Report on the Deliberation Results

May 2, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Imfinzi Injection 120 mg, Imfinzi Injection 500 mg
Non-proprietary Name	Durvalumab (Genetical Recombination) (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	August 30, 2017

Results of Deliberation

In its meeting held on April 25, 2018, the Second Committee on New Drugs concluded that the products may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The products are classified as biological products, and the re-examination period is 8 years. The drug products and their drug substance are classified as powerful drugs.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

April 5, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical products submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Imfinzi Injection 120 mg, Imfinzi Injection 500 mg
Non-proprietary Name	Durvalumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	August 30, 2017
Dosage Form/Strength	Injection: Each vial (2.4 or 10.0 mL) contains 120 or 500 mg of Durvalumab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug(s) with a new active ingredient
Definition	Durvalumab is a recombinant human IgG1 monoclonal antibody against human programmed cell death-ligand 1 (PD-L1). Durvalumab is produced in Chinese hamster ovary cells. Durvalumab is a glycoprotein (molecular weight, ca. 149,000) composed of 2 H-chains (γ1-chains) consisting of 451 amino acid residues each and 2 L-chains (κ-chains) consisting of 215 amino acid residues each.

Structure

Amino acid sequence:

L-chain

EIVLTQSPGT LSLSPGERAT LSCRASQRVS SSYLAWYQQK PGQAPRLLIY

DASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSLPWTFG

QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT ASVVCLLNNF YPREAKVQWK

VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH KVYACEVTHQ

GLSSPVTKSF NRGEC

H-chain

EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYWMSWVRQA PGKGLEWVAN

IKQDGSEKYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG

GWFGELAFDY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV

KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ

TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEFEG GPSVFLFPPK

PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY

NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPASIEKTI SKAKGQPREP

QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP

VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG

K

Intra-chain disulfide bonds: Solid line

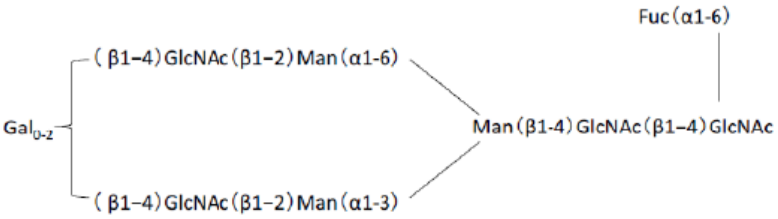
Inter-chain disulfide bonds: L-chain C215-H-chain C224, H-chain C230-H-chain C230, H-chain C233-H-chain C233

Pyroglutamic acid (partial): H-chain E1

Glycosylation site: H-chain N301

Partial processing: H-chain K451

Main proposed carbohydrate structure



Gal, Galactose; GlcNAc, *N*-acetylglucosamine; Man, Mannose; Fuc, Fucose

Molecular formula: $C_{6502}H_{10018}N_{1742}O_{2024}S_{42}$ (protein moiety)
Molecular weight: ca. 149,000

Items warranting special mention None
Reviewing office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the products have efficacy in the maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy, and that the products have acceptable safety in view of their benefits (see Attachment).

As a result of its review, PMDA has concluded that the products may be approved for the indication and dosage and administration shown below, with the following condition. Interstitial lung disease associated with the products needs to be further investigated via post-marketing surveillance.

Indication

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy

Dosage and Administration

The usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks for a maximum of 12 months.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

February 28, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Products Submitted for Approval

Brand Name	Imfinzi Injection 120 mg, Imfinzi Injection 500 mg
Non-proprietary Name	Durvalumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	August 30, 2017
Dosage Form/Strength	Injection: Each vial (2.4 or 10.0 mL) contains 120 or 500 mg of Durvalumab (Genetical Recombination).
Proposed Indication	Locally-advanced, unresectable non-small cell lung cancer

Proposed Dosage and Administration

The usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Overview of products submitted for approval

CD274 (programmed cell death ligand 1 [PD-L1]) is expressed on antigen presenting cells etc. in the body, and is considered to negatively regulate immune responses through binding to CD279 (programmed cell death 1 [PD-1]) and CD80 (B7-1) expressed on activated lymphocytes (T cells, B cells, natural killer T cells) etc. (*Annu Rev Immunol*. 2008; 26: 677-704, *Blood*. 2010; 116: 1291-8). Various tumor cells also express PD-L1 (*Nat Med*. 2002; 8: 793-800, *J immunol*. 2003; 170: 1257-66), and the PD-L1/PD-1 pathway is considered a mechanism by which tumor cells evade antigen-specific T-cell attack, etc.

Durvalumab (Genetical Recombination) (durvalumab) is a human IgG1 monoclonal antibody against human PD-L1 discovered by AstraZeneca (the UK) and Abgenix (the US) (now Amgen). It binds to the extracellular domain of PD-L1, thereby blocking the binding of PD-L1 to PD-1, resulting in enhanced tumor antigen-specific cytotoxic T cell activity and inhibition of tumor growth.

1.2 History of development etc.

In the clinical development of durvalumab for non-small cell lung cancer (NSCLC), a foreign phase I/II study in patients with advanced solid tumors (Study 1108) was initiated by MedImmune (in the US) in August 2012. Then, the following 3 studies were initiated by AstraZeneca (the UK) in (a) September 2013, (b) February 2014, and (c) May 2014, respectively.

(a) A phase I study in patients with advanced solid tumors (Study 02).
(b) A phase II study in patients with advanced/recurrent, unresectable NSCLC who had received at least 2 prior chemotherapy regimens including 1 platinum-based chemotherapy regimen (ATLANTIC study).
(c) A phase III study in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based, concurrent chemoradiotherapy (CRT) (PACIFIC study).

In the US and the EU, a marketing application for durvalumab for the indication of NSCLC was submitted in August 2017, based on the results from the PACIFIC study as the main data. In the US, durvalumab was approved for the following indication in February 2018:

> IMFINZI is indicated for the treatment of patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

The EU application is under review.

As of February 2018, durvalumab has been approved for the indication of NSCLC in the US only.

In Japan, the applicant started to enroll patients in Study 02, the ATLANTIC study, and the PACIFIC study in [redacted] 20[redacted], [redacted] 20[redacted], and [redacted] 20[redacted], respectively.

A marketing application for durvalumab has now been filed based on the results from the PACIFIC study as the main data.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

[redacted] mice were immunized with Chinese hamster ovary (CHO) cells expressing human PD-L1/Fc protein or human PD-L1, and a hybridoma was generated using isolated lymphoid cells. [redacted] obtained from a suitable hybridoma clone [redacted] inserted into an expression vector to generate the expression construct for the production of durvalumab. This expression construct was transfected into CHO cells, and a clone most suitable for the manufacture of durvalumab was selected from the CHO cell line and was used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, end of production cells (EPC), and cells at the limit of *in vitro* cell age (CAL) were characterized and subjected to purity tests in accordance with the ICH Q5A (R1), Q5B, and Q5D guidelines. As a result, genetic stability during the production of durvalumab was demonstrated, and no viral or non-viral adventitious agents were detected other than endogenous retrovirus-like particles, which are generally observed in rodent cell lines, in any of the tests conducted.

The MCB and WCB are stored in [redacted] of [redacted]. MCB [redacted]. A new WCB will be generated as necessary.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of [redacted], [redacted], production culture, harvest, [redacted] chromatography, low pH virus inactivation, [redacted], [redacted], filtration for virus removal, [redacted], [redacted], filling, and testing and storage.

[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] have been defined as critical steps.

Process validation of the commercial-scale manufacturing process of the drug substance has been performed.

2.1.3 Safety evaluation of adventitious agents

Except for the host CHO cells, no raw materials of biological origin etc. are used in the drug substance manufacturing process.

The MCB, WCB, EPC, and CAL were subjected to purity tests [see Section 2.1.1]. Pre-harvest unprocessed bulk at commercial scale was subjected to tests for bioburden and mycoplasma, *in vitro* test for adventitious viruses, and transmission electron microscopy. None of the tests revealed contamination with viral or nonviral

adventitious agents. Tests for bioburden and mycoplasma, and *in vitro* test for adventitious viruses are defined as in-process controls for pre-harvest unprocessed bulk.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process (Table 1).

Table 1. Results of viral clearance studies

Process step	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus (X-MuLV)	Pseudorabies virus (PRV)	Reovirus type 3 (Reo-3)	Murine minute virus (MMV)
[redacted] chromatography	2.03	1.46	1.38	1.01
Low pH virus inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Filtration for virus removal	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>12.81	>11.79	>7.63	>12.96
[redacted]				

2.1.4 Manufacturing process development

Major changes made to the drug substance manufacturing process during development were [redacted], [redacted], [redacted], [redacted], [redacted] etc. [redacted] [see Section 2.2.3] [redacted] (the manufacturing processes before and after changes to [redacted] are referred to as the pre-change process and the proposed commercial process, respectively).

The drug products produced from the drug substance manufactured by the pre-change process were used in clinical studies [see Section 2.2.3]. Comparability studies on quality attributes demonstrated comparability between pre-change and post-change drug substances.

Quality by design (QbD) approaches were used to develop the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization studies performed are shown in Table 2.

Table 2. Characterization attributes

Primary structure	Amino acid sequence, post-translational modifications ([redacted])
Higher-order structure	Secondary structure, tertiary structure, disulfide bonds, free thiol group
Physicochemical properties	Molecular weight, [redacted] variants, [redacted] variants
Carbohydrate structure	N-linked oligosaccharide profile, monosaccharide composition, sialic acid content
Biological	PD-L1 binding activity

properties	[redacted] binding activity, FcRn binding activity
	Inhibitory activity against PD-L1/PD-1 binding
	ADCC activity, CDC activity

Biological properties were determined as follows:

- [redacted] demonstrated the binding affinity of durvalumab to PD-L1.
- [redacted] and PD-L1-expressing [redacted] cells were co-cultured with PD-1-expressing [redacted] cell line. Durvalumab was shown to inhibit the interaction of PD-L1 with PD-1 in a concentration-dependent manner.
- The ability of durvalumab to trigger effector function was determined by surface plasmon resonance (SPR). The results showed that the binding affinity of durvalumab for [redacted] is lower than that of an anti-PD-L1 IgG1 antibody whose H-chains have no mutations that reduce effector functions, and that durvalumab does not trigger antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization etc. presented in Section "2.1.5.1 Structure and properties," [redacted], and [redacted] were considered product-related substances. Aggregates, antibody fragments, disulfide bond variants, particulates (foreign insoluble matter and insoluble particulate matter), oxidized forms, and high-mannose-type oligosaccharides were considered product-related impurities. [redacted] are controlled by the drug substance and drug product specifications. [redacted] and Substance A are controlled by the manufacturing process.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell DNA, Substance B, Substance C, [redacted] were considered process-related impurities. All of the process-related impurities have been demonstrated to be adequately removed in the manufacturing process. [redacted] is controlled by the drug substance specification.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification ([redacted]), osmotic pressure ratio, pH, purity (SDS-gel electrophoresis [under non-reducing and reducing conditions] and [redacted]), capillary isoelectric focusing (cIEF), [redacted], bacterial endotoxins, microbial limits, biological activity (inhibitory activity against PD-L1/PD-1 binding), [redacted], and assay (ultraviolet-visible spectrophotometry).

[redacted]

2.1.7 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 3.

Table 3. Overview of primary stability studies on drug substance

	No. of batches*	Storage conditions	Testing period	Storage package
Long-term	3	5 ± [redacted]°C	24 months	Polyethylene container
Accelerated	3	25 ± [redacted]°C/60 ± [redacted]%RH	6 months	
Stress	3	40 ± [redacted]°C/75 ± [redacted]%RH	3 months	

*: Drug substance batches were manufactured by the proposed commercial process.

The long-term testing showed no significant changes in quality attributes throughout the testing period.

In the accelerated testing, [redacted] tended to increase, [redacted] tended to increase, [redacted] tended to decrease, and [redacted] tended to increase.

In the stress testing, the changes observed at the accelerated condition were more pronounced, and [redacted] increased and [redacted] tended to decrease.

Based on the above, a shelf life of 24 months has been proposed for the drug substance when stored in a polyethylene container at [redacted]°C to [redacted]°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection. Each glass vial (2.4 or 10.0 mL) contains 120 or 500 mg of durvalumab and the following excipients: L-histidine, L-histidine hydrochloride monohydrate, trehalose hydrate, Polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], visual inspection and storage, and labeling, packaging, storage, and testing.

[redacted] and [redacted] have been defined as critical steps.

Process validation of the commercial-scale manufacturing process of the drug product has been performed.

2.2.3 Manufacturing process development

Major changes made to the drug product manufacturing process during development were the change of dosage form (from the lyophilized formulation to the liquid formulation), [redacted], and [redacted]. [redacted] [see Section 2.1.4].

The drug products manufactured by the pre-change process were used in Study 1108, Study 02, the ATLANTIC study, and the PACIFIC study.

Comparability studies on quality attributes demonstrated comparability between pre-change and post-change drug products.

QbD approaches were used to develop the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identification ([redacted]), osmotic pressure ratio, pH, purity (SDS-gel electrophoresis [under non-reducing/reducing conditions] and [redacted]), cIEF, bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, biological activity (inhibitory activity against PD-L1/PD-1 binding), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

The primary stability studies on the drug product are shown in Table 4.

Table 4. Overview of primary stability studies on drug product

	Strength	No. of batches*1	Storage conditions	Testing period	Storage package
Long-term	120 mg	3	5 ± 3°C	24 months*2	Glass vial with a chlorobutyl rubber stopper
	500 mg	3			
Accelerated	120 mg	3	25 ± [redacted]°C/60 ± [redacted]%RH	6 months	
	500 mg	3			
Stress	120 mg	3	40 ± [redacted]°C/75 ± [redacted]%RH	3 months	
	500 mg	3			
Photostability	120 mg	1	25 ± [redacted]°C, an overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		
	500 mg	1			

*1: Drug substance and drug product batches were manufactured by the proposed commercial process. *2: This stability study is ongoing for up to [redacted] months.

The long-term testing showed no significant changes in quality attributes throughout the testing period.

In the accelerated testing, [redacted] tended to increase, [redacted] tended to increase, [redacted] tended to decrease, and [redacted] tended to increase.

In the stress testing, the changes observed at the accelerated condition were more pronounced, and [redacted] increased and [redacted] tended to decrease.

The photostability data showed that the drug product was photosensitive.

Based on the above, a shelf life of 24 months has been proposed for the drug product in a glass vial with a chlorobutyl rubber stopper when stored at 2°C to 8°C in a carton to protect from light.

2.3 QbD

QbD approaches were used to develop the drug substance and the drug product. A quality control strategy was established based on the following considerations, etc.

● Identification of critical quality attributes (CQAs):

The following CQAs were identified based on the information obtained from the development of durvalumab and relevant findings etc. regarding quality attributes including product-related substances, product-related impurities, and process-related impurities [see Section 2.1.5.2 and Section 2.1.5.3] and formulation attributes:

- Color, clarity, [redacted], protein content, [redacted], [redacted], osmotic pressure, extractable volume, [redacted], bioburden, sterility, bacterial endotoxins, viral safety, identification, biological activity, aggregates, [redacted], antibody fragments, [redacted], oxidized form ([redacted]), particulates (foreign insoluble matter and insoluble particulate matter), [redacted], HCP, host cell DNA, Substance B, Substance C, Substance A, oxidized form ([redacted])

● Process characterization:

Process parameters were classified by risk assessment based on their impact on CQAs, and each process step was characterized.

● Development of control methods:

Failure Mode Effects Analysis demonstrated that the quality attributes of durvalumab are adequately controlled by combinations of the control of process parameters, in-process controls, and the specifications established based on the above process characterization etc. [for the control of product-related impurities and process-related impurities, see Section 2.1.5.2 and Section 2.1.5.3].

2.R Outline of the review conducted by PMDA

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

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Binding affinity to PD-L1 (CTD 4.2.1.1.2, 4.2.1.1.3, 4.2.1.1.4, 4.2.1.1.13)

The epitope recognized by durvalumab was characterized by homogeneous time resolved fluorescence (HTRF). The results suggested that arginine at position 95 (R95) in the extracellular domain of human PD-L1 is critical for the binding of human PD-L1 to durvalumab.

The binding affinity of durvalumab to human and cynomolgus monkey PD-L1 (recombinant proteins) were determined by a kinetic exclusion assay. The K_D values of durvalumab (mean [95% confidence interval (CI)], n = 2) were 22.00 [16.31, 28.83] and 78.04 [54.04, 108.57] pmol/L, respectively.

[redacted]

The binding affinity of durvalumab to human PD-L2, B7-H3, CTLA-4, PD-1, B7-H2, and CD28 and murine PD-L1 (recombinant proteins) was determined by an enzyme-linked immunosorbent assay (ELISA). The results showed no binding to any of these recombinant proteins.

The binding affinity of 10F.9G2, anti-murine PD-L1 antibody, to recombinant murine PD-L1 was determined by a kinetic exclusion assay. The K_D value of 10F.9G2 (mean [95%CI], n = 2) was 7.66 [6.09, 9.49] pmol/L.

3.1.2 Inhibition of binding of PD-L1 to PD-1 and B7-1 (CTD 4.2.1.1.5, 4.2.1.1.14)

The ability of durvalumab to inhibit the binding of human PD-L1 to human PD-1 and B7-1 was determined by HTRF. The IC_{50} values of durvalumab (mean, n = 2) were 0.11 and 0.04 nmol/L, respectively.

The ability of 10F.9G2 to inhibit the binding of murine PD-L1 to murine PD-1 and B7-1 was determined by HTRF. The IC_{50} values of 10F.9G2 (mean, n = 2) were 1.90 and 0.31 nmol/L, respectively.

3.1.3 Effects on immune system (CTD 4.2.1.1.6, 4.2.1.1.7, 4.2.1.1.8, 4.2.1.1.10)

The following studies were conducted to evaluate the effects of durvalumab on the immune system.

- The effect of durvalumab 0.02, 0.20, 2.00, and 20.00 μg/mL on the proliferation of human CD4+ T-cells induced by anti-CD3 and anti-CD28 antibody stimulation in the presence of recombinant human PD-L1 was determined by ^{3}H-thymidine incorporation. The results showed that durvalumab suppressed the human PD-L1-mediated inhibition of T-cell proliferation in a concentration-dependent manner.
- Coculture of human CD3+ T-cells with CHO cells expressing anti-human CD3 antibody and human PD-L1 resulted in increased proliferation of T cells, and the effect of durvalumab 0.02, 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.50, 5.00, and 10.00 μg/mL on T-cell proliferation was determined by ^{3}H-thymidine incorporation. The results showed that addition of durvalumab to cocultures increased T-cell proliferation in a concentration-dependent manner.
- Using human peripheral blood mononuclear cells (PBMCs), the effect of durvalumab 0.02, 0.20, 2.00, and 20.00 μg/mL on the function of antigen presenting cells was determined by ^{3}H-thymidine incorporation. The results showed that durvalumab did not induce PBMC proliferation at any concentration tested.
- Using human CD4+ T-cells, the effect of durvalumab 0.02, 0.20, 2.00, and 20.00 μg/mL on the release of IFN-γ induced by anti-CD3 and anti-CD28 antibody stimulation in the presence of recombiant human PD-L1 was determined by flow cytometry. The results showed that durvalumab suppressed the human PD-L1-mediated inhibition of IFN-γ release in a concentration-dependent manner.
- The potential of durvalumab to induce the release of IFN-γ, IL-2, IL-6, and TNF-α in human whole blood was assessed by flow cytometry. The results showed that durvalumab did not induce the release of IFN-γ, IL-2, IL-6, or TNF-α.

3.1.4 CDC and ADCC activities (CTD 4.2.1.1.9)

Using the human breast cancer cell line SKBR3, the ability of durvalumab to trigger CDC was assessed by measuring the amount of ATP from viable cells. The results showed that durvalumab did not trigger CDC.

The ability of durvalumab to trigger ADCC was assessed by measuring luciferase activity. The SKBR3 cell line was used as target cells. Human non-Hodgkin's lymphoma-derived NK92/CD16/NFAT-luciferase clone 8 cell line expressing FcγRIIIa-V158[1)] and NFAT-responsive luciferase reporter, was used as effector cells. The results showed that durvalumab did not trigger ADCC.

3.1.5 Expression of membrane-bound PD-L1 and soluble PD-L1 in human malignant tumors (CTD 4.2.1.1.11, 4.2.1.1.12)

The expression of membrane-bound PD-L1 in the cryosections of human malignant tumors[5)] was assessed by immunohistochemistry (IHC) using 2.14H9 mIgG1.[6)] PD-L1 expression was detected in the tissue sections of lung malignant tumors.

Soluble PD-L1 levels in plasma from healthy adult donors and in plasma and tumor extracts from patients with cancer were determined by electrochemiluminescence (ECL). The results showed that soluble PD-L1 was elevated in the plasma of patients with cancer compared with the healthy adult donors.

3.1.6 Anti-cancer activity against cancerous cell lines (CTD 4.2.1.1.15, 4.2.1.1.16, 4.2.1.1.17)

The anti-cancer activity of durvalumab was evaluated in non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice (6/group). The human pancreatic cancerous cell line (HPAC) and CD4+ and CD8+ T-cell line directed against the HPAC cancerous cell line, were implanted subcutaneously into the mice on Day 1. Animals received durvalumab intraperitoneally on Days 1, 3, 5, 8 and 10 at doses of 0.01, 0.1, 1, or 5 mg/kg. Tumor volumes were measured on Day 22. The results showed that durvalumab at 1 and 5 mg/kg statistically significantly inhibited the growth of the HPAC cancerous cell line as compared with the isotype-control antibody ($P \leq 0.05$, Mann-Whitney rank sum test).

