship to the investigational products could not be ruled out.

4.(iv).A.(2) Japanese phase II study (Study CA184396)

Adverse events were observed in 20 of 20 subjects (100%). Adverse events for which a causal relationship to ipilimumab could not be ruled out occurred in 12 of 20 subjects (60.0%). The following table lists adverse events with an incidence of ≥20%.

Adverse events with an incidence ≥20%

System organ class Preferred term (MedDRA/J ver.17.0)	Number of subjects (%) 20 subjects	
	All Grades	Grade ≥3
All adverse events	20 (100)	11 (55.0)
Gastrointestinal disorders		
Diarrhoea	4 (20.0)	0
General disorders and administration site conditions		
Pyrexia	6 (30.0)	1 (5.0)
Laboratory tests		
ALT increased	4 (20.0)	1 (5.0)
AST increased	4 (20.0)	2 (10.0)
Metabolism and nutrition disorders		
Decreased appetite	5 (25.0)	1 (5.0)
Skin and subcutaneous tissue disorders		
Rash	8 (40.0)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase

Serious adverse events were observed in 11 of 20 subjects (55.0%). The events consisted of malignant neoplasm progression, ALT increased, and AST increased in 2 subjects (10.0%) each and malignant melanoma, metastases to meninges, metastatic pain, tumour pain, brain oedema, cerebral infarction, hydrocephalus, C-reactive protein increased, diabetes mellitus, tumour lysis syndrome, dyspnoea, pulmonary embolism, ileus, multi-organ failure, anaphylactic shock, erysipelas, bone pain, and deep vein thrombosis in 1 subject (5.0%) each. A causal relationship to ipilimumab could not be ruled out for ALT increased and AST increased in 2 subjects each or for C-reactive protein increased and diabetes mellitus in 1 subject each.

One of 20 subjects (5.0%) discontinued treatment with investigational product because of an adverse event (metastases to meninges). However, a causal relationship to ipilimumab was ruled out for the event.

4.(iv).A.(3) Foreign phase II study (Study CA184022)

Adverse events were observed in 68 of 72 subjects (94.4%) in the 0.3 mg/kg group, 69 of 71 subjects (97.2%) in the 3 mg/kg group, and 71 of 71 subjects (100%) in the 10 mg/kg group. Adverse events for which a causal relationship to ipilimumab could not be ruled out were observed in 46 of 72 subjects (63.9%) in the 0.3 mg/kg group, 55 of 71 subjects (77.5%) in the 3 mg/kg group, and 59 of 71 subjects (83.1%) in the 10 mg/kg group. The following table lists adverse events with an incidence of ≥20% in any group.

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

System organ class Preferred term (MedDRA/J ver.12.1)	Number of subjects (%)					
	0.3 mg/kg 72 subjects		3 mg/kg 71 subjects		10mg/kg 71 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	68 (94.4)	36 (50.0)	69 (97.2)	35 (49.3)	71 (100)	44 (62.0)
Gastrointestinal disorders						
Constipation	19 (26.4)	0	11 (15.5)	0	13 (18.3)	3 (4.2)
Diarrhoea	16 (22.2)	0	22 (31.0)	1 (1.4)	31 (43.7)	10 (14.1)
Nausea	19 (26.4)	0	20 (28.2)	1 (1.4)	24 (33.8)	4 (5.6)
Vomiting	10 (13.9)	0	13 (18.3)	1 (1.4)	16 (22.5)	1 (1.4)
General disorders and administration site conditions						
Fatigue	24 (33.3)	5 (6.9)	20 (28.2)	4 (5.6)	22 (31.0)	8 (11.3)
Pyrexia	7 (9.7)	0	8 (11.3)	1 (1.4)	15 (21.1)	1 (1.4)
Metabolism and nutrition disorders						
Decreased appetite	15 (20.8)	4 (5.6)	6 (8.5)	2 (2.8)	8 (11.3)	0
Skin and subcutaneous tissue disorders						
Pruritus	2 (2.8)	0	18 (25.4)	1 (1.4)	23 (32.4)	2 (2.8)
Rash	6 (8.3)	1 (1.4)	19 (26.8)	1 (1.4)	18 (25.4)	0

Serious adverse events were observed in 26 of 72 subjects (36.1%) in the 0.3 mg/kg group, 35 of 71 subjects (49.3%) in the 3 mg/kg group, and 38 of 71 subjects (53.5%) in the 10 mg/kg group. Serious adverse events occurring in ≥2 subjects in each group were as follows: disease progression in 8 subjects (11.1%), death and dyspnoea in 4 subjects (5.6%) each, anaemia in 3 subjects (4.2%), asthenia, general physical health deterioration, pyrexia, malignant neoplasm progression, tumour pain, decreased appetite, bone pain, and haemoglobin decreased in 2 subjects (2.8%) each in the 0.3 mg/kg group; disease progression in 7 subjects (9.9%), vomiting in 4 subjects (5.6%), death, pyrexia, colitis, and diarrhoea in 3 subjects (4.2%) each, asthenia, bone pain, decreased appetite, malignant neoplasm progression, confusional state, and hypophysitis in 2 subjects (2.8%) each in the 3 mg/kg group; and diarrhoea in 11 subjects (15.5%), disease progression in 10 subjects (14.1%), constipation and nausea in 4 subjects (5.6%) each, abdominal pain and colitis in 3 subjects (4.2%) each, and enterocolitis, vomiting, death, pyrexia, facial palsy, malignant melanoma, dehydration, ALT increased, renal failure, hypophysitis, and back pain in 2 subjects (2.8%) each in the 10 mg/kg group. A causal relationship to ipilimumab could not be ruled out for the following events: anaemia in 2 subjects or for asthenia, pyrexia, haemoglobin decreased, decreased appetite, and bone pain in 1 subject each in the 0.3 mg/kg group; for colitis and diarrhoea in 3 subjects each, pyrexia and hypophysitis in 2 subjects each, and asthenia, vomiting, decreased appetite, and confusional state in 1 subject each in the 3 mg/kg group; and for diarrhoea in 11 subjects, colitis in 3 subjects, enterocolitis, vomiting, ALT increased, and hypophysitis in 2 subjects each, and abdominal pain, nausea, dehydration, and facial palsy in 1 subject each in the 10 mg/kg group.

Adverse events led to the discontinuation of ipilimumab in 9 of 72 subjects (12.5%) in the 0.3 mg/kg group, 7 of 71 subjects (9.9%) in the 3 mg/kg group, and 19 of 71 subjects (26.8%) in the 10 mg/kg group. Adverse events occurring in ≥2 subjects in each group and leading to the discontinuation of ipilimumab were disease progression in 5 subjects (6.9%) and death and fatigue in 2 subjects (2.8%) each in the 0.3 mg/kg group and diarrhoea in 6 subjects (8.5%), disease progression in 3 subjects (4.2%),

and malignant melanoma and ALT increased in 2 subjects (2.8%) each in the 10 mg/kg group. A causal relationship to ipilimumab could not be ruled out for diarrhoea in 6 subjects, disease progression in 3 subjects, and malignant melanoma and ALT increased in 2 subjects each in the 10 mg/kg.

4.(iv).A.(4) Foreign phase II study (Study CA184004)

Adverse events were observed in 39 of 40 subjects (97.5%) in the 3 mg/kg group and in 38 of 42 subjects (90.5%) in the 10 mg/kg group. Adverse events for which a causal relationship to ipilimumab could not be ruled out were observed in 33 of 40 subjects (82.5%) in the 3 mg/kg group and in 32 of 42 subjects (76.2%) in the 10 mg/kg group. The following table lists adverse events with an incidence of ≥20% in either group.

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

System organ class Preferred term (MedDRA/J ver.12.1)	Number of subjects (%)			
	3 mg/kg 40 subjects		10 mg/kg 42 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	39 (97.5)	18 (45.0)	38 (90.5)	25 (59.5)
Gastrointestinal disorders				
Diarrhoea	12 (30.0)	2 (5.0)	21 (50.0)	3 (7.1)
Nausea	10 (25.0)	1 (2.5)	16 (38.1)	1 (2.4)
General disorders and administration site conditions				
Fatigue	19 (47.5)	4 (10.0)	16 (38.1)	2 (4.8)
Pyrexia	11 (27.5)	1 (2.5)	10 (23.8)	1 (2.4)
Metabolism and nutrition disorders				
Decreased appetite	7 (17.5)	2 (5.0)	12 (28.6)	2 (4.8)
Respiratory, thoracic, and mediastinal disorders				
Dyspnoea	4 (10.0)	0	9 (21.4)	3 (7.1)
Skin and subcutaneous tissue disorders				
Pruritus	11 (27.5)	0	13 (31.0)	1 (2.4)
Rash	13 (32.5)	0	17 (40.5)	1 (2.4)

Serious adverse events were observed in 18 of 40 subjects (45.0%) in the 3 mg/kg group and in 20 of 42 subjects (47.6%) in the 10 mg/kg group. Serious adverse events occurring in ≥2 subjects in either group were disease progression in 6 subjects (15.0%), haemoglobin decreased in 3 subjects (7.5%), colitis, diarrhoea, pyrexia, vomiting, hypopituitarism, convulsion, and bile duct obstruction in 2 subjects (5.0%) each in the 3 mg/kg group and disease progression in 5 subjects (11.9%), colitis, diarrhoea, dehydration, and dyspnoea in 2 subjects (4.8%) each in the 10 mg/kg group. A causal relationship to ipilimumab could not be ruled out for colitis, diarrhoea, and hypopituitarism in 2 subjects each and vomiting and pyrexia in 1 subject each in the 3 mg/kg group and for colitis, diarrhoea, and dehydration in 2 subjects each in the 10 mg/kg group.

Adverse events led to the discontinuation of ipilimumab in 5 of 40 subjects (12.5%) in the 3 mg/kg group and 11 of 42 subjects (26.2%) in the 10 mg/kg group. Adverse events occurring in ≥2 subjects in each group and leading to the discontinuation of ipilimumab were decreased appetite and hypopituitarism in 2 subjects (5.0%) each in the 3 mg/kg group and colitis in 3 subjects (7.1%) and decreased appetite and diarrhoea in 2 subjects (4.8%) each in the 10 mg/kg group. A causal relationship

to ipilimumab could not be ruled out for decreased appetite and hypopituitarism in 2 subjects each in the 3 mg/kg group and for colitis in 3 subjects, diarrhoea in 2 subjects, and decreased appetite in 1 subject in the 10 mg/kg group.

4.(iv).A.(5) Foreign phase II study (Study MDX010-08)

Adverse events were observed in 35 of 35 subjects (100%) in the ipilimumab/DTIC group and in 39 of 39 subjects (100%) in the ipilimumab group. Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 31 of 35 subjects (88.6%) in the ipilimumab/DTIC group and in 29 of 39 subjects (74.4%) in the ipilimumab group. The following table lists adverse events with an incidence of ≥20% in either group.

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

System organ class Preferred term (MedDRA/J ver.14.1)	Number of subjects (%)			
	Ipilimumab/DTIC 35 subjects		Ipilimumab 39 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	35 (100)	15 (42.9)	39 (100)	19 (48.7)
Gastrointestinal disorders				
Abdominal pain	7 (20.0)	1 (2.9)	8 (20.5)	2 (5.1)
Constipation	13 (37.1)	0	5 (12.8)	0
Diarrhoea	14 (40.0)	1 (2.9)	12 (30.8)	0
Nausea	25 (71.4)	2 (5.7)	14 (35.9)	0
Vomiting	9 (25.7)	1 (2.9)	7 (17.9)	0
General disorders and administration site conditions				
Chest pain	1 (2.9)	0	8 (20.5)	3 (7.7)
Chills	10 (28.6)	0	11 (28.2)	0
Fatigue	23 (65.7)	3 (8.6)	19 (48.7)	1 (2.6)
Pyrexia	11 (31.4)	1 (2.9)	6 (15.4)	0
Metabolism and nutrition disorders				
Decreased appetite	12 (34.3)	0	14 (35.9)	1 (2.6)
Musculoskeletal and connective tissue disorders				
Arthralgia	7 (20.0)	0	3 (7.7)	1 (2.6)
Back pain	8 (22.9)	1 (2.9)	4 (10.3)	1 (2.6)
Pain in extremity	7 (20.0)	0	8 (20.5)	3 (7.7)
Nervous system disorders				
Dizziness	8 (22.9)	0	4 (10.3)	1 (2.6)
Headache	7 (20.0)	0	6 (15.4)	0
Psychiatric disorders				
Insomnia	7 (20.0)	0	4 (10.3)	0
Respiratory, thoracic, and mediastinal disorders				
Cough	13 (37.1)	0	5 (12.8)	0
Dyspnoea	7 (20.0)	1 (2.9)	5 (12.8)	2 (5.1)
Oropharyngeal pain	7 (20.0)	0	0	0
Skin and subcutaneous tissue disorders				
Pruritus	9 (25.7)	0	11 (28.2)	0
Rash	10 (28.6)	1 (2.9)	13 (33.3)	1 (2.6)

Serious adverse events were observed in 13 of 35 subjects (37.1%) in the ipilimumab/DTIC group and 11 of 39 subjects (28.2%) in the ipilimumab group. Serious adverse events occurring in ≥2 subjects in each group were dehydration in 4 subjects (11.4%), pyrexia in 3 subjects (8.6%), and diarrhoea, nausea, and disease progression in 2 subjects (5.7%) each in the ipilimumab/DTIC group and colitis in 3 subjects

(7.7%) and diarrhoea and disease progression in 2 subjects (5.1%) each in the ipilimumab group. A causal relationship to the investigational products could not be ruled out for diarrhoea in 2 subjects and pyrexia in 1 subject in the ipilimumab/DTIC group and for colitis in 3 subjects and diarrhoea in 2 subjects in the ipilimumab group.

Adverse events led to the discontinuation of investigational products in 3 of 39 subjects (7.7%) in the ipilimumab group and in 5 of 35 subjects (14.3%) in the ipilimumab/DTIC group. These adverse events were colitis in 2 subjects (5.1%) and uveitis and disease progression in 1 subject (2.6%) each in the ipilimumab group and pneumonia, rash pruritic, multi-organ failure, AST increased, ALT increased, and rash in 1 subject (2.9%) each in the ipilimumab/DTIC group. A causal relationship to the investigational products could not be ruled out for colitis in 2 subjects and uveitis in 1 subject in the ipilimumab group and for rash pruritic, multi-organ failure, AST increased, ALT increased, and rash in 1 subject each in the ipilimumab/DTIC group.

4.(iv).A.(6) Foreign phase III study (Study MDX010-20)

Adverse events were observed in 127 of 131 subjects (96.9%) in the ipilimumab group, 374 of 380 subjects (98.4%) in the ipilimumab/gp100 group, and 128 of 132 subjects (97.0%) in the gp100 group. Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 103 of 131 subjects (78.6%) in the ipilimumab group, 338 of 380 subjects (88.9%) in the ipilimumab/gp100 group, and 104 of 132 subjects (78.8%) in the gp100 group. The following table lists adverse events with an incidence of ≥20% in any group.

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

System organ class Preferred term (MedDRA/J ver.12.1)	Number of subjects (%)					
	Ipilimumab/gp100 380 subjects		Ipilimumab 131 subjects		gp100 132 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	374 (98.4)	193 (50.8)	127 (96.9)	72 (55.0)	128 (97.0)	69 (52.3)
Gastrointestinal disorders						
Constipation	81 (21.3)	3 (0.8)	27 (20.6)	3 (2.3)	34 (25.8)	1 (0.8)
Diarrhoea	146 (38.4)	17 (4.5)	43 (32.8)	7 (5.3)	26 (19.7)	1 (0.8)
Nausea	129 (33.9)	6 (1.6)	46 (35.1)	3 (2.3)	52 (39.4)	3 (2.3)
Vomiting	75 (19.7)	7 (1.8)	31 (23.7)	3 (2.3)	29 (22.0)	3 (2.3)
General disorders and administration site conditions						
Fatigue	137 (36.1)	19 (5.0)	55 (42.0)	9 (6.9)	41 (31.1)	4 (3.0)
Injection site reaction	110 (28.9)	7 (1.8)	2 (1.5)	0	26 (19.7)	0
Pyrexia	16 (12.2)	0	78 (20.5)	2 (0.5)	23 (17.4)	2 (1.5)
Metabolism and nutrition disorders						
Decreased appetite	88 (23.2)	6 (1.6)	35 (26.7)	2 (1.5)	29 (22.0)	4 (3.0)
Skin and subcutaneous tissue disorders						
Pruritus	79 (20.8)	1 (0.3)	39 (29.8)	0	14 (10.6)	0
Rash	79 (20.8)	5 (1.3)	29 (22.1)	2 (1.5)	9 (6.8)	0

Serious adverse events were observed in 54 of 131 subjects (41.2%) in the ipilimumab group, 145 of 380 subjects (38.2%) in the ipilimumab/gp100 group, and 51 of 132 subjects (38.6%) in the gp100 group.