The anti-cancer activity of durvalumab was evaluated in NOD/SCID mice (6/group). The human melanoma cell line (A375) and CD4+ and CD8+ T-cell line directed against the A375 cancerous cell line were implanted subcutaneously into the mice on Day 1. Animals received durvalumab intraperitoneally on Days 1, 3, 5, 8 and 10 at doses of 0.1, 1, or 5 mg/kg. Tumors volumes were measured on Day 25. The results showed that durvalumab at 0.1, 1, and 5 mg/kg statistically significantly inhibited the growth of the A375 cancerous cell line as compared with the isotype-control antibody ($P \leq 0.05$, Mann-Whitney rank sum test).

The mouse colorectal cancer cell line (CT26) was implanted subcutaneously into mice (8/group). Animals received 10F.9G2 intraperitoneally at doses of 1, 5, 10, or 20 mg/kg twice a week for a total of 8 doses, starting 4 days after implantation, and the survival rate was determined. As a result, 10F.9G2 at 1, 10, and 20 mg/kg statistically significantly increased the survival rate as compared with the isotype-control antibody ($P = 0.006$, 0.0003, and 0.006, respectively; log-rank test).

The CT26 cell line was implanted subcutaneously into mice (8/group) on Day 1. Animals received a single

[5)] Prostatic, liver, renal, pancreatic, colorectal, ovarian, breast, lung, gastric, and bladder tumors
[6)] Anti-PD-L1 antibody with the antigen-binding region derived from durvalumab and the Fc domain from murine IgG1

intraperitoneal dose of oxaliplatin 10 mg/kg on Day 11 and 10F.9G2 10 mg/kg intraperitoneally twice a week for a total of 6 doses, starting on Day 11. Then the survival time was determined. The median survival times were 26.5 days in the 10F.9G2 monotherapy group, 30 days in the oxaliplatin monotherapy group, and 57 days in the 10F.9G2 + oxaliplatin group.

3.2 Safety pharmacology

In 4-week and 13-week toxicity studies in cynomolgus monkeys, the effects of durvalumab on the central nervous, cardiovascular, and respiratory systems were assessed after administration of durvalumab 200 mg/kg IV on Day 1, followed by 100 mg/kg IV QW from Day 8 [see Section 5.2]. The results showed no durvalumab-related effects.

3.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that durvalumab is expected to have efficacy in the treatment of NSCLC.

3.R.1 Mechanism of action of durvalumab and its efficacy in treatment of NSCLC

The applicant's explanation about the mechanism of action of durvalumab and its efficacy in the treatment of NSCLC:

PD-L1 is expressed on antigen presenting cells etc. in the body, and is considered to negatively regulate immune responses through binding to PD-1 and B7-1 expressed on activated lymphocytes (T cells, B cells, natural killer T cells) etc. (*Annu Rev Immunol*. 2008; 26: 677-704, *Blood*. 2010; 116: 1291-8). Various tumor cells also express PD-L1 (*Nat Med*. 2002; 8: 793-800, *J immunol*. 2003; 170: 1257-66). PD-L1 expressed on tumor cells is considered to inhibit the anti-tumor immune response.

Durvalumab is a human IgG1 monoclonal antibody against human PD-L1. It binds to the extracellular domain (R95) of PD-L1, thereby blocking the binding of PD-L1 to PD-1 and B7-1 [see Section 3.1.2], resulting in enhanced tumor antigen-specific cytotoxic T cell activity and inhibition of tumor growth [see Section 3.1.6].

The anti-cancer activity of durvalumab against human NSCLC cell line has not been studied. However, in view of the mechanism of action of durvalumab and PD-L1 expression in tissue samples from patients with lung cancer [see Section 3.1.5], durvalumab is expected to have efficacy in the treatment of NSCLC.

The applicant explained differences in pharmacological properties between durvalumab (a PD-L1 blocking antibody) and other anti-PD-L1/PD-1 antibodies approved in Japan.

The applicant’s explanation:

The pharmacological properties of these drugs are shown in Table 5 (*Clin Cancer Res.* 2017; 23: 1886-90, etc.). Although there are some differences among the drugs, all drugs show anti-tumor activity mainly by blocking the binding of PD-L1 to PD-1 and enhancing the anti-tumor immune response.

Table 5. Pharmacological properties of durvalumab and other anti-PD-L1/PD-1 antibodies approved in Japan

	Target molecule	Molecules to which the target molecule binds	ADCC activity	CDC activity
Nivolumab	PD-1	PD-L1, PD-L2	No	No
Pembrolizumab	PD-1	PD-L1, PD-L2	No	No
Atezolizumab	PD-L1	PD-1, B7-1	No	No
Durvalumab	PD-L1	PD-1, B7-1	No	No
Avelumab*	PD-L1	PD-1, B7-1	Yes	No

*: Unapproved for the indication of NSCLC.

PMDA's discussion:

The applicant's explanation (durvalumab is expected to have efficacy in the treatment of NSCLC) is understandable from the standpoint of the mechanism of action of durvalumab. However, (a) the contribution of blocking of the binding of PD-L1 to B7-1 to the anti-tumor activity of durvalumab, (b) factors affecting the efficacy of durvalumab, and (c) differences in pharmacological properties between durvalumab and nivolumab/pembrolizumab/atezolizumab/avelumab, are not fully understood at present. The applicant should continue to investigate these issues because these data may be beneficial for selecting patients eligible for durvalumab therapy in clinical practice, and should appropriately communicate new findings to healthcare professionals.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Non-clinical PK of durvalumab were studied in monkeys.

4.1 Analytical methods

4.1.1 Quantitative determination of durvalumab

Durvalumab in monkey serum was quantified by either of the following assays. Durvalumab in monkey milk was quantified by (b).

(a) An ELISA using solid phased ovine anti-human IgG antibody and horseradish peroxidase (HRP)-labeled goat anti-human IgG antibody

(b) An ELISA using solid phased anti-durvalumab antibody, biotinylated anti-TM antibody, and HRP-labeled streptavidin

4.1.2 Detection of anti-durvalumab antibodies

Anti-durvalumab antibodies in monkey serum were detected by ECL using solid phased streptavidin, biotinylated durvalumab, and ruthenium-conjugated durvalumab.

4.2 Absorption

Serum durvalumab concentrations were determined in male monkeys following intravenous administration of durvalumab (a) 0.1 or (b) 1 mg/kg on Day 1, followed respectively by durvalumab (a) 10 or (b) 100 mg/kg QW from Day 15 onward (Table 6). For the dose range of 0.1 to 1 mg/kg, C_{max} increased in an approximately dose-proportional manner, but AUC increased in a greater than dose-proportional manner. According to the applicant, elimination via binding to PD-L1 was saturated with increasing dose, which led to decreased CL and resulted in non-linear AUC. The C_{max} and AUC increased more than dose-proportionally over the dose range

of 10 to 100 mg/kg. The applicant explained that this was likely due to a greater effect of the presence of anti-durvalumab antibodies on durvalumab exposure at 10 mg/kg compared with 100 mg/kg, given that anti-durvalumab antibodies were detected in (a) all animals and (b) 4 of 5 animals on Day 29.

Table 6. PK parameters of durvalumab (Male monkeys, repeated intravenous administration)

Study Day (Day)	Dose (mg/kg)	n	C_{max} (μg/mL)	AUC[*1] (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
1	0.1[*2]	4	1.77 ± 0.424	2.10 ± 0.165	0.969 ± 0.211	43.8 ± 3.27	49.1 ± 18.3
	1[*3]	5	20.8 ± 1.27	80.3 ± 14.7	3.05 ± 0.995	11.1 ± 1.11	40.5 ± 7.00
29	10[*2]	4	124 ± 26.9	70.0 ± 57.9	—	—	—
	100[*3]	5	2660 ± 692	7370 ± 7240	—	—	—

Arithmetic mean ± standard deviation (SD),
*1: AUC_{14days} on Day 1, AUC_{10days} on Day 29,
*2: 0.1 mg/kg on Day 1, 10 mg/kg from Day 15 onward, *3: 1 mg/kg on Day 1, 100 mg/kg from Day 15 onward,
—: Not calculated

Serum durvalumab concentrations were determined in male and female monkeys following intravenous administration of durvalumab (c) 30, (d) 60, or (e) 200 mg/kg on Day 1, followed respectively by durvalumab (c) 15, (d) 30, or (e) 100 mg/kg QW from Day 8 onward (Table 7). The C_{max} and AUC_{7days} increased in an approximately dose-proportional manner over the dose range of 15 to 200 mg/kg. No clear sex differences in the PK parameters of durvalumab were observed.

Anti-durvalumab antibodies were detected in (c) 10 of 12 animals, (d) 11 of 12 animals, and (e) 7 of 12 animals.

Table 7. PK parameters of durvalumab (Male and female monkeys, 13-week intravenous administration)

Study Day (Day)	Dose (mg/kg)	Sex	n[*1]	C_{max} (μg/mL)	t_{max}[*2] (day)	AUC_{7days} (μg·day/mL)
1	30[*3]	M	6	850 ± 193	0.271 (0.0625, 3.02)	3720 ± 1190[*6]
		F	6	815 ± 163	0.271 (0.0625, 3.02)	3430 ± 930[*7]
	60[*4]	M	6	1800 ± 319	0.167 (0.0625, 0.271)	6640 ± 1760
		F	6	1650 ± 341	0.0625 (0.0625, 0.271)	5790 ± 806
	200[*5]	M	6	6170 ± 1280	0.271 (0.0625, 0.271)	22,800 ± 4830
		F	6	6680 ± 1760	0.0625 (0.0625, 0.0625)	23,600 ± 4340
36	15[*3]	M	5	1350 ± 532	0.271 (0.0625, 1.02)	5050 ± 1940
		F	4	875 ± 95.8	0.271 (0.0625, 3.02)	3790 ± 1080[*8]
	30[*4]	M	5	2150 ± 787	0.271 (0.0625, 0.271)	8470 ± 3430
		F	4	1500 ± 486	0.0625 (0.0625, 0.0625)	6170 ± 2020
	100[*5]	M	6	6400 ± 1890	0.167 (0.0625, 1.02)	27,900 ± 6210[*6]
		F	6	6110 ± 1170	0.167 (0.0625, 0.271)	28,700 ± 6670[*6]
85	15[*3]	M	5	1390 ± 647	0.0625 (0.0625, 0.271)	6450 ± 3050
		F	4	1360 ± 360	0.167 (0.0625, 0.271)	5520 ± 1020
	30[*4]	M	5	2370 ± 326	0.271 (0.0625, 0.271)	12,300 ± 2220
		F	4	1950 ± 190	0.271 (0.0625, 0.271)	9290 ± 1110
	100[*5]	M	6	7810 ± 2080	0.271 (0.0625, 5.02)	38,600 ± 9770
		F	6	7120 ± 1340	0.0625 (0.0625, 0.271)	31,200 ± 6270

Arithmetic mean ± SD, *1: Animals with PK parameters not calculable and animals that developed anti-durvalumab antibodies with associated change in serum durvalumab concentration were excluded. *2: Median (Range), *3: 30 mg/kg on Day 1, 15 mg/kg from Day 8 onward, *4: 60 mg/kg on Day 1, 30 mg/kg from Day 8 onward, *5: 200 mg/kg on Day 1, 100 mg/kg from Day 8 onward, *6: n = 5, *7: n = 4, *8: n = 3

4.3 Distribution

Pregnant monkeys received durvalumab (a) 60 or (b) 200 mg/kg IV on gestation day 20, followed respectively by durvalumab (a) 30 or (b) 100 mg/kg IV QW from gestation day 27 until delivery, and serum durvalumab

concentrations in infants were determined. The serum durvalumab concentrations in infants (arithmetic mean ± SD) were 242 ± 121 μg/mL for (a) and 1010 ± 491 μg/mL for (b) on post-partum Day 1, which declined below the lower limit of quantification (80 pg/mL) by post-partum Day 180.

The applicant's explanation:
Durvalumab was shown to cross the placenta into the fetus.

The V_{ss} of durvalumab in the repeated intravenous administration study in male monkeys [see Section 4.2] was similar to the plasma volume in monkeys (44.8 mL/kg) (*Pharm Res*. 1993; 10: 1093-5). This suggests that durvalumab is distributed predominantly into circulation. Thus, a tissue distribution study of durvalumab was not conducted.

4.4 Metabolism and excretion

Pregnant monkeys received durvalumab (a) 60 or (b) 200 mg/kg IV on gestation day 20, followed respectively by durvalumab (a) 30 or (b) 100 mg/kg QW from gestation day 27 until delivery, and durvalumab concentrations in milk were determined. The durvalumab concentrations in milk (arithmetic mean ± SD) were 0.453 ± 0.250 μg/mL for (a) and 1.95 ± 0.860 μg/mL for (b) on post-partum Day 28.

The applicant's explanation:
Durvalumab was shown to be excreted in milk.

Since durvalumab is an antibody drug and is considered to be eliminated via normal protein degradation pathways etc., the applicant did not conduct metabolism or excretion studies of durvalumab, in accordance with “Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals” (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's discussion on the absorption, distribution, metabolism, and excretion of durvalumab is acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

Since durvalumab has high affinity for human and cynomolgus monkey PD-L1 [see Section 3.1.1], the toxicity of durvalumab was evaluated based on studies in cynomolgus monkeys.

In this section, unless otherwise specified, a solution containing 25 mmol/L histidine, 265 mmol/L trehalose, and 0.02% polysorbate 80 (pH 6.0) was used as vehicle in *in vivo* studies.

5.1 Single-dose toxicity

Although a single-dose toxicity study was not conducted, the acute toxicity of durvalumab was assessed based on the findings after the first dose in repeated intravenous dose toxicity studies in cynomolgus monkeys. The

approximate lethal dose was determined to be >200 mg/kg (Table 8).

Table 8. Single-dose toxicity

Test system	Route of administration	Dose[a)] (mg/kg)	Principal findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female cynomolgus monkeys	IV	0, 30/15, 60/30, 200/100	Acute toxicity was assessed in 4-week or 13-week intravenous toxicity studies. No toxic signs were observed.	>200	4.2.3.2.2

a) Dose on Day 1 (0, 30, 60, or 200 mg/kg)/dose from Day 8 onward (0, 15, 30, or 100 mg/kg)

5.2 Repeated-dose toxicity

Four-week and 13-week intravenous toxicity studies in cynomolgus monkeys were conducted (Table 9). The mean serum exposure at steady state (AUC_{7days}, 34,900 μg·day/mL) at the no observed adverse effect level (NOAEL) (200/100 mg/kg) in the 13-week intravenous toxicity study was approximately 85 times the human exposure.[7)]

The applicant's explanation:

At the 200/100 mg/kg dose level, durvalumab exposure was affected by anti-durvalumab antibodies in only 1 male in the 4-week intravenous toxicity study. Toxicological evaluation of durvalumab is not affected by the presence of anti-durvalumab antibodies.

Table 9. Repeated-dose toxicity studies

Test system	Route of administration	Dosing period	Dose[a)] (mg/kg)	Principal findings	NOAEL (mg/kg)	Attached document CTD
Male and female cynomolgus monkeys	IV	4 weeks (QW) + 8-week recovery period	0, 30/15, 60/30, 200/100	200/100: Rash on the arms, legs, ears, ocular regions, and head,[b)] red stained urine,[b)] enlarged kidneys,[b)] tubular ischemic necrosis and multifocal vasculitis with fibrinoid necrosis,[b)] inflammation in the choroid plexus, a medium-sized artery in the heart, etc.,[b)] small thymus and lower thymus weight,[c)] reduction in cellularity of the thymic cortex[c)] Reversible	200/100	4.2.3.2.2
Male and female cynomolgus monkeys	IV	13 weeks (QW) + 8-week recovery period	0, 30/15, 60/30, 200/100	200/100: Effects on lymphoid tissues[c)] (atrophy/involution of cortex/medulla in the thymus, decreased germinal center development in the mesenteric lymph node) Reversible	200/100	4.2.3.2.3

a) Dose on Day 1 (0, 30, 60, or 200 mg/kg)/dose from Day 8 onward (0, 15, 30, or 100 mg/kg)
b) These findings were not taken into consideration for the determination of the NOAEL in this study because these findings were observed in only 1 male, considered attributable to drug/anti-durvalumab antibody complex deposition [see Section 5.7.2], and of no human relevance.
c) These findings were considered to have minimal toxicological significance because these findings were not associated with any changes in peripheral blood T-cell counts.

5.3 Genotoxicity

Since durvalumab is an antibody drug, it is not expected to interact directly with DNA or other chromosomal material. Therefore no genotoxicity studies were conducted.

5.4 Carcinogenicity

Since durvalumab is an anticancer agent intended to treat patients with advanced cancer, no carcinogenicity

7) AUC_{14days} (826 μg·day/mL) following the first intravenous dose of durvalumab 10 mg/kg in Study 02 involving Japanese patients with advanced solid tumors.

studies were conducted.

5.5 Reproductive and developmental toxicity

No fertility studies were conducted with durvalumab.

The applicant explained that durvalumab is unlikely to impact male and female fertility for the following reasons.

- In repeated intravenous dose toxicity studies in cynomolgus monkeys [see Section 5.2], no durvalumab-related histopathological findings were observed in the reproductive organs of sexually mature animals following ≤13-week administration of durvalumab.
- In a study using allogeneic pregnant mice, blockade of PD-L1 or PD-L1 deficiency resulted in increases in spontaneous abortion or fetal death (*J Exp Med*. 2005; 202: 231-7), whereas no findings indicative of effects on fertility were reported in PD-L1 knockout mice (*Immunity*. 2004; 20: 327-36, etc.).

An enhanced pre- and postnatal development study in cynomolgus monkeys was conducted (Table 10).

The applicant's explanation:
There was a trend towards increased fetal and neonatal deaths in the durvalumab group, but the trend was within the range of historical control data from the test facility. Thus, this finding was not related to durvalumab, and the NOAEL for maternal, fetal, and neonatal toxicity and infant growth and development was 200/100 mg/kg.

The mean serum exposure at steady state at the NOAEL (AUC_{7days}, 34,800 μg·day/mL) was approximately 84 times the human exposure.[7)]

Table 10. Reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Dosing period	Dose[a)] (mg/kg)	Principal findings	NOAEL (mg/kg)	Attached document CTD
An enhanced pre- and postnatal development study	Female cynomolgus monkeys	IV	Maternal animals: from gestation day 20 until parturition (QW)	0,[b)] 60/30, 200/100	Maternal animals: none Fetuses/neonates: Increased deaths at ≥60/30[c)] Infant growth and development[d)]: none	Maternal animals (general toxicity): 200/100 Fetuses/neonates: 200/100 Infant growth and development: 200/100	4.2.3.5.3.1

a) Dose of durvalumab on gestation day 20 (0, 60, or 200 mg/kg)/dose of durvalumab from gestation day 27 until parturition (0, 30, or 100 mg/kg)
b) A solution containing 26 mmol/L histidine/histidine HCl, 275 mmol/L trehalose dihydrate, and 0.02% polysorbate 80 (pH 6.0)
c) Fetal deaths (0 mg/kg group, 1 of 20 maternal females; 60/30 mg/kg group, 4 of 20 maternal females; 200/100 mg/kg group, 1 of 20 maternal females), stillbirths or infants found dead at birth (0 of 20 maternal females, 1 of 20 maternal females, 1 of 20 maternal females), neonatal deaths (0 of 20 maternal females, 1 of 20 maternal females, 2 of 20 maternal females)
d) Infants underwent neurobehavioral assessments, skeletal development examination, peripheral blood immunophenotyping, assessment of antibody responses to keyhole-limpet hemocyanin, histopathological examination of lymphoid tissues, etc.

5.6 Local tolerance

Although no local tolerance study was conducted, the effects of durvalumab at the intravenous injection site were evaluated based on the Draize criteria and the histopathological findings in repeated intravenous dose toxicity studies in cynomolgus monkeys [see Section 5.2]. As a result, no findings indicative of local irritation

were observed at up to the highest dose of 200/100 mg/kg.

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity studies

Tissue cross-reactivity studies in normal human and cynomolgus monkey tissues were conducted (Table 11). The results of durvalumab-specific staining was consistent with a report that PD-L1 is expressed in mononuclear cells and trophoblastic epithelium (*Nat Immunol*. 2007; 8: 239-45, etc.).

Table 11. Tissue cross-reactivity studies

Test system	Test method	Principal findings	Attached document CTD
Normal human tissues	Durvalumab 0.5 or 5 µg/mL was applied to cryosections of normal human tissues, and durvalumab binding to tissues was detected by an indirect enzyme-linked immunosorbent assay.	Durvalumab-specific staining was present in the membrane and cytoplasm of mononuclear cells and trophoblastic epithelium, and in the cytoplasm of pituitary epithelium.[a)]	4.2.3.7.7.1
Normal cynomolgus monkey tissues	Durvalumab 0.5 or 5 µg/mL was applied to cryosections of normal cynomolgus monkey tissues, and durvalumab binding to tissues was detected by an indirect enzyme-linked immunosorbent assay.	Durvalumab-specific staining was present in the membrane and cytoplasm of mononuclear cells, trophoblastic epithelium, and fallopian tube epithelium.[b)]	4.2.3.7.7.2

a) Since staining was localized to the cytoplasm of pituitary epithelium and the monoclonal antibody cannot access the cytoplasm of the cells, the toxicological significance of this type of binding was considered minimal.
b) Membrane and cytoplasmic staining was observed in the fallopian tube epithelium. This finding was considered to have minimal toxicological significance because repeated dose toxicity studies showed no histopathological findings in female reproductive organs [see Section 5.2].