Serious adverse events with an incidence of ≥2% in each group were as follows: colitis in 7 subjects (5.3%), diarrhoea in 6 subjects (4.6%), anaemia in 4 subjects (3.1%), and vomiting, asthenia, sepsis, renal failure, dyspnoea, and hypotension in 3 subjects (2.3%) in the ipilimumab group; diarrhoea in 16 subjects (4.2%), colitis in 14 subjects (3.7%), and pneumonia and dehydration in 8 subjects (2.1%) each in the ipilimumab/gp100 group; and dyspnoea in 7 subjects (5.3%), anaemia and abdominal pain in 5 subjects (3.8%) each, dehydration, nausea, and pleural effusion in 4 subjects (3.0%) each, and vomiting, disease progression, pneumonia, and urinary tract infection in 3 subjects (2.3%) each in the gp100 group. A causal relationship to the investigational products could not be ruled out for the following events: colitis in 7 subjects, diarrhoea in 5 subjects, hypotension and renal failure in 2 subjects each, and vomiting, asthenia, and sepsis in 1 subject each in the ipilimumab group; for colitis and diarrhoea in 14 subjects each, dehydration in 2 subjects, and pneumonia in 1 subject in the ipilimumab/gp100 group; and for vomiting, nausea, and dehydration in 1 subject each in the gp100 group.

Adverse events led to the discontinuation of investigational products in 17 of 131 subjects (13.0%) in the ipilimumab group, 34 of 380 subjects (8.9%) in the ipilimumab/gp100 group, and 5 of 132 subjects (3.8%) in the gp100 group. Adverse events with an incidence of ≥1% in each group and leading to the discontinuation of investigational products were colitis in 3 subjects (2.3%) and diarrhoea, sepsis, and uveitis in 2 subjects (1.5%) each in the ipilimumab group, and colitis and diarrhoea in 10 subjects (2.6%) each in the ipilimumab/gp100 group. A causal relationship could not be ruled out for colitis in 3 subjects and diarrhoea and uveitis in 2 subjects each in the ipilimumab group and for colitis and diarrhoea in 10 subjects each in the ipilimumab/gp100 group.

4.(iv).A.(7) Japanese phase II study (Study CA184202)

Adverse events were observed in 15 of 15 subjects (100%). Adverse events for which a causal relationship to ipilimumab could not be ruled out were observed in 15 of 15 subjects (100%). The following table lists adverse events with an incidence of ≥20%.

Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA/J ver.17.0)	Number of subjects (%) 15 subjects	
	All Grades	Grade ≥3
All adverse events	15 (100)	11 (73.3)
Gastrointestinal disorders		
Constipation	8 (53.3)	0
Diarrhoea	5 (33.3)	1 (6.7)
Nausea	7 (46.7)	0
General disorders and administration site conditions		
Pyrexia	4 (26.7)	0
Laboratory tests		
ALT increased	12 (80.0)	10 (66.7)
AST increased	11 (73.3)	8 (53.3)
Weight decreased	4 (26.7)	0
Musculoskeletal and connective tissue disorders		
Back pain	4 (26.7)	0
Metabolism and nutrition disorders		
Decreased appetite	3 (20.0)	0
Diabetes mellitus	3 (20.0)	2 (13.3)
Hyperglycaemia	3 (20.0)	1 (6.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Malignant neoplasm progression	3 (20.0)	0
Skin and subcutaneous tissue disorders		
Rash	6 (40.0)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase

Serious adverse events were observed in 14 of 15 subjects (93.3%). The events consisted of ALT increased in 10 subjects (66.7%), AST increased in 7 subjects (46.7%), malignant neoplasm progression in 3 subjects (20.0%), and febrile neutropenia, colitis, diarrhoea, back pain, malignant melanoma, and dizziness in 1 subject (6.7%) each. A causal relationship to ipilimumab could not be ruled out for ALT increased in 10 subjects, aspartate aminotransferase increased in 7 subjects, and colitis, diarrhoea, and dizziness in 1 subject each.

Adverse events led to the discontinuation of investigational products in 9 of 15 subjects (60.0%). These adverse events were ALT increased in 8 subjects (53.3%), aspartate aminotransferase increased in 4 subjects (26.7%), and colitis in 1 subject (6.7%). A causal relationship to ipilimumab could not be ruled out for any of these events.

4.(iv).A.(8) Foreign phase I study (Study CA184087)

Adverse events were observed in 75 of 75 subjects (100%). Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 69 of 75 subjects (92.0%). The following table lists adverse events with an incidence of ≥30%.

Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver.13.0)	Number of subjects (%) 75 subjects	
	All Grades	Grade ≥3
All adverse events	75 (100)	51 (68.0)
Gastrointestinal disorders		
Diarrhoea	41 (54.7)	3 (4.0)
Nausea	30 (40.0)	1 (1.3)
General disorders and administration site conditions		
Fatigue	50 (66.7)	3 (4.0)
Metabolism and nutrition disorders		
Decreased appetite	26 (34.7)	2 (2.7)
Skin and subcutaneous tissue disorders		
Pruritus	40 (53.3)	1 (1.3)
Rash	44 (58.7)	1 (1.3)

Serious adverse events were observed in 40 of 75 subjects (53.3%). Serious adverse events occurring in ≥2 subjects were malignant neoplasm progression in 12 subjects (16.0%), colitis in 10 subjects (13.3%), nausea, vomiting, confusional state, pneumonia, decreased appetite, and dehydration in 3 subjects (4.0%) each, and hyponatraemia, acute myocardial infarction, abdominal pain, pyrexia, diarrhoea, hypopituitarism, dyspnoea, spinal cord compression, back pain, and hypotension in 2 subjects (2.7%) each. A causal relationship to ipilimumab could not be ruled out for colitis in 10 subjects, diarrhoea, hypopituitarism, and dehydration in 2 subjects each, and abdominal pain, pyrexia, confusional state, decreased appetite, hyponatraemia, and hypotension in 1 subject each.

Adverse events led to the discontinuation of ipilimumab in 24 of 75 subjects (32.0%). Adverse events occurring in ≥2 subjects and leading to the discontinuation of investigational products were colitis in 8 subjects (10.7%), malignant neoplasm progression in 4 subjects (5.3%), and diarrhoea in 3 subjects (4.0%). A causal relationship to ipilimumab could not be ruled out for colitis in 8 subjects and diarrhoea in 3 subjects.

4.(iv).A.(9) Foreign phase I study (Study MDX010-15)

Adverse events were observed in 87 of 88 subjects (98.9%). Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 76 of 88 subjects (85.4%). Adverse events with an incidence of ≥30% were fatigue in 45 subjects (51.1%), rash in 37 subjects (42.0%), diarrhoea in 34 subjects (38.6%), and nausea and pruritus in 29 subjects (33.0%) each. Diarrhoea in 5 subjects, fatigue in 4 subjects, nausea in 2 subjects, and rash in 1 subject were Grade 3 or 4.

Serious adverse events were observed in 26 of 88 subjects (29.5%). Serious adverse events occurring in ≥2 subjects were colitis in 5 subjects (5.7%), diarrhoea in 4 subjects (4.5%), nausea, fatigue, dehydration, and dyspnoea in 3 subjects (3.4%) each, and abdominal pain, back pain, pyrexia, and pain in extremity in 2 subjects (2.3%) each. A causal relationship to ipilimumab could not be ruled out for diarrhoea and colitis in 4 subjects each and for abdominal pain, nausea, pyrexia, and dehydration in 1 subject each.

Adverse events led to the discontinuation of ipilimumab in 9 of 88 subjects (10.2%). Adverse events occurring in ≥2 subjects and leading to the discontinuation of ipilimumab were colitis in 4 subjects (4.5%) and metastases to central nervous system in 2 subjects (2.3%). A causal relationship to ipilimumab could not be ruled out for colitis in 4 subjects and metastases to central nervous system in 1 subject.