5.7.2 Mechanistic study

In a 4-week intravenous toxicity study in cynomolgus monkeys, a male receiving durvalumab at a dose level of 200/100 mg/kg had histopathological findings (vasculitis in the kidney, inflammation in the choroid plexus and a medium-sized artery in the heart, etc.) possibly attributed to drug/anti-durvalumab antibody complexes [see Section 5.2]. A mechanistic study was conducted using select tissues from this animal (Table 12).

Table 12. Mechanistic study

Type of study	Test method	Principal findings	Attached document CTD
An investigative study to evaluate deposition of immune complexes	Select tissues from the animal with vasculitis etc. following administration of durvalumab 200/100 mg/kg (brain [choroid plexus], epididymides, sciatic nerve, heart, kidney, liver) were examined for the presence of immune complexes of durvalumab and cynomolgus monkey IgG, IgM, etc. using IHC.	Immune complex-related granular deposits containing durvalumab, cynomolgus monkey IgG, IgM, etc. were demonstrated in the inflamed vessels in the choroid plexus, epididymides, heart, and kidney. No similar findings were found in vessels free of inflammation in this animal or tissues from a control animal.	Reference data 4.2.3.7.7.3

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there is no problem with the clinical use of durvalumab based on non-clinical toxicological evaluation.

5.R.1 Effects of durvalumab on fetuses and neonates

PMDA asked the applicant to explain the possibility that fetal and neonatal deaths observed in an enhanced pre- and postnatal development study in cynomolgus monkeys [see Section 5.5] were related to durvalumab administration.

The applicant's response:

In the durvalumab 0, 60/30, and 200/100 mg/kg groups, (a) 1 of 20 maternal females, 4 of 20 maternal females,

and 1 of 20 maternal females had fetal death, respectively, (b) 0 of 20 maternal females, 1 of 20 maternal females, and 1 of 20 maternal females had stillbirth or infant found dead at birth, respectively, and (c) 0 of 20 maternal females, 1 of 20 maternal females, and 2 of 20 maternal females had neonatal death, respectively. Fetal or neonatal deaths were classified by time of death: early-stage pregnancy, mid-stage pregnancy, late-stage pregnancy, at birth (including stillbirths), and post-partum days 1 to 7. These data were compared with historical control data[8)] from the test facilities. The results showed that fetal and neonatal deaths were largely within the range of historical control data. Suppression of soluble PD-L1 in serum was similar in the 60/30 and 200/100 mg/kg groups, suggesting the saturation of durvalumab binding to PD-L1. Thus durvalumab is unlikely to have dose-dependent potential effects on pregnancy outcome. As females in the 200/100 mg/kg group tended to deliver earlier (duration of gestation, 154 ± 10 days) than females in the control (161 ± 7 days) and 60/30 mg/kg (160 ± 8 days) groups, the neonatal deaths in the 200/100 mg/kg group were considered attributable to their incomplete maturation. An infant that died on post-partum day 9 showed effects on lymphoid tissues such as thymic atrophy. These findings were considered secondary to skin infection because the infant also had scabby skin and marked seropurulent crust. No similar findings were observed in other infants. There were no effects on peripheral blood leukocyte subsets or histopathological findings in lymphoid tissues, etc. also in infants surviving to post-partum day 180.

Based on the above, there should be no relationship between durvalumab administration and fetal and neonatal deaths etc. However, durvalumab therapy poses a potential risk to pregnant or possibly pregnant women because the interaction of PD-L1 with PD-1 has been reported to be important for maintaining maternal immune tolerance to the fetus (*Birth Defects Res B Dev Reprod Toxicol*. 2016: 107; 108-19, etc.). Thus, the clinical use of durvalumab in pregnant or possibly pregnant women may be acceptable only when the expected therapeutic benefits outweigh the possible risks. This precautionary statement will be included in the package insert.

PMDA's discussion:

Given the following points etc., a relationship between fetal deaths during late-stage pregnancy and neonatal deaths and administration of durvalumab cannot be ruled out. Thus, through the package insert, the applicant should appropriately disseminate the information regarding fetal deaths during late-stage pregnancy and neonatal deaths in the durvalumab group observed in the enhanced pre- and postnatal development study in cynomolgus monkeys. The proposed precautionary statement about the use of durvalumab in pregnant or possibly pregnant women is acceptable.

- In the durvalumab group (the 60/30 and 200/100 mg/kg groups combined), 2 of 40 females (5%) had fetal death during late-stage pregnancy and 3 of 40 females (7.5%) had neonatal death. These rates were higher than historical control data from the test facility (4.5% and 6.8%, respectively).
- The duration of gestation in the durvalumab group was within the range of historical control data from the

[8)] Data on pregnancy outcomes of 267 animals in 17 studies conducted between 1993 and 2010: (a) fetal deaths by pregnancy period (gestation days 21-30, gestation days 31-50, gestation days 51-75, gestation days 76-100, gestation days 101-125, gestation days 126-150, gestation day >150); (b) stillbirths or perinatal death; and (c) infant deaths by post-partum period (post-partum day 1, post-partum days 2-7, post-partum day >7).

test facility (122-184 days), and there are no data supporting infants' incomplete maturation.

- The interaction of PD-L1 with PD-1 is important for maintaining maternal immune tolerance to the fetus (*Birth Defects Res B Dev Reprod Toxicol*. 2016: 107; 108-19, etc.), and durvalumab is considered to cross the placenta (*Birth Defects Res B Dev Reprod Toxicol*. 2013: 98; 459-85).

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1.1 Analytical methods

6.1.1.1 Quantitative determination of durvalumab

Durvalumab in human serum was quantified by ECL using solid phased streptavidin, biotinylated anti-durvalumab antibody, and ruthenium-conjugated anti-TM antibody. The lower limit of quantification was 50 ng/mL.

6.1.1.2 Detection of anti-durvalumab antibodies and anti-durvalumab neutralizing antibodies

Anti-durvalumab antibodies in human serum were detected by ECL using solid phased streptavidin, biotinylated durvalumab, and ruthenium-conjugated durvalumab. The limit of detection was 27.16 ng/mL.

Anti-durvalumab neutralizing antibodies in human serum were detected by incubation of human serum with durvalumab and soluble PD-L1, followed by ECL using solid phased anti-PD-L1 antibody, mouse anti-human PD-L1 antibody, and ruthenium-conjugated goat anti-mouse IgG antibody. The limit of detection was 289 ng/mL.

6.1.2 Changes in manufacturing processes of drug substance and drug product during development

Changes were made to the drug substance and drug product manufacturing processes during development [see Section 2.1.4 and Section 2.2.3]. The drug products manufactured by the pre-change process were used in Study 1108, Study 02, the ATLANTIC study, and the PACIFIC study, which were submitted for the present application.

When changes were made to the drug substance and drug product manufacturing processes, comparability studies on quality attributes were performed, which demonstrated comparability between pre-change and post-change drug substances/drug products [see Section 2.1.4 and Section 2.2.3].

6.2 Clinical pharmacology

The PK of durvalumab as monotherapy were studied in patients with cancer.

6.2.1 Global studies

6.2.1.1 Global phase I study (CTD 5.3.3.2-1, Study 02 [ongoing since September 2013 (data cutoff date of [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to evaluate the PK etc. of durvalumab in 25 patients with advanced solid tumors (22 included in PK analysis) during the dose-escalation phase and 140 patients with

unresectable, biliary tract cancer, esophagus cancer, or squamous cell carcinoma of the head and neck who had received prior platinum-based chemotherapy (116 included in PK analysis) during the dose-expansion phase. During the dose-escalation phase, subjects were to receive durvalumab 1, 3, or 10 mg/kg Q2W, durvalumab 15 mg/kg Q3W, or durvalumab 20 mg/kg Q4W via intravenous infusion. During the dose-expansion phase, subjects in the monotherapy cohort were to receive durvalumab 10 mg/kg Q2W via intravenous infusion and subjects in the combination therapy cohort were to receive tremelimumab 1 mg/kg Q4W for 16 weeks in combination with durvalumab 20 mg/kg Q4W via intravenous infusion. Serum durvalumab concentrations were determined.

All of the subjects included in PK analysis during the dose-escalation phase were Japanese patients. The PK parameters of durvalumab following the first dose are shown in Table 13. The C_{max} increased in an approximately dose-proportional manner over the dose range of 1 to 20 mg/kg. The AUC increased in an approximately dose-proportional manner over the dose range of 1 to 10 mg/kg Q2W.

Among 197 subjects who provided evaluable samples for anti-durvalumab antibody assay, 14 subjects tested positive for treatment-emergent anti-durvalumab antibodies, and 1 subject tested positive for anti-durvalumab neutralizing antibodies.

Table 13. Durvalumab PK parameters following the first dose

Dosing regimen	n	C_{max} (μg/mL)	t_{max} *1 (day)	AUC*2 (μg·day/mL)
1 mg/kg Q2W	4	20.8 (24.1)	0.046 (0.045, 0.048)	150 (30.4)
3 mg/kg Q2W	4	54.9 (27.9)	0.044 (0.043, 0.045)	405 (21.8)
10 mg/kg Q2W	3	145 (51.2)	0.047 (0.044, 0.073)	826 (51.4)
15 mg/kg Q3W	3	254 (20.8)	0.044 (0.044, 0.045)	2380 (16.9)
20 mg/kg Q4W	4	311 (26.6)	0.046 (0.043, 0.12)	2440 (31.8)

Geometric mean (Coefficient of variation [CV] %), *1: Median (Range), *2: AUC_{14days} for Q2W regimen, AUC_{21days} for Q3W regimen, AUC_{28days} for Q4W regimen

6.2.1.2 Global phase III study (CTD 5.3.5.1-1, PACIFIC study [ongoing since May 2014 (data cutoff date of February 13, 2017)])

A double-blind, randomized, comparative study was conducted to evaluate the efficacy and safety of durvalumab in 713 patients with locally-advanced, unresectable NSCLC whose disease had not progressed following definitive, platinum-based, concurrent chemoradiotherapy (CRT) (473 included in PK analysis). Subjects were to receive durvalumab 10 mg/kg or placebo Q2W via intravenous infusion, and serum durvalumab concentrations were determined. The C_{max} values of durvalumab (geometric mean [CV %]) following the first and 13th doses were 191 (72.4) and 373 (43.6) μg/mL, respectively. The C_{min} values of durvalumab (geometric mean [CV %]) at pre-dose of the 5th, 13th, and 25th doses were 120 (62.2), 177 (47.8), and 189 (71.8) μg/mL, respectively.

Among 401 subjects who provided evaluable samples for anti-durvalumab antibody assay, 7 subjects tested positive for treatment-emergent anti-durvalumab antibodies, and 2 subjects tested positive for anti-durvalumab neutralizing antibodies.

6.2.2 Foreign clinical study

6.2.2.1 Foreign phase I/II study (CTD 5.3.5.2-1, Study 1108 [ongoing since August 2012 (data cutoff date of [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to evaluate the PK etc. of durvalumab in 1022 patients with advanced solid tumors (993 included in PK analysis). Subjects were to receive durvalumab 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W via intravenous infusion during the dose-escalation phase, durvalumab 10 mg/kg Q2W via intravenous infusion during the dose-expansion phase, and durvalumab 20 mg/kg Q4W via intravenous infusion during the dose-exploration phase. Serum durvalumab concentrations were determined.

Table 14 shows the PK parameters of durvalumab following the first dose during the dose-escalation and dose-exploration phases. The C_{max} increased in an approximately dose-proportional manner over the dose range of 0.1 to 20 mg/kg. The AUC_{14days} increased more than dose-proportionally over the dose range of 0.1 to 3 mg/kg and approximately dose-proportionally at doses of 3 to 20 mg/kg. The applicant explained that non-liner AUC_{14days} was likely due to saturation of the elimination pathway via binding to PD-L1 with increasing dose of durvalumab. The accumulation indices for C_{max} and C_{min} [9)] following intravenous administration of durvalumab 10 mg/kg Q2W during the dose-escalation phase were 1.49 and 4.32, respectively.

Among 835 subjects who provided evaluable samples for anti-durvalumab antibody assay, 25 subjects tested positive for treatment-emergent anti-durvalumab antibodies, and 3 subjects tested positive for anti-durvalumab neutralizing antibodies.

Table 14. Durvalumab PK parameters following the first dose

Dosing regimen	n	C_{max} (μg/mL)	t_{max}* (day)	AUC_{14days} (μg·day/mL)	AUC_{last} (μg·day/mL)
0.1 mg/kg Q2W	4	2.78 (22.1)	0.169 (0.167, 0.174)	6.03 (41.1)	5.14 (45.1)
0.3 mg/kg Q2W	4	7.97 (23.0)	0.0435 (0.042, 0.049)	25.8 (57.4)	25.1 (65.5)
1 mg/kg Q2W	3	22.8 (11.3)	0.0670 (0.042, 0.167)	135 (17.1)	131 (20.1)
3 mg/kg Q2W	3	70.8 (17.0)	0.0450 (0.045, 1.06)	402 (22.0)	400 (21.7)
10 mg/kg Q2W	5	294 (23.4)	0.0440 (0.042, 0.847)	1770 (38.5)	1780 (39.1)
15 mg/kg Q3W	7	427 (25.5)	0.0520 (0.042, 0.951)	2320 (34.4)	2940 (36.3)
20 mg/kg Q4W	18	416 (23.9)	0.0450 (0.003, 0.162)	3290 (21.3)	4500 (23.1)

Geometric mean (Geometric CV %), *: Median (Range)

6.2.3 Assessment of relationship between durvalumab exposure and change in QT/QTc interval

In the ATLANTIC study, serum durvalumab measurements at the time of ECG recording were collected from 239 subjects, and the durvalumab serum concentration-ΔQTcF analysis was performed using a linear mixed-effects model. No significant relationship was identified between durvalumab serum concentration and ΔQTcF. At the serum durvalumab concentration at the end of the first infusion, ΔQTcF [90%CI] (ms) was predicted to be less than 10, i.e., 1.93 [1.82, 2.03].

9) The ratio of C_{max} or C_{min} at steady state (Day 84 or later)/C_{max} or C_{min} after the first dose

The applicant's explanation:
Based on the above, durvalumab at the proposed dosing regimen is unlikely to prolong the QT/QTc interval.

6.2.4 PPK analysis

Based on durvalumab PK data from 2 studies, Study 1108 and the ATLANTIC study (7262 PK samples from 1324 patients), PPK analysis was performed by non-linear mixed effects modeling, and the following assessments were conducted (software, NONMEM Version 7.3.0). The PK of durvalumab were described by a 2-compartment model with parallel linear and nonlinear Michaelis-Menten eliminations.

- Serum albumin, body weight, creatinine clearance (CrCL), lactate dehydrogenase (LDH), soluble PD-L1 level, serum creatinine, age, AST, ALT, total bilirubin, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), tumor type, race, and immunogenicity were tested as potential covariates on (a) CL of durvalumab. These factors excluding immunogenicity were tested as potential covariates on (b) V1 and (c) V2 of durvalumab. As a result, (a) serum albumin, body weight, sex, LDH, ECOG PS, immunogenicity, CrCL, soluble PD-L1 level, and tumor type, (b) body weight and sex, and (c) sex were identified as significant covariates for (a) CL, (b) V1, and (c) V2.
- The $C_{min,ss}$ following intravenous administration of durvalumab 10 mg/kg Q2W was simulated. As a result, 97.8% of patients receiving durvalumab 10 mg/kg Q2W via intravenous infusion were expected to maintain the $C_{min,ss}$ of durvalumab above 53.3 μg/mL,[10)] a concentration that blocks 99% of the PD-L1/PD-1 pathway.

The dataset used for the above PPK modeling was updated by excluding patients on doses ≤3 mg/kg. Based on the updated PK dataset (6984 samples from 1310 patients), PPK analysis was performed by non-linear mixed effects modeling (software, NONMEM Version 7.3.0). The PK of durvalumab were described by a 2-compartment model with linear elimination and time-dependent CL.

Based on the results of the above PPK analysis, the effects of serum albumin, body weight, sex, LDH, ECOG PS, immunogenicity, CrCL, soluble PD-L1 level, and tumor type on (a) CL, the effects of body weight and sex on (b) V1, and the effect of sex on (c) V2 were incorporated in the model. Then the impact of these covariates on durvalumab exposure ($C_{max,ss}$, $C_{min,ss}$, AUC_{ss}) was evaluated. The effect of covariates was estimated to change the $C_{max,ss}$, $C_{min,ss}$, and AUC_{ss} of durvalumab by up to 21%, 25%, and 23%, respectively. The applicant explained that considering the coefficients of variation for the $C_{max,ss}$, $C_{min,ss}$, and AUC_{ss} of durvalumab in the PACIFIC study (27.5%, 41.4%, and 37.5%, respectively[11)]) and exposure-efficacy/safety relationship [see Section 6.2.5], none of the covariates have a clinically relevant effect on durvalumab exposure.

6.2.5 Exposure-efficacy/safety relationship

Based on the data from the PACIFIC study, the potential relationships between durvalumab exposure[11)] and

[10)] Calculated based on Michaelis constant (0.533 μg/mL) estimated from the PPK model [see Section 6.2.4].
[11)] The PPK model constructed for the PPK analysis [see Section 6.2.4] was subjected to external validation using durvalumab PK data from Study 1108 and the PACIFIC study (3408 samples from 679 subjects), to construct another PPK model, which was used to estimate durvalumab exposure levels.

efficacy/safety were assessed.

6.2.5.1 Exposure-efficacy relationship

Subjects in the durvalumab group were divided into 4 quartiles based on their durvalumab exposure ($C_{max,ss}$, $C_{min,ss}$, AUC_{ss}), and PFS was estimated for the placebo group and each exposure quartile using the Kaplan-Meier method. The results suggested that PFS is prolonged with increasing $C_{min,ss}$ and AUC_{ss}. On the other hand, no evident relationship was identified between the $C_{max,ss}$ and PFS.

The applicant's explanation about the relationship between durvalumab exposure and efficacy:
Durvalumab has PK with time-dependent CL [see Section 6.2.4] and the CL of durvalumab is predicted to decrease over time with prolonged treatment. Therefore, the potential relationship between time-dependent CL and PFS was also assessed based on the data from the PACIFIC study. PFS (median) was 12.4 months in (a) patients with a percent reduction in CL from baseline to steady-state at or above the median value (−21%), and 17.95 months in (b) patients with a percent reduction in CL from baseline to steady-state less than the median value. PFS tended to be longer in (b) than in (a).

This finding suggests that the relationship between $C_{min,ss}/AUC_{ss}$ and PFS may be due to a reduction in CL of durvalumab in patients who responded to durvalumab and received durvalumab for a longer period of time. At present, no evident relationship between durvalumab exposure and efficacy has been observed.

6.2.5.2 Exposure-safety relationship

The potential relationships between durvalumab exposure ($C_{max,ss}$, $C_{min,ss}$, AUC_{ss}) and the occurrence of the following adverse events were assessed: Grade 3 or 4 adverse events for which a causal relationship to durvalumab could not be ruled out; Grade 3 or 4 adverse events of special interest[12)]; adverse events leading to treatment discontinuation; and pneumonitis. No evident relationship between durvalumab exposure and the occurrence of the above adverse events was observed.

6.2.6 Effect of decreased renal/hepatic function on PK of durvalumab

No clinical studies were conducted to evaluate the PK of durvalumab in patients with renal or hepatic impairment. However, the applicant explained that given the following points etc., decreased renal or hepatic function is unlikely to affect the PK of durvalumab.

- Since durvalumab is considered to be eliminated via a pathway mediated by binding to the target antigen and a protein catabolic pathway, decreased renal or hepatic function is unlikely to affect durvalumab exposure.
- Durvalumab is a high molecular weight compound (molecular weight, ca. 149,000), and is not renally excreted.
- In the PPK analysis, ALT, AST, or total bilirubin was not identified as a significant covariate for the CL,

12) Defined as pneumonitis, hepatic dysfunction-related events, diarrhea, colitis, endocrinopathies (adrenal dysfunction, type 1 diabetes mellitus, hypophysitis, hypothyroidism, hyperthyroidism), renal dysfunction-related events, dermatitis, rash, pancreatic dysfunction-related events, immune-mediated events, infusion-related reactions, hypersensitivity, and anaphylactic reactions.

V1, or V2 of durvalumab [see Section 6.2.4].

- In the PPK analysis, CrCL had a limited effect on the PK of durvalumab [see Section 6.2.4].

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK of durvalumab between Japanese and non-Japanese populations

The applicant explained differences in the PK of durvalumab between Japanese and non-Japanese patients based on durvalumab PK data from Japanese patients in Study 02 and from Study 1108.

The applicant's explanation:

The C_{max} and AUC_{14days} following the first dose tended to be lower in Japanese patients than in non-Japanese patients [see Section 6.2.1.1 and Section 6.2.2.1]. Considering the following points, the C_{max} and AUC_{14days} values obtained from the 2 studies were dose-normalized, and the PK of durvalumab in Japanese and non-Japanese patients were compared.

- In the PPK analysis, body weight was selected as a significant covariate on the CL of durvalumab [see Section 6.2.4].
- The mean body weights in Japanese patients (Study 02) and non-Japanese patients (Study 1108) who received weight-based doses of durvalumab were 55.4 and 80.9 kg, respectively. Body weight differed between Japanese and non-Japanese patients.

The following are the dose-normalized (a) C_{max} and (b) AUC_{14days} (geometric mean [CV %]) over the dose range of 3 to 20 mg/kg:

(a) 0.307 (25.9) and 0.306 (37.0) μg/mL/mg in Japanese and non-Japanese patients, respectively.

(b) 1.94 (37.2) and 2.08 (33.4) μg·day/mL/mg in Japanese and non-Japanese patients, respectively.

There were no evident differences between Japanese and non-Japanese patients.

Based on the above, taking account of differences in body weight between Japanese and non-Japanese patients enrolled in the clinical studies, there should be no evident differences in the PK of durvalumab between Japanese and non-Japanese populations.

PMDA accepted the applicant's explanation.

6.R.2 Impact of anti-durvalumab antibody on PK of durvalumab

The incidence of anti-durvalumab antibodies was assessed in Study 1108, Study 02, the ATLANTIC study, and the PACIFIC study. Among 1686 patients treated with durvalumab 10 mg/kg Q2W, 99 patients (5.9%) tested positive for anti-durvalumab antibodies, including 8 patients (0.5%) with anti-durvalumab neutralizing antibodies.

The applicant's discussion on whether durvalumab in serum samples interfered with anti-durvalumab antibody assay:

Up to 100 μg/mL of durvalumab in serum samples did not interfere with anti-durvalumab antibody assay [see

Section 6.1.1.2]. In Study 1108, Study 02, the ATLANTIC study, and the PACIFIC study, this assay method was used, and the serum durvalumab concentrations at sampling time points for anti-durvalumab antibody assay were up to 607.1 μg/mL. Given this finding, the presence of durvalumab in serum samples may have interfered with anti-durvalumab antibody assay.

The applicant explained that given the following points etc., the presence of anti-durvalumab antibodies is unlikely to have a clinically significant effect on the PK of durvalumab.

- In Study 1108, Study 02, the ATLANTIC study, and the PACIFIC study, the C_{min} following intravenous administration of durvalumab 10 mg/kg Q2W was lower in anti-durvalumab antibody-positive patients than in antibody-negative patients, except for pre-dose of Dose 8 and pre-dose of Dose 21 (Table 15). However, baseline CL (median) estimated from the PPK analysis [see Section 6.2.4] was higher in patients who tested positive for anti-durvalumab antibodies at pre-dose of Dose 3 (0.389 L/day) than in antibody-negative patients (0.247 L/day). This means that factors other than anti-durvalumab antibody status may have impacted the C_{min}.
- Although immunogenicity was selected as a significant covariate on the CL of durvalumab in the PPK analysis, immunogenicity is not considered to have a clinically relevant effect on durvalumab exposure [see Section 6.2.4].

Table 15. Serum durvalumab concentrations following administration of durvalumab 10 mg/kg Q2W (μg/mL)

Sampling day (Day)	Anti-durvalumab antibody-positive patients		Anti-durvalumab antibody-negative patients	
	n	C_{min}	n	C_{min}
Pre-dose of Dose 3	44	27.7 (209)	1106	84.7 (54.1)
Pre-dose of Dose 8	1	260	26	180 (58.0)
Pre-dose of Dose 9	1	118	535	152 (55.8)
Pre-dose of Dose 21	1	328	256	184 (65.3)
End of treatment	9	28.1 (62.5)	520	125 (105)
30 days follow-up	1	31.2	205	99.9 (96.0)
3 months follow-up	3	7.27 (432)	380	18.0 (195)

Geometric mean (Geometric CV %) (Individual values are shown for n = 1)

PMDA's discussion:

Taking account of the following points, it is difficult to draw a definite conclusion on the impact of anti-durvalumab antibodies on the PK of durvalumab. Thus, the applicant should continue to collect information on the impact of anti-durvalumab antibodies on the PK of durvalumab and appropriately provide any new finding to healthcare professionals in clinical practice.

- The number of anti-durvalumab antibody-positive patients was limited.
- The presence of durvalumab in serum may have affected the results obtained with the antibody assay method used in the clinical studies.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from a total of 2 studies: a global phase I study and a global phase III study presented in Table 16. The applicant also submitted the results from a total of 2 studies: a global phase II study and a foreign phase I/II study presented in Table 16, as reference data.

Table 16. Listing of efficacy and safety clinical studies

Data	Region	Study ID	Phase	Study population	No. of patients enrolled	Dosing regimen (all via intravenous infusion)	Main endpoints
Evaluation	Global	02	I	Dose-escalation phase: (a) Patients with advanced solid tumors Dose-expansion phase: (b) Patients with unresectable, biliary tract cancer, esophagus cancer, or squamous cell carcinoma of the head and neck who had received prior platinum-based chemotherapy	138 (a) 22 (b) 116	(a) Durvalumab 1, 3, or 10 mg/kg Q2W, 15 mg/kg Q3W, or 20 mg/kg Q4W (b) Durvalumab 10 mg/kg Q2W	Safety Tolerability PK
		PACIFIC	III	Patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT	709 (a) 475 (b) 234	(a) Durvalumab 10 mg/kg Q2W (b) Placebo Q2W	Efficacy Safety
Reference	Global	ATLANTIC	II	● Cohort 1: Patients with unresectable, advanced/recurrent, PD-L1+ (TPS ≥25%), *EGFR*+/*ALK*+ NSCLC ● Cohort 2: Patients with unresectable, advanced/recurrent, PD-L1+ (TPS ≥25%), *EGFR* and *ALK* wild type/unknown NSCLC ● Cohort 3: Patients with unresectable, advanced/recurrent, PD-L1+ (TPS ≥90%), *EGFR* and *ALK* wild type/unknown NSCLC	Cohort 1 111 Cohort 2 265 Cohort 3 68	Durvalumab 10 mg/kg Q2W	Efficacy Safety PK
	Foreign	1108	I/II	NSCLC cohort: Patients with unresectable, advanced/recurrent NSCLC	304	Durvalumab 10 mg/kg Q2W	Safety Tolerability PK

These clinical studies are summarized below.

The main adverse events other than deaths observed in the clinical studies are described in Section "7.3 Adverse events etc. observed in clinical studies," and PK study results are described in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global phase I study (CTD 5.3.3.2.1, Study 02 [ongoing since September 2013 (data cutoff date of [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted at 20 sites in 3 countries including Japan to evaluate the safety, tolerability, etc. of durvalumab in patients with advanced solid tumors during the dose-escalation phase (target sample size, 24 subjects) and in patients with unresectable, biliary tract cancer, esophagus cancer, or squamous cell carcinoma of the head and neck who had received prior platinum-based chemotherapy during the dose-expansion phase (target sample size, 60-180 subjects).

Subjects were to receive durvalumab 1, 3, or 10 mg/kg Q2W, durvalumab 15 mg/kg Q3W, or durvalumab 20 mg/kg Q4W, via intravenous infusion, during the dose-escalation phase, and durvalumab 10 mg/kg Q2W via intravenous infusion during the dose-expansion phase, until disease progression or a treatment discontinuation criterion was met.

Among 165 subjects enrolled in the study, 138 subjects who received durvalumab (22 in the dose-escalation phase, 116 in the dose-expansion phase) were included in the safety population.

The dose-limiting toxicity (DLT) evaluation period was defined as the period from the first dose of durvalumab

until Day 28 in the dose-escalation phase, and no DLTs were observed.

As for safety, 94 of 138 subjects (68.1%) died during the durvalumab treatment period or within 90 days after the last dose of durvalumab [18 of 22 subjects (81.8%) during the dose-escalation phase (3 of 4 subjects (75.0%) in the 1 mg/kg Q2W group, 3 of 4 subjects (75.0%) in the 3 mg/kg Q2W group, 3 of 4 subjects (75.0%) in the 10 mg/kg Q2W group, 6 of 6 subjects (100%) in the 15 mg/kg Q3W group, 3 of 4 subjects (75.0%) in the 20 mg/kg Q4W group), 76 of 116 subjects (65.5%) during the dose-expansion phase]. The main cause of death was disease progression (18 subjects during the dose-escalation phase, 72 subjects during the dose-expansion phase). No patient died of other causes during the dose-escalation phase. Other causes of deaths during the dose-expansion phase were gastrointestinal haemorrhage; cardiac death; hepatic function abnormal and dehydration; and haemoptysis (1 subject each). A causal relationship to durvalumab could not be ruled out for gastrointestinal haemorrhage; hepatic function abnormal and dehydration; and haemoptysis (1 subject each).

7.1.1.2 Global phase III study (CTD 5.3.5.1.1, PACIFIC study [ongoing since May 2014 (data cutoff date of February 13, 2017)])

A double-blind, randomized, comparative study was conducted at 235 sites in 26 countries including Japan to evaluate the efficacy and safety of durvalumab versus placebo in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT (target sample size, 702 subjects).[13)]

Subjects were to receive durvalumab 10 mg/kg or placebo Q2W via intravenous infusion for up to 12 months, until disease progression or a discontinuation criteria was met.

All of 713 subjects who were enrolled in the study and randomized (476 in the durvalumab group, 237 in the placebo group) were included in the ITT population, which was used for efficacy analyses. After excluding 4 subjects who did not receive study drug (3 in the durvalumab group, 1 in the placebo group) from the ITT population, 709 subjects were included in the safety population. Note that 2 subjects who were assigned to the placebo group but mistakenly received durvalumab were analyzed as durvalumab-treated subjects (the safety population, 475 in the durvalumab group, 234 in the placebo group).

The co-primary endpoints for this study were overall survival (OS) and progression-free survival (PFS) as assessed by the site investigator per RECIST ver.1.1. An OS interim analysis for efficacy was to be performed at the time of the PFS analysis. A two-sided significance level of 4.5% for analysis of OS and a two-sided significance level of 0.5% for analysis of PFS were to be used to adjust for multiplicity between the endpoints. However, an interim PFS analysis was planned when 275 PFS events had occurred, to analyze the efficacy and safety of durvalumab (Protocol Amendment 1 [as of [redacted], 20[redacted]]) at an early timing. In order to assess PFS events more objectively and assure the desired power of the interim analysis, PFS based on blinded independent

13) The study included patients with Stage III (International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [7th edition]) NSCLC who were confirmed to have disease control (SD, PR, or CR) at randomization following definitive, platinum-based CRT.

central review (BICR) assessments was adopted in addition to PFS based on site investigator assessments. The primary endpoint was changed to PFS by BICR, and PFS by the site investigator was reclassified as a secondary endpoint. Timing of PFS interim analysis was changed to a later time point when 367 events had occurred. Also for an earlier analysis of OS, the second interim analysis of OS was planned when 393 OS events had occurred. Furthermore, in order to assure the power for PFS, the two-sided significance levels for OS and PFS analyses were both changed to 2.5%. In order to adjust for multiplicity between the endpoints, the PFS and OS were to be tested according to the group sequential Holm fixed procedure (*Stat Med.* 2012; 32: 1112-24). If the testing for PFS (OS) was statistically significant at either the interim or final analysis, the significance level for the final analysis of OS (PFS) was to be recalculated based on two-sided 5% significance level (Protocol Amendment 3 [as of [redacted], 20[redacted]]). The Lan-DeMets α spending function that approximates an O'Brien-Fleming approach was to be used to control the type I error rate from PFS and OS interim analyses.

As for efficacy, Table 17 shows the results of the interim analysis of PFS assessed by BICR per RECIST ver.1.1, a co-primary endpoint. Figure 1 shows the Kaplan-Meier curves. The superiority of durvalumab over placebo was demonstrated. At the interim analysis of PFS, the OS hazard ratio for durvalumab vs. placebo was [redacted], and the Independent Data Monitoring Committee (IDMC) recommended that the study should continue.

Table 17. Results of interim analysis of PFS (BICR, ITT population, Data cutoff date of February 13, 2017)

	Durvalumab	Placebo
N	476	237
No. of events (%)	214 (45.0)	157 (66.2)
Median [95% CI] (months)	16.8 [13.0, 18.1]	5.6 [4.6, 7.8]
Hazard ratio [98.9% CI]*1	0.52 [0.39, 0.70]	
P-value (two-sided)*2	<0.0001	

*1: Estimated based on a stratified log-rank test statistic, adjusted for age (<65 years, ≥65 years), sex (male, female), and smoking history (smoker, non-smoker). *2: A stratified log-rank test, adjusted for age (<65 years, ≥65 years), sex (male, female), and smoking history (smoker, non-smoker), with a two-sided significance level of 0.011035

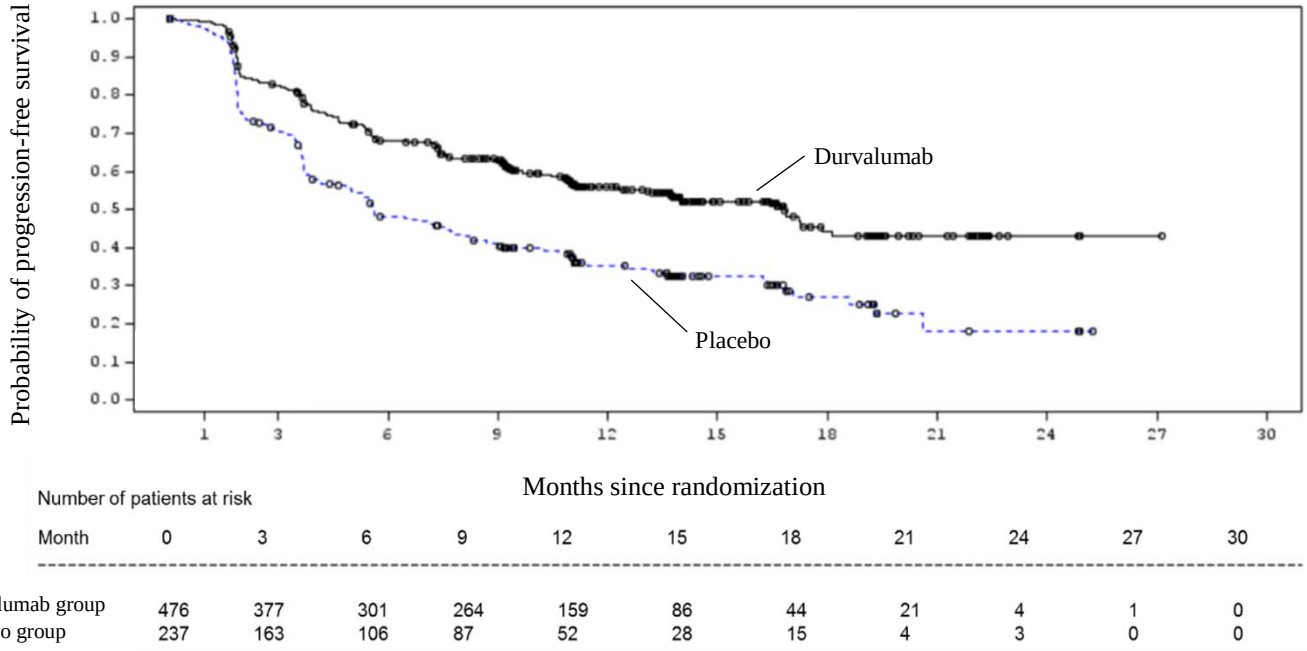


Figure 1. Kaplan-Meier curves for PFS at interim analysis (BICR, ITT population, Data cutoff date of February 13, 2017)

As for safety, 31 of 475 subjects (6.5%) in the durvalumab group and 29 of 234 subjects (12.4%) in the placebo group died during the study treatment period or within 90 days after the last dose of study drug. The causes of death were as follows:

The durvalumab group: disease progression (12 subjects); pneumonia; pneumonia bacterial; septic shock; cardiac arrest; cardiopulmonary failure; myocardial infarction; emphysema; aortic dissection; pneumonitis; pneumonitis and respiratory failure; death; pneumonia pneumococcal and disease progression; sepsis and disease progression; cardiac arrest and disease progression; cardiomyopathy and disease progression; dyspnoea and disease progression; haemoptysis and disease progression; pneumonitis and disease progression; and respiratory distress and disease progression (1 subject each).

The placebo group: [redacted].

A causal relationship to study drug could not be ruled out for pneumonitis; pneumonitis and respiratory failure; cardiomyopathy and disease progression; pneumonitis and disease progression; and respiratory distress and disease progression (1 subject each) in the durvalumab group and [redacted] in the placebo group.

7.2 Reference data

7.2.1 Global study

7.2.1.1 Global phase II study (CTD 5.3.5.2.2, ATLANTIC study [ongoing since February 2014])

An open-label, uncontrolled study was conducted at 145 sites in 18 countries including Japan to evaluate the efficacy and safety of durvalumab in patients with unresectable, advanced/recurrent NSCLC who had received at least 2 prior chemotherapy regimens including 1 platinum-based chemotherapy regimen (target sample size, 94 in Cohort 1, 94 in Cohort 2, 94 in Cohort 3).

Patients in Cohort 1 had PD-L1 positive tumors (TPS ≥25%) with *EGFR* mutations or *ALK* rearrangements. Patients in Cohort 2 had PD-L1 positive tumors (TPS ≥25%) with wild-type or unknown status for *EGFR* and *ALK*. Patients in Cohort 3 had PD-L1 positive tumors (TPS ≥90%) with wild-type or unknown status for *EGFR* and *ALK*.

The safety population included 444 subjects who were enrolled and received durvalumab (111 in Cohort 1, 265 in Cohort 2, 68 in Cohort 3).

As for safety, 159 of 444 subjects died during the durvalumab treatment period or within 90 days after the last dose of durvalumab. The causes of death were disease progression (146 subjects); pneumonia; pneumonia and disease progression; pulmonary sepsis and disease progression; cardio-respiratory arrest; pneumonitis; gastric haemorrhage; gastrointestinal haemorrhage; sudden death; cardiac failure; acute myocardial infarction and disease progression; and pulmonary embolism and disease progression (1 subject each), and unknown (2 subjects). A causal relationship to durvalumab could not be ruled out for 1 case of pneumonitis.

7.2.2 Foreign clinical study

7.2.2.1 Foreign phase I/II study (CTD 5.3.5.2.1, Study 1108, NSCLC cohort [ongoing since August 2012])

An open-label, uncontrolled study was conducted at 77 sites in 9 foreign countries to evaluate the safety, tolerability, etc. of durvalumab in patients with unresectable, advanced/recurrent NSCLC (target sample size, 330 subjects [140 patients with non-squamous NSCLC, 190 patients with squamous NSCLC]).

The safety population included 304 subjects who were enrolled and received durvalumab.

As for safety, 99 of 304 subjects died during the durvalumab treatment period or within 90 days after the last dose of durvalumab. The causes of death were disease progression (76 subjects); respiratory failure (5 subjects); general physical condition decreased and disease progression (3 subjects); sepsis (2 subjects); pulmonary haemorrhage; cardiac arrest; ischaemic cardiomyopathy; dyspnoea; disseminated intravascular coagulation; urosepsis; transient ischaemic attack; acute respiratory failure; pneumonia; death; and lung infection and disease progression (1 subject each), and unknown (2 subjects). A causal relationship to durvalumab could not be ruled out for 1 case of pneumonia.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA review strategy:

Among the evaluation data submitted, the pivotal clinical study to evaluate the efficacy and safety of durvalumab is the PACIFIC study (a global phase III study to evaluate the efficacy and safety of durvalumab versus placebo in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT). The efficacy and safety of durvalumab are evaluated based mainly on this study. The efficacy of durvalumab in Japanese patients is evaluated in terms of the consistency of the results between the overall population and Japanese subgroup in the PACIFIC study, based on "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)"(PFSB/ELD Administrative Notice dated September 5, 2012), etc.

7.R.2 Efficacy

Based on the following considerations, PMDA concluded that durvalumab was shown to have efficacy in patients with locally-advanced, unresectable NSCLC whose disease had not progressed following definitive, platinum-based CRT.

7.R.2.1 Inclusion of a control group

The applicant's explanation about the reason for using placebo as a control group in the PACIFIC study:
At the time of planning the PACIFIC study, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer (the NCCN guidelines) (v.1.2014), etc. recommended that patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT should undergo a period of active surveillance without further treatment until disease progression. There was no standard of care recommended for these patients. Thus, placebo was chosen as a control group.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints and evaluation results

The applicant's explanation about the appropriateness of selecting PFS and OS as the co-primary endpoints for the PACIFIC study:
Selecting PFS and OS as the co-primary endpoints for the PACIFIC study was appropriate for the following reasons: (a) Prolonged PFS in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive CRT is clinically meaningful because it is expected to prolong the time to disease progression and delay the onset of clinical symptoms associated with disease progression. (b) Usually, treatment for the patient population eligible for the PACIFIC study is intended to achieve survival benefit.

The PACIFIC study demonstrated the superiority of durvalumab over placebo in the co-primary endpoint of PFS [see Section 7.1.1.2]. The OS (the other co-primary endpoint) hazard ratio for durvalumab vs. placebo was [redacted] at the interim analysis of PFS.

Table 18 shows the results of the interim analysis of PFS assessed by BICR per RECIST ver.1.1 in Japanese patients in the PACIFIC study. Figure 2 shows the Kaplan-Meier curves.