4.(iv).A.(10) Foreign phase I study (Study CA184078)

Adverse events were observed in 20 of 20 subjects (100%) in the ipilimumab/PTX/CBDCA group, 19 of 19 subjects (100%) in the ipilimumab/DTIC group, and 20 of 20 subjects (100%) in the ipilimumab group. Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 20 of 20 subjects (100%) in the ipilimumab/PTX/CBDCA group, 19 of 19 subjects (100%) in the ipilimumab/DTIC group, and 18 of 20 subjects (90.0%) in the ipilimumab group. The following table lists adverse events with an incidence of ≥30% in any group.

Adverse events with an incidence of ≥30% in any group

System organ class Preferred term (MedDRA/J ver.13.0)	Number of subjects (%)					
	Ipilimumab/PTX/CBDCA 20 subjects		Ipilimumab/DTIC 19 subjects		Ipilimumab 20 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	20 (100)	18 (90.0)	19 (100)	17 (89.5)	20 (100)	13 (65.0)
Gastrointestinal disorders						
Abdominal pain	5 (25.0)	0	7 (36.8)	4 (21.1)	4 (20.0)	0
Constipation	8 (40.0)	0	10 (52.6)	0	3 (15.0)	0
Diarrhoea	10 (50.0)	1 (5.0)	12 (63.2)	4 (21.1)	13 (65.0)	4 (20.0)
Nausea	12 (60.0)	0	15 (78.9)	0	7 (35.0)	0
Vomiting	5 (25.0)	0	8 (42.1)	0	6 (30.0)	0
General disorders and administration site conditions						
Fatigue	13 (65.0)	3 (15.0)	18 (94.7)	1 (5.3)	10 (50.0)	1 (5.0)
Pyrexia	6 (30.0)	0	7 (36.8)	0	3 (15.0)	0
Immune system disorders						
Hypersensitivity	6 (30.0)	2 (10.0)	0	0	1 (5.0)	0
Laboratory tests						
ALT increased	5 (25.0)	0	10 (52.6)	9 (47.4)	3 (15.0)	2 (10.0)
AST increased	5 (25.0)	0	10 (52.6)	5 (26.3)	3 (15.0)	1 (5.0)
Blood ALP increased	6 (30.0)	0	5 (26.3)	0	1 (5.0)	1 (5.0)
Haemoglobin decreased	11 (55.0)	2 (10.0)	6 (31.6)	1 (5.3)	3 (15.0)	0
Neutrophil count decreased	10 (50.0)	8 (40.0)	4 (21.1)	1 (5.3)	0	0
Platelet count decreased	10 (50.0)	6 (30.0)	5 (26.3)	1 (5.3)	0	0
White blood cell count decreased	10 (50.0)	6 (30.0)	2 (10.5)	1 (5.3)	1 (5.0)	0
Metabolism and nutrition disorders						
Decreased appetite	5 (25.0)	0	7 (36.8)	0	3 (15.0)	0
Hyperglycaemia	12 (60.0)	3 (15.0)	6 (31.6)	0	5 (25.0)	1 (5.0)
Hypoalbuminaemia	7 (35.0)	0	2 (10.5)	0	0	0
Hyponatraemia	10 (50.0)	4 (20.0)	4 (21.1)	0	5 (25.0)	2 (10.0)
Nervous system disorders						
Headache	7 (35.0)	0	8 (42.1)	0	6 (30.0)	0
Peripheral neuropathy	7 (35.0)	0	1 (5.3)	0	2 (10.0)	0
Psychiatric disorders						
Insomnia	1 (5.0)	0	6 (31.6)	0	7 (35.0)	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnoea	10 (50.0)	4 (20.0)	5 (26.3)	1 (5.3)	1 (5.0)	1 (5.0)
Skin and subcutaneous tissue disorders						
Alopecia	12 (60.0)	0	1 (5.3)	0	2 (10.0)	0
Pruritus	13 (65.0)	1 (5.0)	13 (68.4)	0	13 (65.0)	0
Rash	16 (80.0)	3 (15.0)	10 (52.6)	0	17 (85.0)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase

Serious adverse events were observed in 9 of 20 subjects (45.0%) in the ipilimumab/PTX/CBDCA group, 8 of 19 subjects (42.1%) in the ipilimumab/DTIC group, and 9 of 20 subjects (45.0%) in the ipilimumab group. These events were malignant neoplasm progression and dyspnoea in 4 subjects (20.0%), pyrexia in 3 subjects (15.0%), fatigue, dehydration, pleural effusion, febrile neutropenia, and atrial fibrillation in 2 subjects (10.0%) each, and asthenia, diarrhoea, autoimmune hepatitis, pulmonary embolism, haematemesis, cystitis, pain in extremity, and rash in 1 subject (5.0%) each in the ipilimumab/PTX/CBDCA group; abdominal pain in 4 subjects (21.1%), autoimmune hepatitis in 2 subjects (10.5%), and diarrhoea, malignant neoplasm progression, dehydration, dyspnoea, ALT increased, AST increased, convulsion, autoimmune pancreatitis, gastrointestinal haemorrhage,

metastasis, psychotic disorder, erythema nodosum, and hypotension in 1 subject (5.3%) each in the ipilimumab/DTIC group; and diarrhoea in 3 subjects (15.0%), dehydration in 2 subjects (10.0%), and abdominal pain, pyrexia, ALT increased, AST increased, convulsion, colitis, diabetic ketoacidosis, hypophosphataemia, radiation necrosis, tumour pain, peripheral motor neuropathy, mental status changes, and acute renal failure in 1 subject (5.0%) each in the ipilimumab group. A causal relationship to the investigational products could not be ruled out for the following events: febrile neutropenia and pyrexia in 2 subjects each and diarrhoea, autoimmune hepatitis, dehydration, and rash in 1 subject each in the ipilimumab/PTX/CBDCA group; autoimmune hepatitis in 2 subjects and diarrhoea, abdominal pain, autoimmune pancreatitis, erythema nodosum, ALT increased, and AST increased in 1 subject each in the ipilimumab/DTIC group; and diarrhoea in 3 subjects, dehydration in 2 subjects, and colitis and pyrexia in 1 subject each in the ipilimumab group.

Adverse events led to the discontinuation of investigational products in 6 of 20 subjects (30.0%) in the ipilimumab/PTX/CBDCA group, 7 of 19 subjects (36.8%) in the ipilimumab/DTIC group, and 5 of 20 subjects (25.0%) in the ipilimumab group. These adverse events were diarrhoea, colitis, lipase increased, febrile neutropenia, pyrexia, hypersensitivity, and rash in 1 subject (5.0%) each in the ipilimumab/PTX/CBDCA group; AST increased in 4 subjects (21.1%), ALT increased in 3 subjects (15.8%), and diarrhoea, nausea, and autoimmune hepatitis in 1 subject (5.3%) each in the ipilimumab/DTIC group; and diarrhoea in 3 subjects (15.0%) and colitis, abdominal pain, ALT increased, and AST increased in 1 subject (5.0%) each in the ipilimumab group. A causal relationship to the investigational products could not be ruled out for diarrhoea, colitis, lipase increased, febrile neutropenia, pyrexia, hypersensitivity, and rash in 1 subject each in the ipilimumab/PTX/CBDCA group; AST increased in 4 subjects, ALT increased in 3 subjects, and diarrhoea, nausea, and autoimmune hepatitis in 1 subject each in the ipilimumab/DTIC group; and diarrhoea in 3 subjects and colitis in 1 subject in the ipilimumab group.

4.(iv).A.(11) Foreign phase II study (Study CA184007)

Adverse events were observed in 56 of 58 subjects (96.6%) in the ipilimumab/budesonide group and in 57 of 57 subjects (100%) in the ipilimumab/placebo group. Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 52 of 58 subjects (89.7%) in the ipilimumab/budesonide group and in 54 of 57 subjects (94.7%) in the ipilimumab/placebo group. The following table lists adverse events with an incidence of ≥30% in either group.