Table 18. Results of interim analysis of PFS in Japanese patients (BICR, ITT population, Data cutoff date of February 13, 2017)

	Durvalumab	Placebo
N	72	40
No. of events (%)	31 (43.1)	25 (62.5)
Median PFS [95% CI] (months)	NE [10.9, NE]	7.2 [2.0, 18.6]
Hazard ratio [95% CI]*1	0.49 [0.26, 0.89]	
P-value (two-sided)*2	0.020	

*1: Estimated based on a stratified log-rank test statistic, adjusted for age (<65 years, ≥65 years), sex (male, female), and smoking history (smoker, non-smoker), *2: A stratified log-rank test, adjusted for age (<65 years, ≥65 years), sex (male, female), and smoking history (smoker, non-smoker)

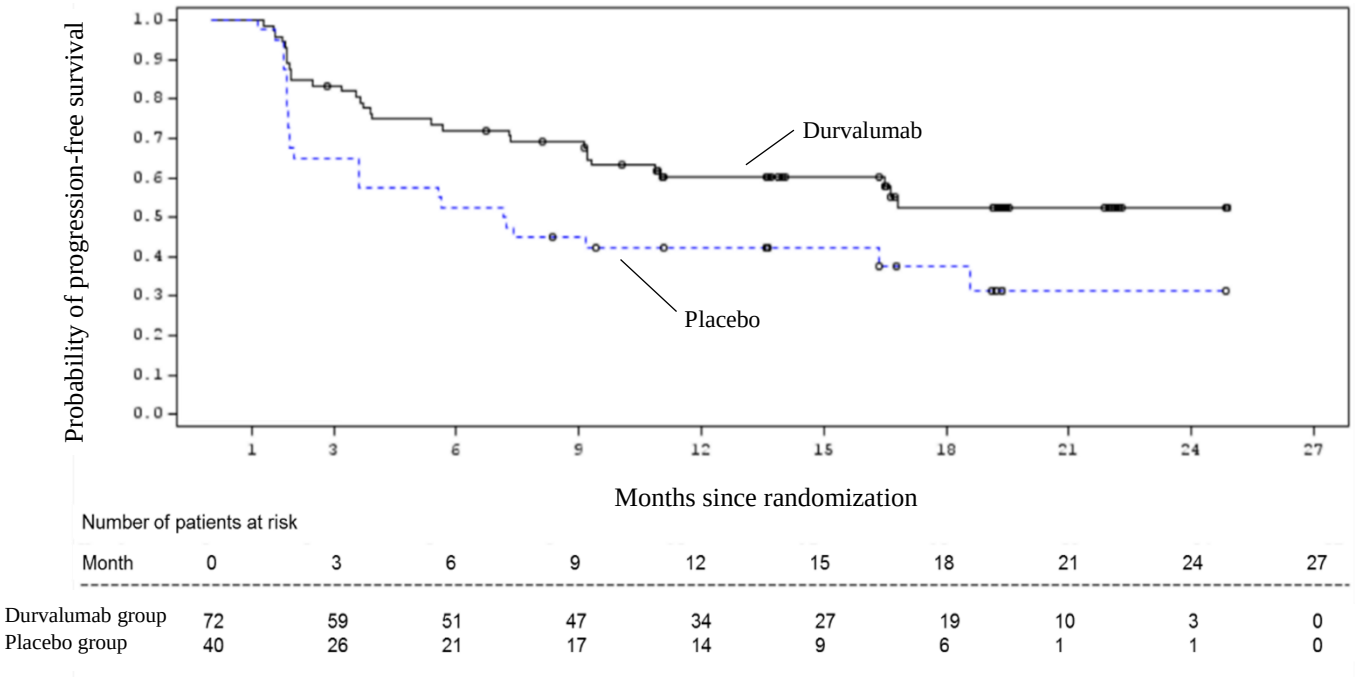


Figure 2. Kaplan-Meier curves for PFS in Japanese patients at interim analysis (BICR, ITT population, Data cutoff date of February 13, 2017)

PMDA's discussion:

PMDA concluded that durvalumab was shown to have efficacy in patients included in the PACIFIC study, for the following reasons.

- The applicant's explanation regarding the co-primary endpoint of PFS (i.e., prolonged PFS is clinically meaningful to a certain extent) is understandable. The superiority of durvalumab over placebo was demonstrated, and the magnitude of the observed effects of durvalumab was clinically relevant.
- At the interim analysis of PFS, the OS (the other co-primary endpoint) hazard ratio for durvalumab vs. placebo was [redacted], as assessed by the IDMC, and there was no trend towards shortened OS in the durvalumab group compared with the placebo group.
- The above results of analysis in the Japanese subgroup were consistent with those in the overall population.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies"]

Based on the following review, PMDA considers that attention should be paid to the possible occurrence of the following adverse events when using durvalumab in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT:

Interstitial lung disease (ILD), hepatic dysfunction, renal disorders, infusion-related reaction (IRR), and endocrine dysfunction (thyroid dysfunction, adrenal dysfunction).

However, PMDA concluded that durvalumab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures (e.g. monitoring of adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and durvalumab dose delay) during the use of durvalumab.

7.R.3.1 Safety profile of durvalumab and differences between Japanese and non-Japanese populations

The applicant's explanation about the safety profile of durvalumab, based on the safety information of durvalumab from the PACIFIC study:

The safety summary in the PACIFIC study is shown in Table 19.

Table 19. Summary of safety (PACIFIC study)

	n (%)	
	Durvalumab N = 475	Placebo N = 234
All adverse events	460 (96.8)	222 (94.9)
Grade 3 or higher adverse events	163 (34.3)	74 (31.6)
Adverse events leading to death	21 (4.4)	14 (6.0)
Serious adverse events	136 (28.6)	53 (22.6)
Adverse events leading to treatment discontinuation	73 (15.4)	23 (9.8)
Adverse events leading to dose delay	202 (42.5)	72 (30.8)

In the PACIFIC study, adverse events of any grade reported at a ≥5% higher incidence in the durvalumab group than in the placebo group were cough (168 subjects [35.4%] in the durvalumab group, 59 subjects [25.2%] in the placebo group), pyrexia (70 subjects [14.7%], 21 subjects [9.0%]), pneumonia (62 subjects [13.1%], 18 subjects [7.7%]), pruritus (58 subjects [12.2%], 11 subjects [4.7%]), hypothyroidism (55 subjects [11.6%], 4 subjects [1.7%]), and hyperthyroidism (35 subjects [7.4%], 4 subjects [1.7%]). Serious adverse events reported at a ≥2% higher incidence in the durvalumab group than in the placebo group were radiation pneumonitis (17 subjects [3.6%], 3 subjects [1.3%]). Adverse events leading to treatment discontinuation reported at a ≥2% higher incidence in the durvalumab group than in the placebo group were pneumonitis (23 subjects [4.8%], 6 subjects [2.6%]). Adverse events leading to dose delay reported at a ≥2% higher incidence in the durvalumab group than in the placebo group were radiation pneumonitis (39 subjects [8.2%], 14 subjects [6.0%]), pneumonia (31 subjects [6.5%], 7 subjects [3.0%]), and pneumonitis (24 subjects [5.1%], 7 subjects [3.0%]). There were no Grade 3 or higher adverse events or adverse events leading to death reported at a ≥2% higher incidence in the durvalumab group than in the placebo group.

The applicant's explanation about differences in safety between Japanese and non-Japanese populations:

Table 20 shows the safety summary in Japanese and non-Japanese patients treated with durvalumab in the PACIFIC study.

Table 20. Summary of safety (PACIFIC study)

	n (%)	
	Japanese patients N = 72	Non-Japanese patients N = 403
All adverse events	71 (98.6)	389 (96.5)
Grade 3 or higher adverse events	17 (23.6)	146 (36.2)
Adverse events leading to death	1 (1.4)	20 (5.0)
Serious adverse events	18 (25.0)	118 (29.3)
Adverse events leading to treatment discontinuation	9 (12.5)	64 (15.9)
Adverse events leading to dose delay	36 (50.0)	166 (41.2)

In the PACIFIC study, adverse events of any grade reported at a ≥10% higher incidence in Japanese patients than in non-Japanese patients were radiation pneumonitis (39 Japanese patients [54.2%], 57 non-Japanese patients [14.1%]) and nasopharyngitis (14 Japanese patients [19.4%], 27 non-Japanese patients [6.7%]). The Grade 3 or higher adverse event reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients was radiation pneumonitis (4 Japanese patients [5.6%], 4 non-Japanese patients [1.0%]). The serious adverse event reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients was radiation pneumonitis (7 Japanese patients [9.7%], 10 non-Japanese patients [2.5%]). Adverse events leading to dose delay reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients were radiation pneumonitis (12 Japanese patients [16.7%], 27 non-Japanese patients [6.7%]), pneumonitis (5 Japanese patients [6.9%], 19 non-Japanese patients [4.7%]), lung infection (3 Japanese patients [4.2%], 3 non-Japanese patients [0.7%]), pneumothorax ([redacted]), and hyperthyroidism (2 Japanese patients [2.8%], 3 non-Japanese patients [0.7%]). There were no adverse events leading to death or treatment discontinuation reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's discussion:
Some adverse events were reported at a higher incidence in the durvalumab group than in the placebo group in the PACIFIC study, but most events were of Grade 2 or less severity. Thus, durvalumab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures (e.g. monitoring of adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and durvalumab dose delay).

The incidence of radiation pneumonitis (including Grade 3 or higher radiation pneumonitis and serious adverse events of radiation pneumonitis) was higher in Japanese patients than in non-Japanese patients. Although rigorous comparison between Japanese and non- Japanese patients is difficult (due to the limited number of Japanese patients with NSCLC treated with durvalumab), PMDA further discusses radiation pneumonitis, including the cause of the difference in the incidence between Japanese and non- Japanese patients, in Section 7.R.3.2.

In the following sections, PMDA conducted a safety review based mainly on the safety results of durvalumab in the PACIFIC study. PMDA focused on adverse events reported at a higher incidence in the durvalumab group than in the placebo group, and adverse events that require attention when using other drugs having a similar mechanism of action as durvalumab.

7.R.3.2 ILD

The applicant explained ILD associated with durvalumab in terms of (a) the occurrence of ILD, (b) differences in the occurrence of ILD between Japanese and non-Japanese patients in the PACIFIC study, and (c) the characteristics of and risk factors for ILD associated with durvalumab.

The applicant's explanation:

(a) Occurrence of ILD:

Events coded to the MedDRA PTs "acute interstitial pneumonitis," "alveolitis," "diffuse alveolar damage," "interstitial lung disease," "pneumonitis," "pulmonary fibrosis," and "radiation pneumonitis" were counted as ILD.

The occurrence of ILD in the PACIFIC study is shown in Table 21. The study excluded patients who presented with Grade 2 or higher ILD due to prior definitive CRT.

Table 21. Occurrence of ILD (PACIFIC study)

PT (MedDRA ver.19.1)	n (%)			
	Durvalumab N = 475		Placebo N = 234	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
ILD	161 (33.9)	21 (4.4)	58 (24.8)	10 (4.3)
Radiation pneumonitis	96 (20.2)	8 (1.7)	36 (15.4)	2 (0.9)
Pneumonitis	60 (12.6)	12 (2.5)	18 (7.7)	7 (3.0)
Interstitial lung disease	[redacted]	[redacted]	[redacted]	[redacted]
Acute interstitial pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary fibrosis	[redacted]	[redacted]	[redacted]	[redacted]

In the PACIFIC study, fatal ILD occurred in 5 of 475 subjects (1.1%) in the durvalumab group and 4 of 234 subjects (1.7%) in the placebo group. Serious ILD occurred in 34 of 475 subjects (7.2%) in the durvalumab group (radiation pneumonitis [redacted], pneumonitis [redacted], acute interstitial pneumonitis [redacted]) and 12 of 234 subjects (5.1%) in the placebo group (pneumonitis [redacted]; radiation pneumonitis [redacted] [redacted]). A causal relationship to study drug could not be ruled out for those reported by 21 of 475 subjects (4.4%) in the durvalumab group (pneumonitis [redacted]; radiation pneumonitis [redacted]; acute interstitial pneumonitis [redacted]) and 5 of 234 subjects (2.1%) in the placebo group (pneumonitis [redacted]; [redacted]). ILD leading to treatment discontinuation occurred in 30 of 475 subjects (6.3%) in the durvalumab group (pneumonitis [redacted]; radiation pneumonitis [redacted]; acute interstitial pneumonitis [redacted]) and 10 of 234 subjects (4.3%) in the placebo group (pneumonitis [redacted]; radiation pneumonitis [redacted] [redacted]). ILD leading to dose delay occurred in 65 of 475 subjects (13.7%) in the durvalumab group (radiation pneumonitis [39 subjects]; pneumonitis [24 subjects]; interstitial lung disease [2 subjects]) and 22 of 475 subjects (9.4%) in the placebo group (radiation pneumonitis [redacted]; pneumonitis [redacted] [redacted]).

In the PACIFIC study, the median time to the first onset of ILD (range), calculated from (i) the first dose of

durvalumab, was 55 (−3[14] to 406) days in the durvalumab group and 55 (1-255) days in the placebo group, and the median time to the first onset of ILD (range), calculated from (ii) the last day of radiation, was 73.0 days (20-433 days) in the durvalumab group and 76.5 days (24-280 days) in the placebo group.

The details of patients with fatal ILD associated with durvalumab in the PACIFIC study are shown in Table 22.

Table 22. Listing of patients with fatal ILD (PACIFIC study)

Group	Age	Sex	Race	PT (MedDRA ver19.1)	Time to onset (days)	Causal relationship with study drug
Durvalumab	6[redacted]	Female	Non-Japanese	Pneumonitis	3	Yes
	5[redacted]	Male	Non-Japanese	Pneumonitis	21	Yes
	7[redacted]	Male	Non-Japanese	Pneumonitis	26	Yes
	7[redacted]	Male	Japanese	Radiation pneumonitis	15	Yes
	6[redacted]	Male	Non-Japanese	Pneumonitis	43	Yes
Placebo	7[redacted]	Male	Japanese	Pneumonitis	29	No
	6[redacted]	Male	Non-Japanese	Pneumonitis	293	Yes
	7[redacted]	Male	Non-Japanese	Radiation pneumonitis	29	No
	7[redacted]	Male	Non-Japanese	Pneumonitis	36	Yes

(b) Differences in the occurrence of ILD between Japanese and non-Japanese patients:
The occurrence of ILD in Japanese and non-Japanese patients in the PACIFIC study is shown in Table 23.

Table 23. Occurrence of ILD in Japanese and non-Japanese patients (PACIFIC study)

PT (MedDRA ver.19.1)	n (%)							
	Japanese patients				Non-Japanese patients			
	Durvalumab N = 72		Placebo N = 40		Durvalumab N = 403		Placebo N = 194	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
ILD	53 (73.6)	5 (6.9)	24 (60.0)	2 (5.0)	108 (26.8)	16 (4.0)	34 (17.5)	8 (4.1)
Radiation pneumonitis	39 (54.2)	[redacted]	19 (47.5)	[redacted]	57 (14.1)	4 (1.0)	17 (8.8)	2 (1.0)
Pneumonitis	13 (18.1)	1 (1.4)	4 (10.0)	1 (2.5)	47 (11.7)	11 (2.7)	14 (7.2)	6 (3.1)
Interstitial lung disease	1 (1.4)	[redacted]	1 (2.5)	[redacted]	2 (0.5)	0	2 (1.0)	0
Acute interstitial pneumonitis	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary fibrosis	0	0	0	0	1 (0.2)	0	1 (0.5)	0

The reason for the higher incidence of ILD in Japanese patients than in non-Japanese patients is unknown. Attention should be paid to the possible occurrence of ILD associated with durvalumab. However, ILD will not become a particular problem in Japanese patients, considering the following findings:

- In the PACIFIC study, the difference in the incidence of ILD between the placebo and durvalumab groups was13.6% in Japanese patients and 9.3% in non-Japanese patients. The increased risk of ILD associated with durvalumab is similar in Japanese and non-Japanese patients.
- Most of the events of ILD observed in Japanese patients were of Grade 2 or less severity.
- The incidence of radiation pneumonitis due to definitive CRT in Japanese patients with NSCLC has been reported to be 10% to 80% for all Grades and 1% to 10% for Grade 3 or higher (*Int J Radiat Oncol Biol Phys*. 2012; 82: 1791-6, etc.). Though the variability is high and evaluation has limitations, the incidences

[14] The subject had Grade 1 radiation pneumonitis 3 days prior to initiation of durvalumab, which worsened to Grade 3 on Day 8. Thus, this event was counted as a treatment emergent adverse event.

of ILD in Japanese patients in the PACIFIC study fall within these reported ranges.

(c) Characteristics of and risk factors for ILD associated with durvalumab:
The safety information available from all clinical studies of durvalumab, as of the data cutoff date of [redacted], 20[redacted], was analyzed to determine the characteristics of and risk factors for ILD associated with durvalumab, but neither risk factors for ILD nor unique image findings were identified.

The occurrence of ILD associated with durvalumab, excluding the influence of radiation pneumonitis, was investigated based on the ATLANTIC study and Study 1108. The incidence of ILD was 2.3% for all Grades and 0.5% for Grade 3 or higher, and the median time to the onset of ILD from the first dose (range) was 75.5 days (24-232 days).

PMDA's discussion:
Special attention should be paid to the possible occurrence of ILD following administration of durvalumab, because (a) ILD associated with durvalumab, including fatal cases, occurred in the PACIFIC study, and (b) patients who have had prior lung radiation (i.e., the target population of durvalumab) are at high risk for ILD and serious ILD (Manuals for management of individual serious adverse drug reactions - Interstitial lung disease (pneumonitis, alveolitis, pulmonary fibrosis) [MHLW, November 2006]). Thus, healthcare professionals in clinical practice should appropriately be informed of the following points and the incidence of ILD in clinical studies, via package insert etc.

- Patients with Grade 2 or higher ILD due to prior definitive CRT were excluded from the PACIFIC study.
- Prior to the use of durvalumab, whether patients have current or prior ILD, etc., should be checked, and eligibility of each patient for durvalumab therapy should be examined carefully. Continuous attention should be paid to the possible occurrence of ILD during treatment with durvalumab, and if clinical symptoms etc. suggestive of ILD occur, appropriate actions should be taken.

The reason for the higher incidence of radiation pneumonitis in Japanese patients than in non-Japanese patients is unknown and, after the market launch, durvalumab will probably be used in patients with a history of radiation pneumonitis. Therefore, the risk factors for durvalumab-related ILD including radiation pneumonitis (e.g. the incidence of ILD following administration of durvalumab by presence or absence of a past history of radiation pneumonitis due to definitive CRT) should continue to be investigated after the market launch.

7.R.3.3 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with durvalumab:
Events coded to the following MedDRA PTs were counted as hepatic dysfunction: "acute hepatic failure," "alanine aminotransferase increased," "aspartate aminotransferase increased," "autoimmune hepatitis," "blood bilirubin increased," "drug-induced liver injury," "hepatic enzyme increased," "hepatic failure," "hepatic function abnormal," "hepatitis," "hepatitis acute," "hepatitis fulminant," "hepatitis toxic," "hepatocellular injury," "hepatotoxicity," "hyperbilirubinaemia," "hypertransaminasaemia," "jaundice," "jaundice hepatocellular," "liver function test increased," "subacute hepatic failure," and "transaminases increased."

The occurrence of hepatic dysfunction in the PACIFIC study is shown in Table 24.

Table 24. Occurrence of hepatic dysfunction (PACIFIC study)

PT (MedDRA ver.19.1)	n (%)			
	Durvalumab N = 475		Placebo N = 234	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Hepatic dysfunction	35 (7.4)	9 (1.9)	7 (3.0)	[redacted]
AST increased	17 (3.6)	6 (1.3)	2 (0.9)	[redacted]
ALT increased	16 (3.4)	4 (0.8)	3 (1.3)	[redacted]
Transaminases increased	6 (1.3)	2 (0.4)	[redacted]	[redacted]
Blood bilirubin increased	3 (0.6)	0	[redacted]	0
Hepatic function abnormal	[redacted]	0	[redacted]	0
Autoimmune hepatitis	[redacted]	0	[redacted]	0
Hepatic enzyme increased	1 (0.2)	0	1 (0.4)	0
Hepatitis	1 (0.2)	0	1 (0.4)	0
Hepatocellular injury	[redacted]	0	[redacted]	0
Hypertransaminasaemia	[redacted]	0	[redacted]	0
Hepatic function abnormal	[redacted]	0	[redacted]	0
Liver function test increased	[redacted]	0	[redacted]	0

In the PACIFIC study, no hepatic dysfunction leading to death or serious hepatic dysfunction was reported. Hepatic dysfunction leading to treatment discontinuation occurred in 2 of 475 subjects (0.4%) in the durvalumab group (AST increased [1 subject]; and transaminases increased [1 subject]), [redacted]. Hepatic dysfunction leading to dose delay occurred in 10 of 475 subjects (2.1%) in the durvalumab group (ALT increased [5 subjects]; AST increased [3 subjects]; transaminases increased [3 subjects]; blood bilirubin increased [1 subject]; hepatitis [1 subject] [some subjects were counted more than once because they had more than one event]) and 2 of 234 subjects (0.9%) in the placebo group ([redacted]).

The following tables show the details of patients with serious hepatic dysfunction (Table 25) or autoimmune hepatitis (Table 26) associated with durvalumab in all clinical studies submitted for the present application. In non-NSCLC cohorts in Study 1108,[15)] 1 patient had fatal autoimmune hepatitis whose causal relationship to durvalumab could not be ruled out. The patient had Grade 3 autoimmune hepatitis at onset and received corticosteroids, but developed hepatic failure.

[15)] The study is ongoing to evaluate the efficacy and safety of durvalumab 10 mg/kg Q2W in patients with advanced solid tumors excluding NSCLC (target sample size, 666 subjects).

Table 25. Listing of patients with serious hepatic dysfunction

Study ID	Age	Sex	PT*	Grade	Time to onset (days)	Causal relationship to durvalumab	Outcome
ATLANTIC	7[redacted]	Male	Hepatic enzyme increased	3	78	Yes	Not recovered
	6[redacted]	Male	ALT increased	3	147	No	Recovered
	7[redacted]	Male	Transaminases increased	3	7	No	Not recovered
	7[redacted]	Female	Transaminases increased	3	43	Yes	Recovered
	6[redacted]	Male	Hepatic enzyme increased	3	43	No	Recovered
1108	5[redacted]	Female	Hyperbilirubinaemia	3	15	No	Recovered
	5[redacted]	Male	Blood bilirubin increased	3	10	No	Not recovered
02	4[redacted]	Male	Blood bilirubin increased	3	184	Yes	Not recovered
	6[redacted]	Male	Hepatic function abnormal	5	9	Yes	Fatal

*: MedDRA ver.19.1 for ATLANTIC study and Study 1108, MedDRA ver.19.0 for Study 02

Table 26. Listing of patients with autoimmune hepatitis

Study ID	Age	Sex	PT (MedDRA ver.19.1)	Grade	Seriousness	Time to onset (days)	Causal relationship to durvalumab	Outcome
PACIFIC	6[redacted]	Male	Autoimmune hepatitis	2	Non-serious	28	Yes	Recovered
1108	7[redacted]	Male	Autoimmune hepatitis	3	Non-serious	113	Yes	Recovered

In any of the clinical studies submitted for the present application, there were no cases of hepatic dysfunction meeting Hy's law laboratory criteria (defined based on Guidance for industry. Drug-Induced Liver Injury: premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009).

PMDA's discussion:

Serious/fatal hepatic dysfunction and autoimmune hepatitis associated with durvalumab have been reported in clinical studies, and attention should be paid to the possible occurrence of hepatic dysfunction (e.g. periodic monitoring of hepatic function) following administration of durvalumab. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of hepatic dysfunction in clinical studies and how to manage hepatic dysfunction, etc. via package insert etc.

7.R.3.4 Renal disorders

The applicant's explanation about renal disorders associated with durvalumab:

Events coded to the following MedDRA PTs were counted as renal disorders: "acute kidney injury," "autoimmune nephritis," "blood creatinine increased," "blood urea increased," "creatinine renal clearance decreased," "glomerular filtration rate decreased," "glomerulonephritis," "glomerulonephritis acute," "glomerulonephritis membranous," "glomerulonephritis minimal lesion," "glomerulonephritis proliferative," "glomerulonephritis rapidly progressive," "nephritis," "renal failure," "renal tubular necrosis," and "tubulointerstitial nephritis."

The occurrence of renal disorders in the PACIFIC study is shown in Table 27.

Table 27. Occurrence of renal disorders (PACIFIC study)

PT (MedDRA ver.19.1)	n (%)			
	Durvalumab N = 475		Placebo N = 234	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Renal disorders	30 (6.3)	2 (0.4)	[redacted]	[redacted]
Blood creatinine increased	22 (4.6)	1 (0.2)	6 (2.6)	[redacted]
Acute kidney injury	7 (1.5)	1 (0.2)	[redacted]	[redacted]
Renal failure	3 (0.6)	0	1 (0.4)	0
Creatinine renal clearance decreased	[redacted]	0	[redacted]	0
Glomerulonephritis membranous	[redacted]	0	[redacted]	0
Tubulointerstitial nephritis	[redacted]	0	[redacted]	0

In the PACIFIC study, no fatal renal disorder was reported. Serious renal disorders occurred in 3 of 475 subjects (0.6%) in the durvalumab group (acute kidney injury [2 subjects]; glomerulonephritis membranous [1 subject]), [redacted], and a causal relationship to study drug could not be ruled out for the event reported by 1 of 475 subjects (0.2%) in the durvalumab group (glomerulonephritis membranous [1 subject]). Renal disorder leading to treatment discontinuation occurred in 1 of 475 subjects (0.2%) in the durvalumab group (glomerulonephritis membranous [1 subject]), [redacted]. Renal disorders leading to dose delay occurred in 5 of 475 subjects (1.1%) in the durvalumab group (blood creatinine increased [5 subjects]) and 1 of 234 subjects (0.4%) in the placebo group ([redacted]).

The details of patients with serious renal disorders associated with durvalumab in all clinical studies submitted for the present application are shown in Table 28.

Table 28. Listing of patients with serious renal disorders

Study ID	Age	Sex	PT (MedDRA ver.19.1)	Grade	Time to onset (days)	Causal relationship to durvalumab	Outcome
PACIFIC	6[redacted]	Female	Acute kidney injury	2	42	No	Recovered
	5[redacted]	Male	Glomerulonephritis membranous	2	29	Yes	Not recovered
	5[redacted]	Male	Acute kidney injury	4	189	No	Recovered
ATLANTIC	7[redacted]	Male	Nephritis	2	60	Yes	Recovered
1108	6[redacted]	Female	Acute kidney injury	1	28	Yes	Recovered

PMDA's discussion:

Since serious renal disorders such as acute kidney injury associated with durvalumab have been reported in Japanese and foreign clinical studies, attention should be paid to the possible occurrence of renal disorders following administration of durvalumab. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of renal disorders in clinical studies etc. and advised to monitor the renal function of patients receiving durvalumab and take appropriate action such as dose delay if any abnormality occurs, via package insert etc.

7.R.3.5 IRR

The applicant's explanation about IRR associated with durvalumab:

Events coded to the following MedDRA PTs were counted as adverse events indicative of IRR: "infusion

related reaction," "urticaria,[16)]" "allergy to immunoglobulin therapy," "anaphylactic reaction," "anaphylactic shock," "anaphylactoid reaction," "anaphylactoid shock," "drug cross-reactivity," "drug eruption," "drug hypersensitivity," "hypersensitivity," "serum sickness," "serum sickness-like reaction," "systemic immune activation," "Type I hypersensitivity," "Type II hypersensitivity," "Type III immune complex mediated reaction," and "Type IV hypersensitivity reaction."

The occurrence of IRR in the PACIFIC study is shown in Table 29.

Table 29. Occurrence of IRR (PACIFIC study)

PT (MedDRA ver.19.1)	n (%)			
	Durvalumab N = 475		Placebo N = 234	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
IRR	11 (2.3)	0	1 (0.4)	0
Infusion related reaction	5 (1.1)	0	[redacted]	0
Urticaria	4 (0.8)	0	[redacted]	0
Drug hypersensitivity	2 (0.4)	0	[redacted]	0

In the PACIFIC study, no fatal IRR was reported. Serious IRR occurred in [redacted] ([redacted]%) in the durvalumab group (infusion related reactions [redacted][17)]), and their causal relationship to study drug could not be ruled out. No IRR leading to treatment discontinuation or dose delay was reported.

In the durvalumab group, the median time to the first onset of IRR (range) was 31.0 days (1-225 days).

The protocol of the PACIFIC study included the Dosing Modification and Toxicity Management Guidelines (the infusion rate adjustment, the discontinuation criteria, etc.) for IRR during treatment with durvalumab. The Guidelines will be provided via information materials etc. The protocol of the PACIFIC study did not stipulate any prophylactic treatment against IRR.

PMDA's discussion:
Although the incidence of IRR was not high in the PACIFIC study, attention should be paid to the possible occurrence of IRR following administration of durvalumab, because (a) durvalumab is an antibody drug and therefore expected to cause IRR, and (b) some patients had recurrent IRR or serious IRR. If IRR occurs, appropriate actions (e.g. infusion rate adjustment) should be taken based on the Dosing Modification and Toxicity Management Guidelines of the PACIFIC study. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of IRR in clinical studies and how to manage IRR (e.g. criteria for infusion rate adjustment) via the package insert etc.

7.R.3.6 Endocrine dysfunction

The applicant's explanation about endocrine dysfunction associated with durvalumab [(a) thyroid dysfunction,

16) Only events of urticaria that occurred on the day of study drug infusion were counted.
17) A total of 5 infusion related reactions (all Grade 2) occurred following the 2nd to 6th doses of durvalumab, but no IRR occurred following the 7th and subsequent doses. Treatment with durvalumab was therefore continued.

(b) adrenal dysfunction, (c) pituitary dysfunction, (d) diabetes mellitus]:

(a) Thyroid dysfunction:
Events coded to the following MedDRA PTs were counted as thyroid dysfunction: "autoimmune thyroiditis," "Basedow's disease," "blood thyroid stimulating hormone decreased," "hyperthyroidism," "primary hyperthyroidism," "secondary hyperthyroidism," "thyroiditis," "thyroiditis acute," "thyroiditis subacute," "thyrotoxic crisis," "thyroxine free increased," "thyroxine increased," "toxic goitre," "toxic nodular goitre," "tri-iodothyronine free increased," "tri-iodothyronine increased," "autoimmune hypothyroidism," "blood thyroid stimulating hormone increased," "Hashimoto's encephalopathy," "hypothyroidism," "primary hypothyroidism," "secondary hypothyroidism," "tertiary hypothyroidism," "thyroxine decreased," "thyroxine free decreased," "tri-iodothyronine decreased," and "tri-iodothyronine free decreased."

The occurrence of thyroid dysfunction in the PACIFIC study is shown in Table 30.

Table 30. Occurrence of thyroid dysfunction (PACIFIC study)

PT (MedDRA ver.19.1)	n (%)			
	Durvalumab N = 475		Placebo N = 234	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Thyroid dysfunction	93 (19.6)	[redacted]	14 (6.0)	[redacted]
Hypothyroidism	55 (11.6)	[redacted]	4 (1.7)	[redacted]
Hyperthyroidism	35 (7.4)	0	4 (1.7)	0
Blood thyroid stimulating hormone decreased	9 (1.9)	0	2 (0.9)	0
Blood thyroid stimulating hormone increased	8 (1.7)	0	3 (1.3)	0
Thyroiditis	3 (0.6)	0	1 (0.4)	0
Autoimmune thyroiditis	[redacted]	0	[redacted]	0
Thyroxine free decreased	[redacted]	0	[redacted]	0

In the PACIFIC study, no fatal thyroid dysfunction, serious thyroid dysfunction, or thyroid dysfunction leading to treatment discontinuation was reported. Thyroid dysfunction leading to dose delay occurred in 14 of 475 subjects (2.9%) in the durvalumab group (hypothyroidism [8 subjects]; hyperthyroidism [5 subjects]; thyroiditis [1 subject]), [redacted].

In the PACIFIC study, the median time to the first onset of thyroid dysfunction (range) in the durvalumab group was 56 days (9-378 days).

The details of patients with serious thyroid dysfunction associated with durvalumab in all clinical studies submitted for the present application are shown in Table 31.

Table 31. Listing of patients with serious thyroid dysfunction

Study ID	Age	Sex	PT*	Grade	Time to onset (days)	Administration of durvalumab	Intervention/ treatment	Causal relationship to durvalumab	Outcome
ATLANTIC	5[redacted]	Female	Hypothyroidism	2	72	Continued	Thyroid hormone	Yes	Recovered
02	7[redacted]	Male	Tri-iodothyronine free decreased	3	36	Continued	Thyroid hormone	Yes	Not recovered

*: MedDRA ver.19.1 for ATLANTIC study, MedDRA ver.19.0 for Study 02

(b) Adrenal dysfunction:

Events coded to the MedDRA PTs "Addison's disease," "adrenal insufficiency," "adrenocortical insufficiency acute," "primary adrenal insufficiency," and "secondary adrenocortical insufficiency" were counted as adrenal dysfunction.

The occurrence of adrenal dysfunction in the PACIFIC study is shown in Table 32.

Table 32. Occurrence of adrenal dysfunction (PACIFIC study)

PT (MedDRA ver.19.1)	n (%)			
	Durvalumab N = 475		Placebo N = 234	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Adrenal dysfunction	[redacted]	0	[redacted]	0
Adrenal insufficiency	[redacted]	0	[redacted]	0
Addison's disease	[redacted]	0	[redacted]	0

In the PACIFIC study, no fatal adrenal dysfunction, serious adrenal dysfunction, or adrenal dysfunction leading to treatment discontinuation was reported. Adrenal dysfunction leading to dose delay occurred in [redacted] ([redacted]%) in the durvalumab group (adrenal insufficiency [redacted]), [redacted].

The details of patients with serious adrenal dysfunction associated with durvalumab in all clinical studies submitted for the present application are shown in Table 33.

Table 33. Listing of patients with serious adrenal dysfunction

Study ID	Age	Sex	PT (MedDRA ver.19.1)	Grade	Time to onset (days)	Administration of durvalumab	Intervention/ treatment	Causal relationship to durvalumab	Outcome
ATLANTIC	7[redacted]	Male	Adrenal insufficiency	3	210	Interrupted	Corticosteroids	Yes	Not recovered
	5[redacted]	Male	Adrenal insufficiency	3	333	Continued	Sodium chloride	No	Recovered
1108	5[redacted]	Male	Adrenal insufficiency	2	265	Interrupted	Corticosteroids	Yes	Not recovered

(c) Pituitary dysfunction:

Events coded to the following MedDRA PTs were counted as pituitary dysfunction: "adrenocorticotropic hormone deficiency," "diabetes insipidus," "hypophysitis," "hypopituitarism," "hypothalamic pituitary adrenal axis suppression," "hypothalamo-pituitary disorder," and "lymphocytic hypophysitis."

The details of patients with pituitary dysfunction associated with durvalumab in all clinical studies submitted for the present application are shown in Table 34.

Table 34. Listing of patients with pituitary dysfunction

Study ID	Age	Sex	PT (MedDRA ver.19.1)	Grade	Seriousness	Time to onset (days)	Administration of durvalumab	Intervention/ treatment	Causal relationship to durvalumab	Outcome
ATLANTIC	7[redacted]	Male	Hypopituitarism	3	Serious	44	Interrupted	Corticosteroids	Yes	Not recovered
			Diabetes insipidus	3	Serious	75	Continued	Vasopressin	Yes	Not recovered

(d) Diabetes mellitus:

Events coded to the following MedDRA PTs were counted as diabetes mellitus: "diabetic ketoacidosis," "diabetic ketoacidotic hyperglycaemic coma," "fulminant type 1 diabetes mellitus," "type 1 diabetes mellitus," "type 2 diabetes mellitus," "diabetes mellitus," "diabetes mellitus inadequate control," "diabetes with hyperosmolarity," "increased insulin requirement," "insulin autoimmune syndrome," and "insulin-requiring type 2 diabetes mellitus."

The details of patients with diabetes mellitus associated with durvalumab in all clinical studies submitted for the present application are shown in Table 35.

Table 35. Listing of patients with diabetes mellitus

Study ID	Age	Sex	PT (MedDRA ver.19.1)	Grade	Seriousness	Time to onset (days)	Administration of durvalumab	Intervention/ treatment	Causal relationship to durvalumab	Outcome
PACIFIC	6[redacted]	Male	Type 1 diabetes mellitus	3	Serious	43	Discontinued	Insulin	Yes	Recovered
	8[redacted]	Male	Type 2 diabetes mellitus	3	Non-serious	15	Continued	Unknown	No	Recovered
	6[redacted]	Male	Type 2 diabetes mellitus	2	Non-serious	99	Continued	Unknown	No	Not recovered
	5[redacted]	Male	Type 2 diabetes mellitus	1	Non-serious	324	Continued	Unknown	No	Not recovered
ATLANTIC	6[redacted]	Female	Diabetes mellitus	2	Non-serious	414	Continued	Unknown	No	Not recovered
	5[redacted]	Male	Type 2 diabetes mellitus	1	Non-serious	136	Continued	Unknown	No	Not recovered
	6[redacted]	Female	Diabetes mellitus	2	Non-serious	20	Continued	Unknown	No	Not recovered
1108	8[redacted]	Male	Diabetes mellitus	2	Non-serious	199	Continued	Unknown	No	Not recovered

In clinical studies and overseas post-marketing experience of durvalumab, there has been no reported case of fulminant type 1 diabetes mellitus associated with durvalumab at present.

PMDA's discussion:

The clinical studies have reported multiple cases of serious thyroid dysfunction/adrenal dysfunction for which a causal relationship to durvalumab could not be ruled out. Therefore, attention should be paid to the possible

occurrence of thyroid dysfunction/adrenal dysfunction following administration of durvalumab.

There have been pituitary dysfunction and type 1 diabetes mellitus for which a causal relationship to durvalumab could not be ruled out, but it is difficult to draw a definite conclusion on their relationship to durvalumab from the currently available information because of the limited number of patients who experienced these events. Nevertheless, attention should be paid to the possible occurrence of these events as well for the following reasons: (a) Pituitary dysfunction and type 1 diabetes mellitus are expected to occur in light of the mechanism of action of durvalumab. (b) Serious cases have been reported in clinical studies. (c) If pituitary dysfunction or type 1 diabetes mellitus occurs, they may become serious.

Based on the above, healthcare professionals in clinical practice should appropriately be informed of the incidence of thyroid dysfunction, adrenal dysfunction, pituitary dysfunction, and type 1 diabetes mellitus in clinical studies, via package insert etc. It is necessary to monitor the occurrence etc. of pituitary dysfunction and type 1 diabetes mellitus after the market launch, assess their causal relationship to durvalumab, and appropriately provide any new information to healthcare professionals in clinical practice.

7.R.3.7 Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders associated with durvalumab:

Events in the following MedDRA SMQs events and those coded to the following MedDRA PTs were counted as gastrointestinal disorders:

MedDRA SMQs: "gastrointestinal perforation" and "gastrointestinal obstruction."

MedDRA PTs: "acute haemorrhagic ulcerative colitis," "autoimmune colitis," "colitis," "colitis erosive," "colitis microscopic," "colitis ulcerative," "enteritis," "enterocolitis," "enterocolitis haemorrhagic," "necrotising colitis," "proctitis," "proctitis haemorrhagic," "diarrhoea," "diarrhoea haemorrhagic," and "frequent bowel movements."

The occurrence of gastrointestinal disorders in the PACIFIC study is shown in Table 36.

Table 36. Occurrence of gastrointestinal disorders (PACIFIC study)

PT (MedDRA ver.19.1)	n (%)			
	Durvalumab N = 475		Placebo N = 234	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Gastrointestinal disorders	92 (19.4)	5 (1.1)	50 (21.4)	5 (2.1)
Diarrhoea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Colitis	[redacted]	0	[redacted]	0
Oesophageal stenosis	2 (0.4)	[redacted]	1 (0.4)	[redacted]
Acquired tracheo-oesophageal fistula	1 (0.2)	[redacted]	1 (0.4)	[redacted]
Anal abscess	[redacted]	0	[redacted]	0
Enteritis	[redacted]	[redacted]	[redacted]	[redacted]
Enterocolitis	1 (0.2)	0	1 (0.4)	0
Proctitis	[redacted]	0	[redacted]	0
Abdominal abscess	[redacted]	0	[redacted]	0
Frequent bowel movements	[redacted]	0	[redacted]	0
Intestinal obstruction	[redacted]	[redacted]	[redacted]	[redacted]
Peritonitis	[redacted]	[redacted]	[redacted]	[redacted]

In the PACIFIC study, fatal gastrointestinal disorders [redacted]. Serious gastrointestinal disorders occurred in 3 of 475 subjects (0.6%) in the durvalumab group (diarrhoea; oesophageal stenosis; acquired tracheo-oesophageal fistula; and enteritis, [redacted] each [redacted]) and 4 of 234 subjects (1.7%) in the placebo group (diarrhoea [redacted], [redacted]), and a causal relationship to study drug could not be ruled out for [redacted] ([redacted]%) in the durvalumab group (diarrhoea [redacted]). Gastrointestinal disorders leading to treatment discontinuation occurred in 2 of 475 subjects (0.4%) in the durvalumab group (diarrhoea; and enteritis, [redacted] each) and 1 of 234 subjects (0.4%) in the placebo group ([redacted][1 subject]). Gastrointestinal disorders leading to dose delay occurred in 7 of 475 subjects (1.5%) in the durvalumab group (diarrhoea [6 subjects]; acquired tracheo-oesophageal fistula [1 subject]) and 4 of 234 subjects (1.7%) in the placebo group (diarrhoea [redacted]; [redacted]).

The details of patients with serious colitis or diarrhoea associated with durvalumab in all clinical studies submitted for the present application are shown in Table 37.

Table 37. Listing of patients with serious colitis or diarrhoea

Study ID	Age	Sex	PT (MedDRA ver.19.1)	Grade	Time to onset (days)	Causal relationship to durvalumab	Outcome
PACIFIC	6[redacted]	Female	Diarrhoea	3	28	Yes	Recovered
ATLANTIC	6[redacted]	Female	Diarrhoea	2	217	No	Recovered
	6[redacted]	Male	Diarrhoea	2	94	No	Recovered
	6[redacted]	Male	Diarrhoea	3	21	Yes	Recovered
1108	7[redacted]	Female	Colitis	3	68	No	Recovered
	7[redacted]	Male	Colitis	3	132	Yes	Recovered
	6[redacted]	Male	Colitis	3	141	Yes	Recovered
			Colitis	1	144	Yes	Recovered
	6[redacted]	Female	Colitis	4	18	Yes	Not recovered
			Diarrhoea	4	18	Yes	Not recovered

PMDA's discussion:

The results of the PACIFIC study showed no increased incidence of gastrointestinal disorders in the durvalumab group compared with the placebo group, and it is difficult to draw a definite conclusion on the relationship between durvalumab and gastrointestinal disorders from the currently available information. However, serious colitis/diarrhoea for which a causal relationship to durvalumab could not be ruled out have been reported, and the occurrence of such events is anticipated in light of the mechanism of action of durvalumab. Thus, it is necessary to monitor the occurrence etc. of colitis and diarrhoea also after the market launch and appropriately provide any new information to healthcare professionals in clinical practice.