Adverse events with an incidence of ≥30% in either group

System organ class Preferred term (MedDRA/J ver.12.1)	Number of subjects (%)			
	Ipilimumab/budesonide 58 subjects		Ipilimumab/placebo 57 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	56 (96.6)	41 (70.7)	57 (100)	36 (63.2)
Gastrointestinal disorders				
Diarrhoea	28 (48.3)	8 (13.8)	27 (47.4)	10 (17.5)
General disorders and administration site conditions				
Fatigue	32 (55.2)	4 (6.9)	27 (47.4)	1 (1.8)
Skin and subcutaneous tissue disorders				
Pruritus	24 (41.4)	0	21 (36.8)	0
Rash	28 (48.3)	3 (5.2)	35 (61.4)	1 (1.8)

Serious adverse events were observed in 34 of 58 subjects (58.6%) in the ipilimumab/budesonide group and in 31 of 57 subjects (54.4%) in the ipilimumab/placebo group. Serious adverse events occurring in ≥2 subjects in each group were diarrhoea in 7 subjects (12.1%), colitis in 6 subjects (10.3%), disease progression in 5 subjects (8.6%), autoimmune hepatitis in 4 subjects (6.9%), hypopituitarism in 3 subjects (5.2%), pyrexia, abdominal distension, diarrhoea haemorrhagic, nausea, and vomiting in 2 subjects (3.4%) each in the ipilimumab/budesonide group and colitis and diarrhoea in 7 subjects (12.3%) each, disease progression in 6 subjects (10.5%), abdominal pain in 4 subjects (7.0%), autoimmune hepatitis, dehydration, ALT increased, and AST increased in 3 subjects (5.3%) each, and jaundice, pyrexia, hypopituitarism, and hypothyroidism in 2 subjects (3.5%) each in the ipilimumab/placebo group. A causal relationship to the investigational products could not be ruled out for colitis and diarrhoea in 6 subjects each, autoimmune hepatitis in 4 subjects, hypopituitarism in 3 subjects, pyrexia and diarrhoea haemorrhagic in 2 subjects each, and nausea and vomiting in 1 subject each in the ipilimumab/budesonide group and for colitis and diarrhoea in 7 subjects each, abdominal pain, autoimmune hepatitis, and dehydration in 3 subjects each, jaundice, hypopituitarism, hypothyroidism, pyrexia, ALT increased, and AST increased in 2 subjects each in the ipilimumab/placebo group.

Adverse events led to the discontinuation of investigational products in 15 of 58 subjects (25.9%) in the ipilimumab/budesonide group and in 18 of 57 subjects (31.6%) in the ipilimumab/placebo group. Adverse events occurring in ≥2 subjects in each group and leading to the discontinuation the investigational products were diarrhoea in 7 subjects (12.1%) and colitis and autoimmune hepatitis in 2 subjects (3.4%) each in the ipilimumab/budesonide group and diarrhoea in 5 subjects (8.8%), colitis and autoimmune hepatitis in 3 subjects (5.3%) each, and jaundice, ALT increased, and AST increased in 2 subjects (3.5%) each in the ipilimumab/placebo group. A causal relationship to the investigational products could not be ruled out for diarrhoea in 4 subjects and autoimmune hepatitis in 2 subjects in the ipilimumab/budesonide group and diarrhoea in 3 subjects, autoimmune hepatitis in 2 subjects, and ALT increased and AST increased in 1 subject each in the ipilimumab/placebo group.

4.(iv).A.(12) Foreign phase II study (Study CA184008)

Adverse events were observed in 149 of 155 subjects (96.1%). Adverse events for which a causal relationship to ipilimumab could not be ruled out were observed in 130 of 155 subjects (83.9%). Adverse

events with an incidence of ≥30% were diarrhoea in 52 subjects (33.5%) and fatigue in 51 subjects (32.9%). Diarrhoea in 13 subjects (8.4%) and fatigue in 9 subjects (5.8%) were Grade 3 or 4. Serious adverse events were observed in 83 of 155 subjects (53.5%). Serious adverse events with an incidence of ≥2% were diarrhoea in 17 subjects (11.0%), disease progression in 14 subjects (9.0%), colitis in 13 subjects (8.4%), malignant neoplasm progression in 7 subjects (4.5%), pyrexia and anaemia in 6 subjects (3.9%), and asthenia, fatigue, vomiting, and aspartate aminotransferase increased in 4 subjects (2.6%) each. A causal relationship to the investigational products could not be ruled out in diarrhoea in 17 subjects, colitis in 13 subjects, vomiting, pyrexia, and aspartate aminotransferase increased in 4 subjects, anaemia in 3 subjects, and asthenia and fatigue in 2 subjects each.

Adverse events led to the discontinuation of investigational products in 42 of 155 subjects (27.1%). Adverse events with an incidence of ≥2% and leading to the discontinuation of investigational products were colitis in 9 subjects (5.8%), diarrhoea in 8 subjects (5.2%), disease progression in 6 subjects (3.9%), and malignant neoplasm progression and aspartate aminotransferase increased in 4 subjects (2.6%). A causal relationship to the investigational products could not be ruled out for colitis in 9 subjects, diarrhoea in 8 subjects, and AST increased in 4 subjects.

4.(iv).A.(13) Foreign phase II study (Study CA184041)

Adverse events were observed in 112 of 113 subjects (99.1%) in the simultaneous treatment group, 104 of 109 subjects (95.4%) in the sequential treatment group, and 107 of 109 subjects (98.2%) in the control group. Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 92 of 113 subjects (81.4%) in the simultaneous treatment group, 96 of 109 subjects (88.1%) in the sequential treatment group, and 94 of 109 subjects (86.2%) in the control group. The following table lists adverse events with an incidence of ≥30% in any group.

Adverse events with an incidence of ≥30% in any group

System organ class Preferred term (MedDRA/J ver.13.0)	Number of subjects (%)					
	Simultaneous treatment 113 subjects		Sequential treatment 109 subjects		Control 109 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	112 (99.1)	91 (80.5)	104 (95.4)	80 (73.4)	107 (98.2)	70 (64.2)
Blood and lymphatic system disorders						
Anaemia	35 (31.0)	8 (7.1)	30 (27.5)	8 (7.3)	31 (28.4)	10 (9.2)
Gastrointestinal disorders						
Diarrhoea	35 (31.0)	9 (8.0)	39 (35.8)	8 (7.3)	25 (22.9)	5 (4.6)
Nausea	33 (29.2)	2 (1.8)	40 (36.7)	3 (2.8)	36 (33.0)	3 (2.8)
General disorders and administration site conditions						
Fatigue	41 (36.3)	11 (9.7)	41 (37.6)	13 (11.9)	43 (39.4)	9 (8.3)
Musculoskeletal and connective tissue disorders						
Arthralgia	31 (27.4)	1 (0.9)	34 (31.2)	5 (4.6)	25 (22.9)	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnoea	41 (36.3)	9 (8.0)	25 (22.9)	5 (4.6)	34 (31.2)	7 (6.4)
Skin and subcutaneous tissue disorders						
Alopecia	51 (45.1)	0	61 (56.0)	0	59 (54.1)	0
Rash	40 (35.4)	4 (3.5)	21 (19.3)	2 (1.8)	9 (8.3)	1 (0.9)

Serious adverse events were observed in 74 of 113 subjects (65.5%) in the simultaneous treatment group, 57 of 109 subjects (52.3%) in the sequential treatment group, and 53 of 109 subjects (48.6%) in the control group. Serious adverse events occurring in 3 or more subjects in each group were diarrhoea and lung neoplasm malignant in 8 subjects (7.1%) each, neoplasm progression in 7 subjects (6.2%), disease progression and dyspnoea in 6 subjects (5.3%) each, pyrexia and pneumonia in 5 subjects (4.4%) each, anaemia, pulmonary embolism, and general physical health deterioration in 4 subjects (3.5%) each, and neutropenia, febrile neutropenia, pleural effusion, ALT increased, and AST increased in 3 subjects (2.7%) each in the simultaneous treatment group, lung neoplasm malignant in 10 subjects (9.2%), diarrhoea in 7 subjects (6.4%), anaemia in 6 subjects (5.5%), death in 4 subjects (3.7%), and neutropenia, thrombocytopenia, fatigue, pyrexia, colitis, neoplasm progression, and dyspnoea in 3 subjects (2.8%) each in the sequential treatment group and lung neoplasm malignant in 10 subjects (9.2%), neutropenia and neoplasm progression in 6 subjects (5.5%) each, diarrhoea and disease progression in 5 subjects (4.6%) each, vomiting, dehydration, and pneumonia in 4 subjects (3.7%) each, and anaemia, thrombocytopenia, muscular weakness, dyspnoea, pulmonary haemorrhage, and hypotension in 3 subjects (2.8%) each in the control group. A causal relationship to the investigational products could not be ruled out for diarrhoea in 7 subjects, pyrexia, ALT increased, and AST increased in 3 subjects each, neutropenia and febrile neutropenia in 2 subjects each, and anaemia, disease progression, and general physical health deterioration in 1 subject each in the simultaneous treatment group; diarrhoea in 6 subjects, anaemia in 5 subjects, colitis in 3 subjects, neutropenia, thrombocytopenia, and fatigue in 2 subjects each, and pyrexia in 1 subject in the sequential treatment group; and neutropenia in 4 subjects, anaemia and diarrhoea in 3 subjects each, thrombocytopenia, vomiting, and hypotension in 2 subjects each, and dehydration, muscular weakness, and pulmonary haemorrhage in 1 subject each in the control group.

Adverse events led to the discontinuation of investigational products in 42 of 113 subjects (37.2%) in the simultaneous treatment group, 32 of 109 subjects (29.4%) in the sequential treatment group, and 27 of 109 subjects (24.8%) in the control group. Adverse events occurring in ≥ 2 subjects in each group and leading to the discontinuation of investigational products were diarrhoea in 5 subjects (4.4%), neoplasm progression in 4 subjects (3.5%), lung neoplasm malignant in 3 subjects (2.7%), and disease progression, general physical health deterioration, ALT increased, AST increased, pneumonia, peripheral neuropathy, hypersensitivity, and rash in 2 subjects (1.8%) each in the simultaneous treatment group; fatigue in 5 subjects (4.6%), diarrhoea and lung neoplasm malignant in 3 subjects (2.8%) each, and pulmonary embolism, asthenia, colitis, and neoplasm progression in 2 subjects (1.8%) each in the sequential treatment group; and anaemia and peripheral neuropathy in 3 subjects (2.8%) each, and lung neoplasm malignant, peripheral sensory neuropathy, diarrhoea, and fatigue in 2 subjects (1.8%) each in the control group. A causal relationship to the investigational products could not be ruled out for diarrhoea in 5 subjects, hypersensitivity, ALT increased, AST increased, peripheral neuropathy, and rash in 2 subjects each, and disease progression and general physical health deterioration in 1 subject each in the simultaneous treatment group; diarrhoea in 3 subjects and asthenia, fatigue, and colitis in 2 subjects each in the sequential treatment group; and anaemia and peripheral neuropathy in 3 subjects each and diarrhoea and peripheral sensory neuropathy in 2 subjects each in the control group.

4.(iv).A.(14) Foreign phase III study (Study CA184024)

Adverse events were observed in 244 of 247 subjects (98.8%) in the ipilimumab/DTIC group and in 236 of 251 subjects (94.0%) in the DTIC group. Adverse events for which a causal relationship to the investigational products could not be ruled out were observed in 221 of 247 subjects (89.5%) in the ipilimumab/DTIC group and in 192 of 251 subjects (76.5%) in the DTIC group. The following table lists adverse events with an incidence of ≥30% in either group.

Adverse events with an incidence of ≥30% in either group

System organ class Preferred term (MedDRA/J ver.13.1)	Number of subjects (%)			
	Ipilimumab/DTIC 247 subjects		DTIC 251 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	244 (98.8)	184 (74.5)	236 (94.0)	133 (53.0)
Gastrointestinal disorders				
Diarrhoea	90 (36.4)	10 (4.0)	62 (24.7)	0
Nausea	120 (48.6)	4 (1.6)	122 (48.6)	3 (1.2)
Vomiting	78 (31.6)	8 (3.2)	70 (27.9)	4 (1.6)
General disorders and administration site conditions				
Fatigue	103 (41.7)	27 (10.9)	98 (39.0)	12 (4.8)
Pyrexia	91 (36.8)	0	23 (9.2)	0
Laboratory tests				
ALT increased	82 (33.2)	54 (21.9)	14 (5.6)	2 (0.8)

ALT: alanine aminotransferase

Serious adverse events were observed in 170 of 247 subjects (68.8%) in the ipilimumab/DTIC group and in 121 of 251 subjects (48.2%) in the DTIC group. Serious adverse events with an incidence of ≥2%

in each group were ALT increased in 50 subjects (20.2%), AST increased in 48 subjects (19.4%), malignant neoplasm progression in 35 subjects (14.2%), pyrexia in 18 subjects (7.3%), diarrhoea in 16 subjects (6.5%), vomiting in 10 subjects (4.0%), colitis in 8 subjects (3.2%), fatigue and thrombocytopenia in 6 subjects (2.4%) each, and pneumonia and headache in 5 subjects (2.0%) each in the ipilimumab/DTIC group, and malignant neoplasm progression in 58 subjects (23.1%), nausea in 7 subjects (2.8%), and dyspnoea and dehydration in 6 subjects (2.4%) each in the DTIC group. A causal relationship to the investigational products could not be ruled out for ALT increased and AST increased in 47 subjects each, diarrhoea in 16 subjects, pyrexia in 14 subjects, vomiting in 10 subjects, colitis in 8 subjects, thrombocytopenia in 5 subjects, headache in 4 subjects, and fatigue in 3 subjects in the ipilimumab/DTIC group and for nausea in 3 subjects in the placebo/DTIC group.

Adverse events led to the discontinuation of investigational products in 114 of 247 subjects (46.2%) in the ipilimumab/DTIC group and in 46 of 251 subjects (18.3%) in the DTIC group. Adverse events with an incidence of ≥2% in each group and leading to the discontinuation of investigational products were ALT increased and AST increased in 42 subjects (17.0%) each, malignant neoplasm progression in 12 subjects (4.9%), diarrhoea in 10 subjects (4.0%), and thrombocytopenia in 5 subjects (2.0%) in the ipilimumab/DTIC group, and malignant neoplasm progression in 16 subjects (6.4%) and neutropenia in 6 subjects (2.4%) in the DTIC group. A causal relationship to the investigational products could not be ruled out for AST increased in 42 subjects, ALT increased in 41 subjects, diarrhoea in 10 subjects, and thrombocytopenia in 5 subjects in the ipilimumab/DTIC group and neutropenia in 5 subjects in the DTIC 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

Document-based compliance 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. The area for improvement was the electronic data capture system being used by the sponsor, in which did not allow investigators to view some of modified case report data. Despite this, the final case report data were checked and confirmed by the investigators after all, and PMDA concluded that there should be no problems with conducting a regulatory review based on the submitted application documents.

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

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 (5.3.5.2-1). PMDA concluded that there should be no problems with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

The data submitted demonstrated a certain level of efficacy of ipilimumab in the treatment of unresectable malignant melanoma. The safety of ipilimumab is acceptable in light of the benefits observed. Ipilimumab is a human monoclonal antibody against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). PMDA considers ipilimumab a clinically significant therapeutic option for unresectable malignant melanoma. PMDA will further discuss clinical positioning, indications, dosage and administration, post-marketing investigations, etc. of ipilimumab at the Expert Discussion.

Ipilimumab may be approved if the drug is not considered to have any particular problems, taking account of comments from the Expert Discussion.

Review Report (2)

May 18, 2015

I. Product Submitted for Registration

[Brand name]	Yervoy Injection 50 mg (for intravenous use)
[Non-proprietary name]	Ipilimumab (Genetical Recombination)
[Applicant]	Bristol-Myers Squibb K.K.
[Date of application]	September 19, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

A foreign phase III study (Study MDX010-20) was conducted in previously treated patients with unresectable malignant melanoma to investigate the efficacy and safety of combination therapies: ipilimumab (genetical recombination) plus gp100* (the ipilimumab/gp100 group); gp100 plus placebo (the gp100 group); and ipilimumab plus placebo (the ipilimumab group).

* Antigen peptide derived from malignant melanoma (not approved)

PMDA's conclusion based on the discussion in "4.(iii).B.(2) Efficacy" of Review Report (1):

Study MDX010-20 did not demonstrate ipilimumab to be superior to gp100 in overall survival (OS) but showed a certain efficacy of ipilimumab monotherapy in patients in the study. The following findings support this conclusion:

- The ipilimumab/gp100 group was shown to be superior to the gp100 group in OS.
- OS tended to be longer in the ipilimumab group than in the gp100 group.
- No clear difference was observed in OS between the ipilimumab/gp100 group and the ipilimumab group.
- Gp100 is unlikely to adversely affect OS in patients with unresectable malignant melanoma.

The expert advisors in the Expert Discussion supported this conclusion by PMDA.