7.R.3.8 Others

The adverse events reported with other anticancer agents that block PD-L1/PD-1 binding (nivolumab, pembrolizumab, etc.), as does durvalumab, suggest that durvalumab may cause (a) myositis/rhabdomyolysis, (b) meningitis, (c) serious skin disorder, (d) myocarditis, (e) immune-related cytopenia, and (f) organ transplant

rejection or graft versus host disease. The applicant's explanation about these events:

(a) Myositis/rhabdomyolysis:

The details of patients with myositis/rhabdomyolysis associated with durvalumab in clinical studies and overseas post-marketing experience of durvalumab are shown in Table 38.

Table 38. Listing of patients with myositis/rhabdomyolysis

Study ID	Age	Sex	Primary disease	Dosing regimen of durvalumab	PT[*1]	Grade	Seriousness	Time to onset (days)	Causal relationship to durvalumab	Outcome
PACIFIC	5[redacted]	Male	NSCLC	10 mg/kg Q2W	Myositis	1	Non-serious	335	No	Not recovered
	6[redacted]	Male	NSCLC	10 mg/kg Q2W	Myositis	1	Non-serious	80	No	Recovered
1108 non-NSCLC cohort	6[redacted]	Male	Bladder cancer	10 mg/kg Q2W	Myositis	2	Serious	139	Yes	Recovered
					Myositis	3	Non-serious	215	Yes	Recovered
MYSTIC [*2]	6[redacted]	Female	NSCLC	10 mg/kg Q2W	Rhabdomyolysis	4	Serious	30	Yes	Recovered

*1: MedDRA ver.19.1 for PACIFIC study and Study 1108, MedDRA ver.20.0 for MYSTIC study
*2: A global phase III study in chemotherapy-naïve patients with advanced/recurrent NSCLC

(b) Meningitis:

The details of patients with serious meningitis associated with durvalumab in clinical studies and overseas post-marketing experience of durvalumab are shown in Table 39.

Table 39. Listing of patients with serious meningitis

Study ID	Age	Sex	Grade	Time to onset (days)	Causal relationship to durvalumab	Outcome
ATLANTIC	7[redacted]	Male	3	57	Yes	Recovered

(c) Serious skin disorder:

The details of patients with serious skin disorder associated with durvalumab in clinical studies and overseas post-marketing experience of durvalumab are shown in Table 40. Pemphigoid, toxic epidermal necrolysis, or Stevens-Johnson syndrome associated with durvalumab has not been reported.

Table 40. Listing of patients with erythema multiforme

Study ID	Age	Sex	Primary disease	Dosing regimen of durvalumab	Grade	Seriousness	Time to onset (days)	Causal relationship to durvalumab	Outcome
1108	6[redacted]	Male	NSCLC	10 mg/kg Q2W	1	Non-serious	Unknown	No	Recovered
02	4[redacted]	Male	Thyroid cancer	3 mg/kg Q2W	1	Non-serious	6	Yes	Not recovered

(d) Myocarditis:

The details of patients with serious myocarditis associated with durvalumab in clinical studies and overseas post-marketing experience of durvalumab are shown in Table 41.

Table 41. Listing of patients with serious myocarditis

Study ID	Age	Sex	Primary disease	Dosing regimen of durvalumab	Grade	Time to onset (days)	Causal relationship to durvalumab	Outcome
1108 non-NSCLC cohort	7[redacted]	Male	Pancreatic cancer	10 mg/kg Q2W	3	4	No	Recovered

The autopsy of this patient revealed multiple metastases of pancreatic cancer to the myocardium. The causal relationship to durvalumab was therefore ruled out.

(e) Immune-related cytopenia:
Events coded to the following MedDRA PTs were counted as immune-related cytopenia: "antiphospholipid syndrome," "cold type haemolytic anaemia," "Coombs positive haemolytic anaemia," "pernicious anaemia," "warm type haemolytic anaemia," "Evans syndrome," "autoimmune neutropenia," "autoimmune pancytopenia," "autoimmune aplastic anaemia," "autoimmune haemolytic anaemia," and "immune thrombocytopenic purpura."

The details of patients with serious immune-related cytopenia in clinical studies and overseas post-marketing experience of durvalumab are shown in Table 42.

Table 42. Listing of patients with serious immune thrombocytopenic purpura

Study ID	Age	Sex	Primary disease	Dosing regimen of durvalumab	Grade	Time to onset (days)	Causal relationship to durvalumab	Outcome
1108 non-NSCLC cohort	6[redacted]	Female	Breast cancer	10 mg/kg Q2W	3	14	Yes	Recovered
					4	21	Yes	Recovered
					5	35	Yes	Fatal

(f) Organ transplant rejection or graft versus host disease:
To date, graft rejection or graft versus host disease has not been reported in organ transplant patients (including hematopoietic stem cell transplant patients) treated with durvalumab from clinical studies or overseas post-marketing experience of durvalumab.

PMDA's discussion:
The cases of the above (a) to (e) have been reported in clinical studies and overseas post-marketing experience, but it is difficult to draw a definite conclusion on their relationship to durvalumab from the currently available information because of the limited number of patients with the events. Thus, it is necessary to collect post-marketing information on these events and appropriately provide any new information to healthcare professionals in clinical practice.

As for the above (f), the package inserts for other anticancer agents that block PD-L1/PD-1 binding, as does durvalumab, state that graft rejection occurred after administration of anti-PD-1 antibody in patients with a solid organ transplant (including hematopoietic stem cell transplant recipients). However, since graft rejection

or graft versus host disease has not been reported in patients receiving durvalumab, it is difficult to draw a definite conclusion on their relationship to durvalumab. Thus, no specific precaution about these events is needed at present, but it is necessary to collect post-marketing information and appropriately provide any new information to healthcare professionals in clinical practice.

7.R.4 Clinical positioning and indication

The proposed indication for durvalumab was "locally-advanced, unresectable non-small cell lung cancer." The following statements were included in the precautions concerning indication section of the proposed package insert.

- Durvalumab should be used in patients whose disease has not progressed following platinum-based chemoradiotherapy.
- The efficacy and safety of durvalumab in adjuvant chemotherapy have not been established.
- Eligible patients should be selected with a full knowledge of the content of the clinical studies section and a good understanding of the efficacy and safety of durvalumab.

Based on Section "7.R.2 Efficacy" and Section "7.R.3 Safety" and the considerations in the following sections, PMDA concluded that the following statement should be included in the precautions concerning indication section and that the indication should be "maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy."

● The efficacy and safety of durvalumab in adjuvant chemotherapy have not been established.

7.R.4.1 Clinical positioning of durvalumab and target population

Durvalumab for patients with NSCLC is described as follows in the foreign clinical practice guidelines. At present, durvalumab for patients with NSCLC is not mentioned in the Japanese clinical practice guideline or New Clinical Oncology 4th edition (Nankodo, 2015).

● NCCN guidelines (v.2.2018):

Durvalumab therapy (for up to 12 months) is recommended for locally-advanced, unresectable NSCLC in patients whose disease has not progressed following definitive platinum-based CRT.

The applicant's explanation about the clinical positioning of and the indication for durvalumab:

In current clinical practice in Japan, patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive platinum-based CRT undergo a period of active surveillance until disease progression, and there is no recommended treatment for them. Thus, the use of durvalumab in these patients is clinically meaningful, based on the results of the PACIFIC study.

The efficacy and safety results of the PACIFIC study of durvalumab by histology are shown in Table 43 and Table 44, respectively. No obvious differences were found in the efficacy and safety of durvalumab between the histologic types. Durvalumab is thus expected to have efficacy irrespective of histology.

Table 43. Efficacy by histology (PACIFIC study, Data cutoff date of February 13, 2017)

Histology	Treatment group	N	PFS	
			Median [95% CI] (months)	Hazard ratio* [95% CI]
Non-squamous	Durvalumab	252	NE [16.6, NE]	0.45 [0.33, 0.59]
	Placebo	135	6.9 [5.0, 8.7]	
Squamous	Durvalumab	224	11.1 [9.1, 16.9]	0.68 [0.50, 0.92]
	Placebo	102	5.4 [3.6, 9.2]	

*: Unstratified Cox regression

Table 44. Summary of safety by histology (PACIFIC study)

	n (%)			
	Non-squamous		Squamous	
	Durvalumab N = 254	Placebo N = 132	Durvalumab N = 221	Placebo N = 102
All adverse events	249 (98.0)	126 (95.5)	211 (95.5)	96 (94.1)
Grade 3 or higher adverse events	80 (31.5)	38 (28.8)	83 (37.6)	36 (35.3)
Adverse events leading to death	8 (3.1)	7 (5.3)	13 (5.9)	7 (6.9)
Serious adverse events	63 (24.8)	24 (18.2)	73 (33.0)	29 (28.4)
Adverse events leading to treatment discontinuation	34 (13.4)	8 (6.1)	39 (17.6)	15 (14.7)
Adverse events leading to dose delay	112 (44.1)	43 (32.6)	90 (40.7)	29 (28.4)

Furthermore, the use of durvalumab in patients who are candidates for adjuvant chemotherapy is not recommended because no clinical studies have demonstrated the clinical usefulness of durvalumab in this patient population.

Based on the above, the detailed information on the patient population of the PACIFIC study has been included in the clinical studies section of the proposed package insert, and the following statements have been included in the precautions concerning indication section. The wording of the indication for durvalumab has been proposed as "locally-advanced, unresectable non-small cell lung cancer."

- Durvalumab should be used in patients whose disease has not progressed following platinum-based chemoradiotherapy.
- Eligible patients should be selected with a full knowledge of the content of the clinical studies section and a good understanding of the efficacy and safety of durvalumab.
- The efficacy and safety of durvalumab in adjuvant chemotherapy have not been established.

PMDA's discussion:

PMDA largely accepted the applicant's explanation. Based on the patient population of the PACIFIC study that demonstrated the clinical usefulness of durvalumab, the applicant included the following statement in the proposed precautions concerning indication section.

> Durvalumab should be used in patients whose disease has not progressed following platinum-based CRT.[18)]

However, since this information is important for selecting eligible patients for durvalumab, the target

[18)] Japanese and foreign clinical practice guidelines recommend platinum-based chemotherapy only as part of definitive CRT for patients with locally-advanced NSCLC.

population should be further defined in the indication section:

Based on the above, PMDA concluded that the following statement should be included in the precautions concerning indication section of the package insert, and that the indication should be "maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy."

- The efficacy and safety of durvalumab in adjuvant chemotherapy have not been established.

The following statement was included in the proposed precautions concerning indication section. This statement is unnecessary because it does not particularly worth mentioning.

- Eligible patients should be selected with a full knowledge of the content of the clinical studies section and a good understanding of the efficacy and safety of durvalumab.

7.R.4.2 Efficacy and safety of durvalumab by PD-L1 expression status, etc.

Since durvalumab is an antibody drug directed against human PD-L1, PMDA asked the applicant to explain the efficacy and safety of durvalumab by PD-L1 expression status, and the target population for durvalumab.

The applicant's response:

In the PACIFIC study, tumor tissue samples were assessed for PD-L1 expression using VENTANA clone SP263, and (a) efficacy and (b) safety of durvalumab by PD-L1 expression status were analyzed.

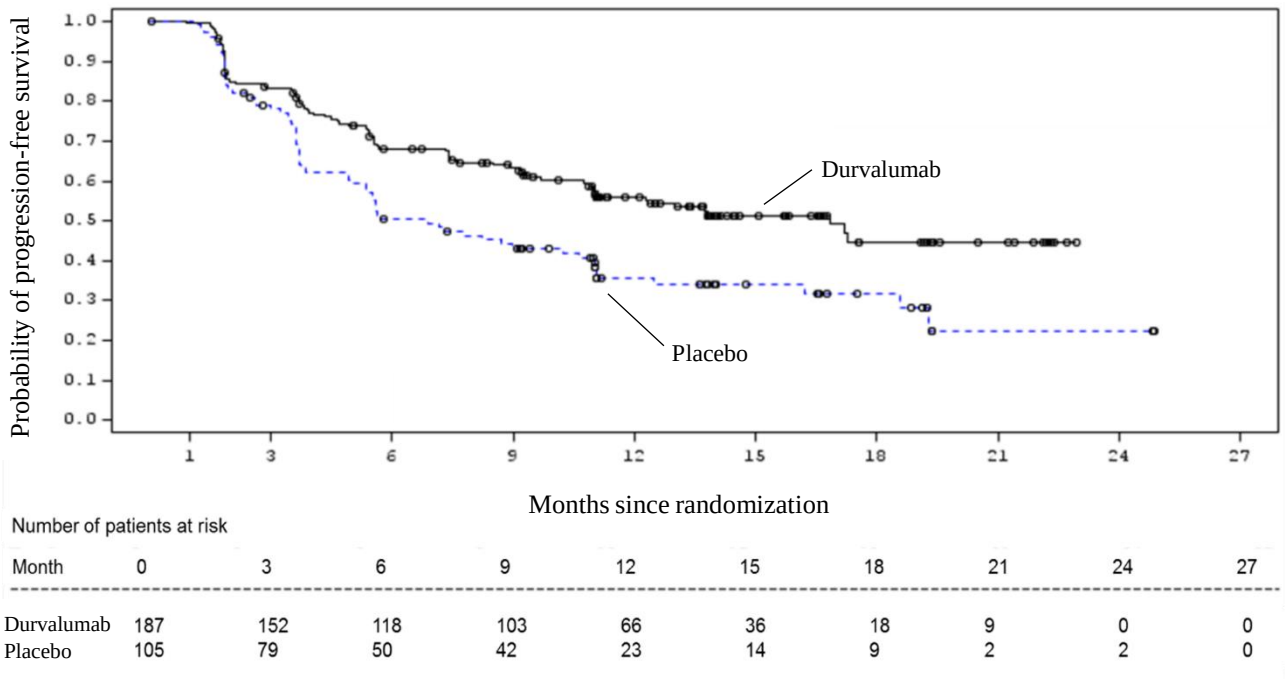
(a) Efficacy:

The efficacy of durvalumab was analyzed by PD-L1 expression status in tumor tissue samples (cutoff value, 25%) in patients whose tumor tissue samples were assessable for PD-L1 expression in the PACIFIC study. The results of the interim analysis of PFS by PD-L1 expression status are shown in Table 45, Figure 3, and Figure 4. The results showed that durvalumab prolonged PFS compared with placebo in both PD-L1 negative (TPS <25%) and positive (TPS ≥25%) patient subgroups. Durvalumab is thus expected to have efficacy irrespective of PD-L1 expression level.

Table 45. Efficacy by PD-L1 expression status in tumor tissue samples (PACIFIC study, BICR, Data cutoff date of February 13, 2017)

PD-L1 expression	Treatment group	N	PFS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
TPS <25%	Durvalumab	187	16.9 [11.0, NE]	0.59 [0.43, 0.82]	0.139
	Placebo	105	6.9 [5.0, 11.0]		
TPS ≥25%	Durvalumab	115	17.8 [11.1, NE]	0.41 [0.26, 0.65]	
	Placebo	44	3.7 [2.0, 13.2]		

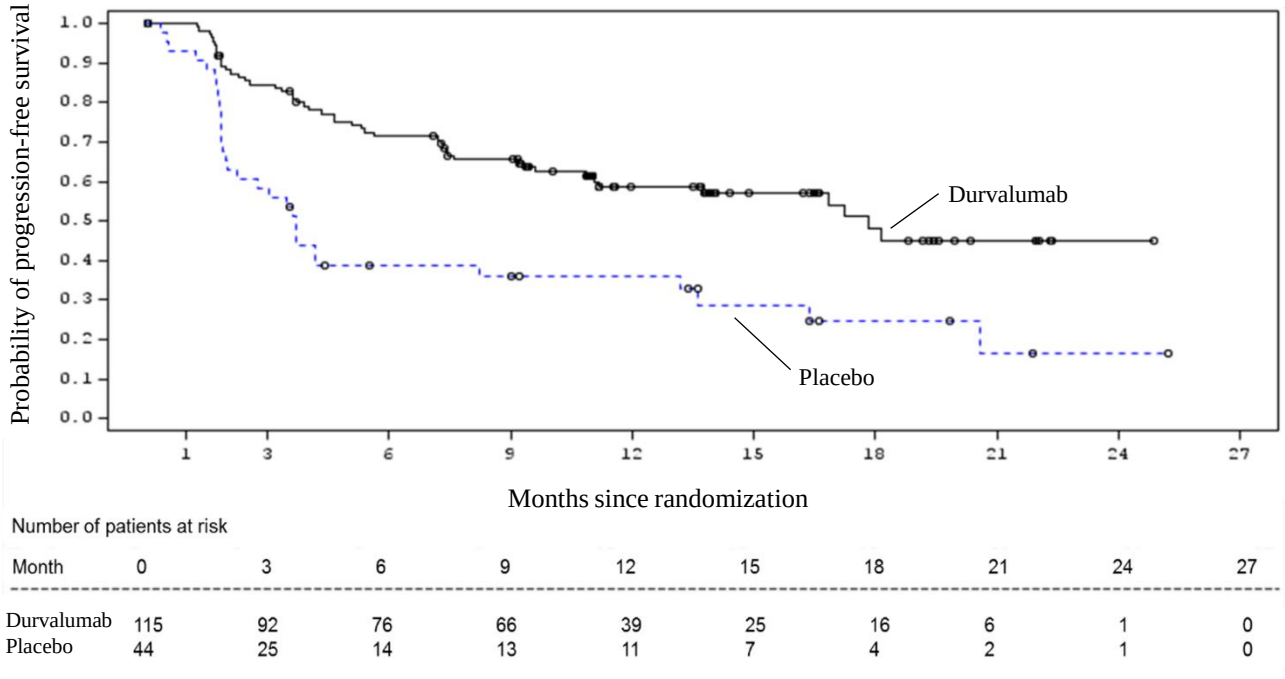
*: Unstratified Cox regression



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27
Durvalumab	187	152	118	103	66	36	18	9	0	0
Placebo	105	79	50	42	23	14	9	2	2	0

Figure 3. Kaplan-Meier curves for PFS by PD-L1 expression status at interim analysis (PD-L1-negative [TPS <25%] patient subgroup, Data cutoff date of February 13, 2017)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27
Durvalumab	115	92	76	66	39	25	16	6	1	0
Placebo	44	25	14	13	11	7	4	2	1	0

Figure 4. Kaplan-Meier curves for PFS by PD-L1 expression status at interim analysis (PD-L1-positive (TPS ≥25%) patient subgroup, Data cutoff date of February 13, 2017)

The efficacy by PD-L1 expression status and histology is shown in Table 46.

Durvalumab was superior in PFS to placebo in both PD-L1 negative (TPS <25%) and positive (TPS ≥25%) patient subgroups, regardless of squamous or non-squamous histology. Therefore, neither histologic type nor PD-L1 expression status can be conclusively identified as the best predictive factors for response (in terms of

PFS) to durvalumab. Durvalumab is expected to have efficacy, irrespective of histology and PD-L1 expression level.

Table 46. Efficacy by histology and PD-L1 expression status in tumor tissue samples (PACIFIC study, BICR, Data cutoff date of February 13, 2017)

PD-L1 expression	Treatment group	N	PFS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
Non-squamous					
TPS <25%	Durvalumab	81	13.7 [10.9, NE]	0.50 [0.32, 0.79]	0.078
	Placebo	56	7.2 [4.8, 10.6]		
TPS ≥25%	Durvalumab	59	NE [17.2, NE]	0.29 [0.14, 0.59]	
	Placebo	24	4.2 [3.0, 13.2]		
Squamous					
TPS <25%	Durvalumab	106	16.9 [8.9, NE]	0.69 [0.44, 1.10]	0.581
	Placebo	49	5.6 [3.6, 16.2]		
TPS ≥25%	Durvalumab	56	10.9 [7.2, 16.9]	0.59 [0.31, 1.10]	
	Placebo	20	2.0 [1.7, 13.6]		

(b) Safety:

Summary of safety by PD-L1 expression status is shown in Table 47. There was no obvious association between PD-L1 expression status in tumor tissue samples and the safety of durvalumab.

Table 47. Summary of safety by PD-L1 expression status (PACIFIC study)

	n (%)			
	PD-L1-negative patients (TPS <25%)		PD-L1-positive patients (TPS ≥25%)	
	Durvalumab N = 189	Placebo N = 103	Durvalumab N = 115	Placebo N = 44
All adverse events	184 (97.4)	100 (97.1)	109 (94.8)	37 (84.1)
Grade 3 or higher adverse events	58 (30.7)	25 (24.3)	43 (37.4)	16 (36.4)
Adverse events leading to death	6 (3.2)	5 (4.9)	5 (4.3)	3 (6.8)
Serious adverse events	51 (27.0)	17 (16.5)	31 (27.0)	12 (27.3)
Adverse events leading to treatment discontinuation	31 (16.4)	12 (11.7)	15 (13.0)	3 (6.8)
Adverse events leading to dose delay	81 (42.9)	29 (28.2)	54 (47.0)	16 (36.4)

The safety by PD-L1 expression status and histology is shown in Table 48 and Table 49. There was no obvious association between PD-L1 expression status in tumor tissue samples and the safety of durvalumab for either squamous or non-squamous histology.