(2) Safety

PMDA's conclusion based on the discussion in "4.(iii).B.(3) Safety" of Review Report (1):

The adverse events requiring attention during treatment with ipilimumab are diarrhoea, colitis, gastrointestinal perforation, skin disorders, hepatic disorders, hypophysitis, hypopituitarism,

hypothyroidism, adrenal insufficiency, peripheral neuropathy, renal disorders, interstitial lung disease, and infusion reaction. Patients on ipilimumab should be carefully monitored for these events.

Nevertheless, ipilimumab is tolerable as long as the patient is treated by a physician with expertise and experience in cancer chemotherapy who takes appropriate measures, including the monitoring and management of adverse events and the suspension or discontinuation of treatment as necessary.

The applicant's explanation on the timing of onset of serious adverse events during treatment with ipilimumab. (This issue was under investigation by the applicant when Review Report (1) was being prepared.):
In Study MDX010-20, serious adverse events were observed from the start of ipilimumab to 30 days after the completion of treatment in 139 of 380 subjects (36.6%) in the ipilimumab/gp100 group, 47 of 131 subjects (35.9%) in the ipilimumab group, and 46 of 132 subjects (34.8%) in the gp100 group. Serious adverse events were also observed ≥31 days after the completion of treatment[*1] in 35 of 332 subjects (10.5%) in the ipilimumab/gp100 group, 17 of 117 subjects (14.5%) in the ipilimumab group, and 11 of 107 subjects (10.3%) in the gp100 group. Adverse events resulted in death ≥31 days after the completion of treatment in 3 of 332 subjects (myelofibrosis, disease progression, and cardiopulmonary failure in 1 subject each) in the ipilimumab/gp100 group, 3 of 117 subjects (coronary artery disease, metastatic malignant melanoma, and large intestine perforation in 1 subject each) in the ipilimumab group, and 2 of 107 subjects (pulmonary embolism and multi-organ failure in 1 subject each) in the gp100 group. A causal relationship to the investigational products could not be ruled out for myelofibrosis in 1 subject[*2] in the ipilimumab/gp100 group and large intestine perforation in 1 subject in the ipilimumab group. Serious adverse events other than death were observed ≥31 days after the completion of treatment in 32 of 332 subjects (9.6%) in the ipilimumab/gp100 group, 17 of 117 subjects (14.5%) in the ipilimumab group, and 9 of 107 subjects (8.4%) in the gp100 group (see the table below). A causal relationship to the investigational products could not be ruled out for colitis in 2 subjects and anaemia/hyponatraemia/leukocytosis, hypopituitarism, dehydration/diarrhoea, and diarrhoea in 1 subject each in the ipilimumab/gp100 group and for arterial thrombosis limb, blood corticotrophin decreased/hypotension, upper gastrointestinal haemorrhage, adrenal insufficiency, colitis/perirectal abscess/proctalgia, gastrointestinal infection, thrombocytopenia, hypophysitis, and hypopituitarism in 1 subject each in the ipilimumab group.

Serious adverse events occurring ≥31 days after the completion of treatment (other than death) (Study MDX010-20)

Ipilimumab/gp100	The following events occurred in 1 patient each: ileus, intestinal perforation/pneumonia, anaemia/atrial fibrillation/sepsis/dehydration/hyponatraemia/mental status changes, hypopituitarism, cellulitis, dehydration/diarrhoea, bronchopneumonia, colitis, congestive cardiac failure/respiratory failure, abdominal pain upper, pain/lethargy, pleuritic pain/pulmonary embolism/deep vein thrombosis, malignant melanoma, spinal cord compression, ileus/respiratory arrest/haemorrhage of lesion in right parietal lobe,* pulmonary embolism, hydronephrosis, diarrhoea/lower respiratory tract infection, tumour haemorrhage, confusional state/pulmonary embolism, pseudomonal sepsis, multi-organ failure, nausea, catheter placement due to urinary retention,* general physical health deterioration, ureteric obstruction/deep vein thrombosis, gastritis/nausea/vomiting/decreased appetite, metastatic neoplasm, metastatic pain, colitis/haemorrhoids, diarrhoea, and bone pain
Ipilimumab	The following events occurred in 1 patient each: arterial thrombosis limb, blood corticotrophin decreased/hypotension, upper gastrointestinal haemorrhage, adrenal insufficiency, urine output decreased, colitis/proctalgia/perirectal abscess, bedsore,* large intestinal obstruction/vomiting/dyspnoea, gastrointestinal infection, anaemia/neutropenia, asthenia, thrombocytopenia/tumour pain, hypophysitis, pulmonary embolism, cardiac failure, and hypopituitarism
gp100	Tumour haemorrhage in 2 subjects. The following events occurred in 1 patient each: abdominal pain/bone pain, intussusception, coma, pneumonia, abdominal pain/urinary tract infection/back pain, intracranial tumour haemorrhage, and anaemia

* These events could not be coded with any preferred term from MedDRA ver. 12.1

In Study CA184396, serious adverse events were observed from the start of ipilimumab to 30 days after the completion of treatment in 8 of 20 subjects (40.0%) and ≥31 days after the completion of treatment[*3] in 7 of 17 subjects (41.2%). Adverse events resulted in death ≥31 days after the completion of treatment in 2 of 17 subjects (malignant melanoma and malignant neoplasm progression in 1 subject each). However, a causal relationship to ipilimumab was ruled out for both events. Serious adverse events other than death were observed ≥31 days after the completion of treatment in 5 of 17 subjects (29.4%, brain oedema, diabetes mellitus, hypopituitarism, hydrocephalus, and malignant neoplasm progression/metastatic pain in 1 subject each). A causal relationship to ipilimumab could not be ruled out for diabetes mellitus and hypopituitarism.

[*1] Including adverse events occurring ≥71 days after the completion of treatment.

[*2] A man aged 5[redacted] years: This patient experienced thrombocytopenia on Day 252 after the start of ipilimumab (the last dose of ipilimumab was administered on Day 64). Thrombocytopenia worsened subsequently and was rated Grade 4 on Day 375. On Day 385, a bone marrow aspiration was dry tap, and a bone marrow biopsy was performed, resulting in a diagnosis of myelofibrosis. Thrombocytopenia and anemia due to myelofibrosis were treated by blood transfusion, etc. The patient died of cardiac arrest caused by myelofibrosis on Day 489.

[*3] Including adverse events occurring ≥91 days after the completion of treatment.

PMDA's conclusion based on the above explanation by the applicant:

Since serious adverse events occurred after the completion of treatment with ipilimumab in Studies MDX010-20 and CA184396, patients and healthcare professionals should be cautioned about these events in an appropriate manner via the package insert, etc. Some patients died as a result of diarrhoea, colitis, or gastrointestinal perforation occurring after the completion of treatment; therefore these events should be mentioned in the "Warnings" section of the package insert.

The expert advisors in the Expert Discussion supported this conclusion by PMDA.

Thus, PMDA instructed the applicant to duly implement the above measures. The applicant agreed.

(3) Clinical positioning and indications

PMDA's conclusion based on the discussion in "4.(iii).B.(4) Clinical positioning and indications" of Review Report (1):

The indication should be "unresectable malignant melanoma" because ipilimumab is a therapeutic option for patients with unresectable malignant melanoma. The "Clinical Studies" section of the package insert should mention previous treatment, etc. of patients enrolled in the clinical studies. The following statements should be included in the "Precautions for Indications" section.

- Eligibility of patients for treatment with ipilimumab should be determined based on a good understanding of the "Clinical Studies" section of the package insert and the efficacy and safety of ipilimumab. In particular for previously untreated patients, other therapeutic options should also be carefully considered.
- The efficacy and safety of ipilimumab in postoperative adjuvant chemotherapy have not been established.

The expert advisors in the Expert Discussion supported this conclusion by PMDA.

Thus, PMDA instructed the applicant to modify the indication and precautions for indications as mentioned above. The applicant agreed.

(4) Dosage and administration

Based on the discussion in "4.(iii).B.(5) Dosage and administration" of Review Report (1), PMDA concluded that the dosage and administration of ipilimumab and precautions for dosage and administration should be described as follows:

Dosage and administration

The usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 times.

Precautions of Dosage and Administration

- Ipilimumab should not be used in combination with other antineoplastic agents.
- In the event of adverse reactions, treatment should be suspended or discontinued according to the following criteria:

Criteria for suspension or discontinuation of treatment

Adverse reactions	Actions
• Grade 2 adverse reactions (excluding endocrine or skin disorders) • Symptomatic endocrine disorders • Grade 3 skin disorders	Suspend treatment until the event resolves to Grade ≤1 or baseline. For endocrine disorders, suspend treatment until symptoms resolve. If the event fails to meet any of these criteria, discontinue treatment.
• Grade 3 adverse reactions (excluding endocrine or skin disorders) • Grade ≥2 eye disorders for which local immunosuppressive therapy is ineffective • Grade 4 skin disorders	Discontinue treatment

Events are graded according to the Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver.3.0.

- Ipilimumab should be administered intravenously over a period of 90 minutes. When necessary, ipilimumab should be diluted with normal saline or 5% glucose solution for injection.

The expert advisors in the Expert Discussion supported this conclusion by PMDA.

Thus, PMDA instructed the applicant to specify the dosage and administration and precautions for dosage and administration as mentioned above. The applicant agreed.

(5) Risk management plan (draft)

The applicant plans to conduct all-case post-marketing surveillance (the surveillance) of patients with malignant melanoma treated with ipilimumab, to investigate the safety and other aspects of ipilimumab used in clinical practice in the post-marketing settings. The target sample size is 100. The observation period is 12 months after the start of ipilimumab. The priority investigation item is immune-related adverse reactions.

PMDA's conclusion based on the discussion in "4.(iii).B.(6) Post-marketing investigations" of Review Report (1):

Only extremely limited information is currently available on the safety of ipilimumab in Japanese patients. Therefore the applicant should conduct post-marketing surveillance covering all patients treated with ipilimumab over a certain period of time, to collect safety information promptly and impartially. Safety information collected should be provided to healthcare professionals immediately.

PMDA's conclusion on the surveillance plan:

(a) Priority investigation items should be the following adverse events requiring attention during treatment with ipilimumab: (i) diarrhoea, colitis, gastrointestinal perforation; (ii) skin disorders; (iii) hepatic disorders; (iv) hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency; (v) peripheral neuropathy; (vi) renal disorders; (vii) interstitial lung disease; and (viii) infusion reaction.

(b) The observation period can be defined as 6 months after the start of ipilimumab, because (i) most adverse events, including those requiring attention during treatment with ipilimumab, were observed

within 6 months after the start of ipilimumab, and (ii) no adverse events tended to increase in incidence >6 months after the start of ipilimumab.

In the Expert Discussion, this conclusion by PMDA was generally supported by the expert advisors. The expert advisors expressed the following opinion:

- The action of ipilimumab may last even after the completion of treatment. Adverse events for which a causal relationship to ipilimumab could not be ruled out occurred >6 months after the start of ipilimumab. The observation period should therefore be 12 months after the start of ipilimumab. The applicant should explore efficient ways of collecting safety information. For example, information on serious adverse events alone should be collected from patients receiving ipilimumab for >6 months, because most adverse events occurred within 6 months after the start of ipilimumab in the clinical studies.

In light of comments from the Expert Discussion, PMDA concluded that the observation period should be 12 months after the start of ipilimumab.

Accordingly, PMDA asked the applicant to review the surveillance plan.

The applicant's response:

- The events presented in (a) above are defined as the priority investigation items.
- The surveillance will collect data from approximately 400 patients with malignant melanoma treated with ipilimumab over a period of 2 years. The target sample size is 400 patients because this number allows for the evaluation of adverse events, including the priority investigation items, with a certain level of precision. In order to promptly provide healthcare professionals with information including safety data obtained through the surveillance, an interim analysis will be performed when a certain period of time has passed since the start of surveillance. The interim analysis results will be used to decide whether to increase the sample size and discuss other matters.
- The observation period is 12 months after the start of ipilimumab. Investigation items will be selected so that safety information can be collected efficiently. For example, information on serious adverse events alone will be collected from patients receiving ipilimumab for >6 months.

PMDA accepted the applicant's response concerning the surveillance plan (draft).

PMDA's conclusion in light of the above discussion:

The risk management plan (draft) should define the safety and efficacy specifications listed in the following table, and additional pharmacovigilance activities and risk minimization activities should be implemented.

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

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Diarrhoea, colitis, gastrointestinal perforation • Skin disorders • Hepatic disorders • Hypophysitis, hypopituitarism, hypothyroidism, adrenal insufficiency • Peripheral neuropathy • Renal disorders • Interstitial lung disease • Infusion reaction	• Reproductive and developmental toxicity • Sepsis • Excessive immune response	None
Efficacy specification		
• Efficacy in clinical use (specified use-results survey)		

Outline of additional pharmacovigilance activities and risk-minimizing activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance; see the table below for the outline of the survey plan [draft])	• Information provision through early post-marketing phase vigilance • Preparation and distribution of information materials for healthcare professionals (guide to proper use) • Preparation and distribution of information materials for patients

Outline of the plan for specified use-results survey (draft)

Objective	To investigate the safety, etc. of ipilimumab in clinical use
Survey method	All-case surveillance by the central registration method
Population	All patients treated with ipilimumab
Observation period	12 months after the start of ipilimumab administration
Planned number of patients	400
Main investigation items	Priority investigation items: diarrhoea, colitis, gastrointestinal perforation; skin disorders; hepatic disorders; peripheral neuropathy; hypophysitis, hypopituitarism, hypothyroidism, adrenal insufficiency; renal disorders; interstitial lung disease; infusion reaction Other main investigation items: patient characteristics (sex, age, previous treatment, primary site, etc.), status of use of ipilimumab, concomitant drugs and therapies, adverse events (including changes in laboratory test values), efficacy, etc.

III. Overall Evaluation

Based on the above review, PMDA concludes that the product may be approved for the modified indication and dosage and administration shown below with the following conditions, provided that necessary precautionary advice and information on the proper use of the product are offered through the package insert in the post-marketing settings, and that the product is used under the supervision of physicians with expertise and experience in cancer chemotherapy and at medical institutions capable of emergency response. The re-examination period is 10 years because ipilimumab is an orphan drug. Both the drug substance and the drug product are classified as powerful drugs and biological products.

[Indication]

Unresectable malignant melanoma

[Dosage and administration]

The usual adult dosage is 3 mg/kg (body weight) of ipilimumab (genetical recombination) administered intravenously every 3 weeks for a total of 4 times.

[Conditions for approval]

1. The applicant is required to establish and appropriately implement a risk management plan.
2. An extremely small number of patients were involved in the Japanese clinical studies. The applicant is therefore required to conduct a use-results survey covering all patients treated with the product after the market launch until data from a certain number of patients are available, to identify the characteristics of these patients and to promptly collect safety and efficacy data so that necessary measures are taken for the proper use of the product.

[Warnings]

1. The product should be administered only to eligible patients under the supervision of a physician with expertise and experience in cancer chemotherapy and at medical institutions capable of emergency response. Before the start of treatment, consent should be obtained from the patient or their family members who have been fully informed of the risks and benefits of the product.
2. The product may cause serious diarrhoea, colitis, or gastrointestinal perforation. Some patients experienced these events a few months after the completion of treatment, resulting in death. Patients must be adequately monitored after the completion of treatment as well as during treatment with the product. Should any abnormalities arise, appropriate measures, including corticosteroid therapy, should be taken.

[Contraindications]

Patients with a history of severe hypersensitivity to any ingredient of the product

[Precautions for Indications]

1. Eligibility of patients for treatment with ipilimumab should be determined based on a good understanding of the “Clinical Studies” section of the package insert and the efficacy and safety of the product. In particular for previously untreated patients, other therapeutic options should also be carefully considered.
2. The efficacy and safety of the product in postoperative adjuvant chemotherapy have not been established.

[Precautions of Dosage and Administration]

1. The product should not be used in combination with other antineoplastic agents.
2. In the event of adverse reactions, treatment should be suspended or discontinued according to the following criteria:

Criteria for suspension or discontinuation of treatment

Adverse reactions	Actions
• Grade 2 adverse reactions (excluding endocrine or skin disorders) • Grade 3 skin disorders • Symptomatic endocrine disorders	Suspend treatment until the event resolves to Grade ≤1 or baseline. For endocrine disorders, suspend treatment until symptoms resolve. If the event fails to meet any of these criteria, discontinue treatment.
• Grade 3 adverse reactions (excluding endocrine or skin disorders) • Grade ≥2 eye disorders for which local immunosuppressive therapy is ineffective • Grade 4 skin disorders	Discontinue treatment.

Events are graded according to the NCI-CTCAE ver.3.0.

3. The product should be administered intravenously over a period of 90 minutes. When necessary, the product should be diluted with normal saline or 5% glucose solution for injection.