Table 48. Summary of safety by PD-L1 expression status (PACIFIC study, non-squamous)

	n (%)			
	PD-L1-negative patients (TPS <25%)		PD-L1-positive patients (TPS ≥25%)	
	Durvalumab N = 83	Placebo N = 54	Durvalumab N = 59	Placebo N = 24
All adverse events	80 (96.4)	53 (98.1)	59 (100)	20 (83.3)
Grade 3 or higher adverse events	22 (26.5)	13 (24.1)	22 (37.3)	8 (33.3)
Adverse events leading to death	1 (1.2)	2 (3.7)	3 (5.1)	2 (8.3)
Serious adverse events	21 (25.3)	6 (11.1)	15 (25.4)	6 (25.0)
Adverse events leading to treatment discontinuation	11 (13.3)	4 (7.4)	6 (10.2)	1 (4.2)
Adverse events leading to dose delay	36 (43.4)	16 (29.6)	30 (50.8)	7 (29.2)

Table 49. Summary of safety by PD-L1 expression status (PACIFIC study, squamous)

	n (%)			
	PD-L1-negative (TPS <25%) patients		PD-L1-positive (TPS ≥25%) patients	
	Durvalumab N = 106	Placebo N = 49	Durvalumab N = 56	Placebo N = 20
All adverse events	104 (98.1)	47 (95.9)	50 (89.3)	17 (85.0)
Grade 3 or higher adverse events	36 (34.0)	12 (24.5)	21 (37.5)	8 (40.0)
Adverse events leading to death	5 (4.7)	3 (6.1)	2 (3.6)	1 (5.0)
Serious adverse events	30 (28.3)	11 (22.4)	16 (28.6)	6 (30.0)
Adverse events leading to treatment discontinuation	20 (18.9)	8 (16.3)	9 (16.1)	2 (10.0)
Adverse events leading to dose delay	45 (42.5)	13 (26.5)	24 (42.9)	9 (45.0)

Based on the above (a) and (b), the use of durvalumab is recommended, irrespective of PD-L1 expression level.

PMDA's discussion:

PMDA accepted the above explanation by the applicant. However, it is necessary to continue to collect information on the predictive factors for response to durvalumab, including factors other than PD-L1, and appropriately provide any new information to healthcare professionals in clinical practice.

7.R.5 Dosage and administration

The proposed dosage and administration statement was "the usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks." The following statements were included in the proposed precautions concerning dosage and administration section.

- The efficacy and safety of durvalumab in combination with other anti-cancer agents have not been established.
- Recommended treatment modifications for adverse reactions

Based on Section "7.R.2 Efficacy" and Section "7.R.3 Safety" and the considerations in the following sections, PMDA concluded that the following statements should be included in the precautions concerning dosage and administration section, and that the dosage and administration should be "the usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks for a maximum of 12 months."

- The efficacy and safety of durvalumab in combination with other anti-cancer agents have not been established.
- Recommended treatment modifications for adverse reactions

7.R.5.1 Dosage and administration for durvalumab

The applicant's rationale for the proposed dosage and administration:

The PACIFIC study used the dosing regimen selected based on the following study results etc.:

- Study 02 demonstrated the safety of durvalumab 1, 3, or 10 mg/kg Q2W.
- PPK analysis using durvalumab PK data from Study 1108 and the ATLANTIC study showed that 97.8% of patients receiving durvalumab 10 mg/kg Q2W were expected to maintain the $C_{min,ss}$ of durvalumab above

the concentration that achieves 99% blockade of the PD-L1/PD-1 pathway [see Section 6.2.4].

The PACIFIC study demonstrated the clinical usefulness of durvalumab at the dosing regimen in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT. Thus, the applicant selected the proposed dosage and administration based on the PACIFIC study. There are no data on the efficacy and safety of durvalumab in combination with other anti-cancer agents; this information will be included in the precautions concerning dosage and administration section.

The PACIFIC study limited the duration of durvalumab therapy to ≤12 months, but treatment duration is not specified in the proposed dosage and administration section. PMDA asked the applicant to discuss the necessity of defining the duration of durvalumab therapy in the dosage and administration section.

The applicant's response:
No clinical studies have evaluated the clinical usefulness of durvalumab administered for >12 months in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT. However, durvalumab is expected to have efficacy without any safety concerns in patients who continue to receive durvalumab until disease progression, for the following reasons:

- In the PACIFIC study, only 6 of 443 patients (1.4%) in the durvalumab group had CR, and there were patients who had not achieved CR and had residual tumor after the completion of 12-month treatment with durvalumab. Thus, offering such patients the option to receive durvalumab for >12 months is considered clinically meaningful.
- Pooled analysis of the PACIFIC study and clinical studies conducted to evaluate the clinical usefulness of durvalumab monotherapy was performed to determine the time to onset of adverse events unique to durvalumab (pneumonitis, dermatitis, diarrhoea/colitis, hyperthyroidism, hypothyroidism). Most of these adverse events occurred within 6 months following the first dose of durvalumab, and there was no increase in the incidence of adverse events beyond Month 6.

Thus, the duration of durvalumab therapy need not be limited to ≤12 months, even though the PACIFIC study restricted treatment duration to this period.

PMDA's discussion:
PMDA accepted the applicant's explanation (the proposed dosing regimen of 10 mg/kg Q2W, the precautions concerning dosage and administration section advises against concomitant use with other anti-cancer agents).

On the other hand, with respect to the duration of treatment with durvalumab, no clinical studies have evaluated the clinical usefulness of durvalumab administered for >12 months in the patient population of the PACIFIC study, and there is little evidence for recommending >12 months of durvalumab therapy in this patient population. In addition, definitive, platinum-based CRT is expected to provide complete cure to the patient population of the PACIFIC study, and patients who have completed a 12-month maintenance therapy with durvalumab should not continue durvalumab aimlessly. Therefore, the duration of treatment with durvalumab

should be specified in the dosage and administration section.

Based on the above, the dosage and administration statement should be "the usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks for a maximum of 12 months." Further, the following statement should be included in the precautions concerning dosage and administration section.

● The efficacy and safety of durvalumab in combination with other anti-cancer agents have not been established.

7.R.5.2 Recommended treatment modifications for durvalumab

The applicant's explanation about the recommended treatment modifications for durvalumab:

In the PACIFIC study, the criteria for dose delay/interruption or permanent discontinuation of durvalumab in the event of adverse reactions were provided, and treatment for management of adverse reactions was specified. The study showed that durvalumab was tolerable and safe if the guidelines are followed. Thus, based on the guidelines, the recommended treatment modifications for durvalumab and specific treatment for adverse reactions will be included in the precautions concerning dosage and administration section.

- The dose modification guidelines for neurotoxicity and peripheral neuromotor syndrome were provided in the PACIFIC study. However, these guidelines will not be included in the precautions concerning dosage and administration section because of the small number of patients who experienced Grade 3 or higher adverse events or serious adverse events in the study.

Moreover, the Company Core Data Sheet for durvalumab was amended as of [redacted], 20[redacted] to caution about hypophysitis, myocarditis, and myositis/polymyositis associated with durvalumab, and to include durvalumab dose modification guidelines for these events. Thus, these guidelines will also be included.

PMDA's discussion:

PMDA largely accepted the applicant's explanation, taking into account that durvalumab is used by physicians with adequate knowledge of and experience in cancer chemotherapy. However, the recommended treatment modifications for durvalumab should be specified as shown in Table 50, based on the following points:

- The criteria for resuming durvalumab administration upon resolution of adverse reactions and a guide for adjustment of the infusion rate in the event of IRR should be added.
- The protocol of PACIFIC study did not stipulate guidelines for durvalumab treatment modification in the event of hypothyroidism. Thus such guidelines are not necessary.
- Management of adverse reactions should be tailored to individual patients' condition. Therefore information regarding the management of adverse reactions should be appropriately provided not through the package insert, but through information materials etc., (as reference information), to healthcare professionals in clinical practice.
- The safety etc. of durvalumab is unknown when the dose modification guidelines for hypophysitis, myocarditis, and myositis/polymyositis are followed. Thus, the dose modification guidelines for these events should not be provided at present.

Table 50. Recommended treatment modifications for adverse reactions

Adverse reaction	Severity*	Durvalumab treatment modification
ILD	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hepatic dysfunction	● AST or ALT 3-5 × ULN or total bilirubin 1.5-3 × ULN ● AST or ALT ≤8 × ULN or total bilirubin ≤5 × ULN	Withhold dose until resolution to Grade ≤1
	● AST or ALT >8 × ULN or total bilirubin >5 × ULN ● Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN with no other cause	Permanently discontinue
Colitis or diarrhea	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hyperthyroidism, Adrenal insufficiency, Hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Type 1 diabetes mellitus	Grade 2-4	Withhold dose until clinically stable
Renal dysfunction	Serum creatinine 1.5-3 × ULN or baseline	Withhold dose until resolution to Grade ≤1
	Serum creatinine >3 × ULN or baseline	Permanently discontinue
Skin disorder	● Grade 2 for ≥1 week ● Grade 3	Withhold dose until resolution to Grade ≤1.
	Grade 4	Permanently discontinue
IRR	Grade 1 or 2	Interrupt or decrease the rate of infusion by 50%
	Grade 3 or 4	Permanently discontinue
Other adverse reactions	Grade 2 or 3	Withhold dose until resolution to Grade ≤1
	Grade 4	Permanently discontinue

*: Severity grade based on NCI-CTCAE v4.03

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:

Taking account of the following reasons etc., ILD is included in the safety specification, and the applicant plans to conduct post-marketing surveillance to assess the association between patient characteristics such as the presence/absence and severity of prior radiation pneumonitis and the occurrence of ILD following administration of durvalumab. Since there is limited safety information from Japanese patients treated with durvalumab, the post-marketing surveillance will cover all patients treated with durvalumab, in order to obtain information on the characteristics of patients treated with durvalumab, safety information, etc.

- The safety profile of durvalumab is considered similar to those of currently approved anti-cancer agents that block PD-L1/PD-1 binding. Nevertheless, particular attention should be paid to the occurrence of ILD, because the target population for durvalumab is patients after CRT.
- The incidence of radiation pneumonitis was higher in Japanese patients in the PACIFIC study.
- The association between durvalumab-related ILD and the presence/absence or severity of prior radiation pneumonitis is unknown.

The planned sample size is 500 because this number allows the investigation of risk factors for ILD based on the comparison of patient characteristics between those with and without ILD.

The observation period is 1 year because most events of ILD occurred within 1 year following the first dose of durvalumab in the PACIFIC study.

PMDA's discussion:
As it is important to determine the risk factors for ILD including radiation pneumonitis associated with durvalumab [see Section 7.R.3.2], the surveillance plan proposed by the applicant is acceptable.

The applicant plans to conduct all-case surveillance. Given the following points, there is little need to promptly and unbiasedly collect information on the characteristics of patients treated with durvalumab or safety information. Thus, all-case surveillance is not necessary.

- As there are many patients eligible for durvalumab therapy, the surveillance can enroll many patients promptly even if it is not designed as “all-case” surveillance.
- Safety information from a certain number of Japanese patients treated with durvalumab has been obtained from clinical studies.
- Other anti-cancer agents that block PD-L1/PD-1 binding, as does durvalumab, have already been approved in Japan, and there is some clinical experience with these agents.

7.3 Adverse events etc. observed in clinical studies

Among clinical study results submitted for safety evaluation, deaths are described in Section "7.1 Evaluation data" and Section "7.2 Reference data." The main adverse events other than deaths are described below.

7.3.1 Global phase I study (Study 02)

7.3.1.1 Dose-escalation phase

Adverse events occurred in 4 of 4 subjects (100%) in the 1 mg/kg Q2W group, 4 of 4 subjects (100%) in the 3 mg/kg Q2W group, 3 of 4 subjects (75.0%) in the 10 mg/kg Q2W group, 5 of 6 subjects (83.3%) in the 15 mg/kg Q3W group, and 3 of 4 subjects (75.0%) in the 20 mg/kg Q4W group. Adverse events for which a causal relationship to study drug could not be ruled out occurred in 3 of 4 subjects (75.0%) in the 1 mg/kg Q2W group, 3 of 4 subjects (75.0%) in the 3 mg/kg Q2W group, 3 of 4 subjects (75.0%) in the 10 mg/kg Q2W group, 5 of 6 subjects (83.3%) in the 15 mg/kg Q3W group, and 2 of 4 subjects (50.0%) in the 20 mg/kg Q4W group.

Serious adverse events occurred in 1 subject (25.0%) in the 3 mg/kg Q2W group (pneumonitis) and 1 subject (25.0%) in the 10 mg/kg Q2W group (tri-iodothyronine free decreased), and a causal relationship to study drug could not be ruled out for both events.

Adverse events leading to study drug discontinuation occurred in 1 subject (25.0%) in the 10 mg/kg Q2W group (pneumonitis) and 1 subject (25.0%) in the 20 mg/kg Q4W group (colitis), and a causal relationship to study drug could not be ruled out for both events.

7.3.1.2 Dose-expansion phase

Adverse events occurred in 103 of 116 subjects (88.8%), and those for which a causal relationship to study drug could not be ruled out occurred in 74 of 116 subjects (63.8%). Adverse events reported in ≥10% of subjects

are shown in Table 51.

Table 51. Adverse events reported in ≥10% of subjects

SOC PT (MedDRA/J ver.19.0)	n (%) N = 116 All Grades	 Grade 3 or higher
Any adverse event	103 (88.8)	31 (26.7)
Gastrointestinal disorders		
Diarrhoea	18 (15.5)	0
Nausea	17 (14.7)	2 (1.7)
Stomatitis	16 (13.8)	0
Constipation	12 (10.3)	0
General disorders and administration site conditions		
Fatigue	19 (16.4)	1 (0.9)
Pyrexia	16 (13.8)	0
Metabolism and nutrition disorders		
Decreased appetite	19 (16.4)	2 (1.7)
Endocrine disorders		
Hypothyroidism	12 (10.3)	0
Psychiatric disorders		
Insomnia	12 (10.3)	0

Serious adverse events occurred in 21 of 116 subjects (18.1%). The observed serious adverse events were ILD (3 subjects [2.6%]); dyspnoea; lung infection; and decreased appetite (2 subjects each [1.7%]); haemoptysis; respiratory failure; gastrointestinal haemorrhage; nausea; oesophageal perforation; cardiac death; fatigue; malaise; pneumonia; dehydration; hypoglycaemia; haemobilia; hepatic function abnormal; pericardial effusion; thyroid disorder; radiation pneumonitis; blood bilirubin increased; spondylitis; tumour haemorrhage; and brain oedema (1 subject each [0.9%]). A causal relationship to study drug could not be ruled out for ILD (3 subjects); dyspnoea; haemoptysis; gastrointestinal haemorrhage; nausea; oesophageal perforation; haemobilia; hepatic function abnormal; thyroid disorder; fatigue; blood bilirubin increased; decreased appetite; and tumour haemorrhage (1 subject each).

Adverse events leading to study drug discontinuation occurred in 6 of 116 subjects (5.2%). The observed adverse events leading to study drug discontinuation were ILD (3 subjects [2.6%]); pneumonia aspiration; thyroid disorder; and oesophageal perforation (1 subject each [0.9%]). A causal relationship to study drug could not be ruled out for 3 cases of ILD, 1 case of thyroid disorder, and 1 case of oesophageal perforation.

7.3.2 Global phase III study (PACIFIC study)

Adverse events occurred in 460 of 475 subjects (96.8%) in the durvalumab group and 222 of 234 subjects (94.9%) in the placebo group. Adverse events for which a causal relationship to study drug could not be ruled out occurred in 322 of 475 subjects (67.8%) in the durvalumab group and 125 of 234 subjects (53.4%) in the placebo group. Adverse events reported in ≥10% of subjects in either group are shown in Table 52.

Table 52. Adverse events reported in ≥10% of subjects in either group

SOC PT (MedDRA/J ver.19.1)	n (%)			
	Durvalumab N = 475		Placebo N = 234	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Any adverse event	460 (96.8)	163 (34.3)	222 (94.9)	74 (31.6)
Respiratory, thoracic and mediastinal disorders				
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Dyspnoea	106 (22.3)	8 (1.7)	56 (23.9)	6 (2.6)
Pneumonitis	60 (12.6)	12 (2.5)	18 (7.7)	7 (3.0)
Infections and infestations				
Pneumonia	62 (13.1)	22 (4.6)	18 (7.7)	12 (5.1)
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
General disorders and administration site conditions				
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Gastrointestinal disorders				
Diarrhoea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Nausea	66 (13.9)	0	31 (13.2)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Skin and subcutaneous tissue disorders				
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	59 (12.4)	0	26 (11.1)	0
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Nervous system disorders				
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Metabolism and nutrition disorders				
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Injury, poisoning and procedural complications				
Radiation pneumonitis	96 (20.2)	8 (1.7)	36 (15.4)	2 (0.9)
Endocrine disorders				
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Blood and lymphatic system disorders				
Anaemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Serious adverse events occurred in 136 of 475 subjects (28.6%) in the durvalumab group and 53 of 234 subjects (22.6%) in the placebo group. Those reported by ≥2 subjects in the durvalumab group were pneumonia (27 subjects [5.7%]); radiation pneumonitis (17 subjects [3.6%]); pneumonitis (16 subjects [3.4%]); lung infection (6 subjects [1.3%]); chronic obstructive pulmonary disease (5 subjects [1.1%]); sepsis; atrial fibrillation; and cardiac failure congestive (4 subjects each [0.8%]); herpes zoster; and myocardial infarction (3 subjects each [0.6%]); lung abscess; pneumocystis jirovecii pneumonia; septic shock; upper respiratory tract infection; prostate cancer; anaemia; cerebrovascular accident; acute myocardial infarction; angina pectoris; cardiac arrest; pericardial effusion; acute respiratory failure; respiratory failure; dyspnoea; haemoptysis; hypoxia; pneumothorax; pulmonary embolism; inguinal hernia; vomiting; acute kidney injury; and pyrexia (2 subjects each [0.4%]). Those reported by ≥2 subjects in the placebo group were pneumonia (12 subjects [5.1%]); pneumonitis (7 subjects [3.0%]); radiation pneumonitis (3 subjects [1.3%]); lung infection; pneumonia necrotising; sepsis; diarrhoea; and fatigue (2 subjects each [0.9%]). A causal relationship to study drug could not be ruled out for pneumonitis (16 subjects), radiation pneumonitis (4 subjects), pneumonia (3 subjects), herpes zoster (2 subjects), lung infection (2 subjects), pneumocystis jirovecii pneumonia (1 subject),

dyspnoea (1 subject), and respiratory failure (1 subject) in the durvalumab group and pneumonitis (4 subjects), lung infection (1 subject), and diarrhoea (1 subject) in the placebo group.

Adverse events leading to study drug discontinuation occurred in 73 of 475 subjects (15.4%) in the durvalumab group and 23 of 234 subjects (9.8%) in the placebo group. Those reported by ≥3 subjects in the durvalumab group were pneumonitis (23 subjects [4.8%]), radiation pneumonitis (6 subjects [1.3%]), pneumonia (5 subjects [1.1%]), and dyspnoea (3 subjects [0.6%]). Those reported by ≥3 subjects in the placebo group were pneumonitis (6 subjects [2.6%]), pneumonia (3 subjects [1.3%]), and radiation pneumonitis (3 subjects [1.3%]). A causal relationship to study drug could not be ruled out for pneumonitis (20 subjects), pneumonia (3 subjects), radiation pneumonitis (3 subjects), and dyspnoea (2 subjects) in the durvalumab group and pneumonitis (3 subjects) and radiation pneumonitis (1 subject) in the placebo group.

7.3.3 Global phase II study (ATLANTIC study)

Adverse events occurred in 103 of 111 subjects (92.8%) in Cohort 1, 256 of 265 subjects (96.6%) in Cohort 2, and 66 of 68 subjects (97.1%) in Cohort 3. Adverse events for which a causal relationship to study drug could not be ruled out occurred in 53 of 111 subjects (47.7%) in Cohort 1, 157 of 256 subjects (59.2%) in Cohort 2, and 46 of 68 subjects (67.6%) in Cohort 3. Adverse events reported in ≥15% of subjects in any cohort are shown in Table 53.

Table 53. Adverse events reported in ≥15% of subjects in any cohort

SOC PT (MedDRA/J ver.19.1)	n (%)					
	Cohort 1* N = 111		Cohort 2* N = 265		Cohort 3* N = 68	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Any adverse event	103 (92.8)	26 (23.4)	256 (96.6)	110 (41.5)	66 (97.1)	31 (45.6)
General disorders and administration site conditions						
Fatigue	15 (13.5)	0	70 (26.4)	3 (1.1)	20 (29.4)	2 (2.9)
Pyrexia	12 (10.8)	0	53 (20.0)	0	2 (17.6)	0
Asthenia	13 (11.7)	1 (0.9)	54 (20.4)	3 (1.1)	4 (5.9)	0
Gastrointestinal disorders						
Nausea	14 (12.6)	0	47 (17.7)	1 (0.4)	13 (19.1)	0
Constipation	14 (12.6)	0	38 (14.3)	0	15 (22.1)	0
Diarrhoea	11 (9.9)	0	40 (15.1)	1 (0.4)	8 (11.8)	2 (2.9)
Respiratory, thoracic and mediastinal disorders						
Cough	24 (21.6)	0	54 (20.4)	1 (0.4)	12 (17.6)	0
Dyspnoea	14 (12.6)	4 (3.6)	49 (18.5)	14 (5.3)	7 (10.3)	1 (1.5)
Metabolism and nutrition disorders						
Decreased appetite	16 (14.4)	1 (0.9)	72 (27.2)	4 (1.5)	10 (14.7)	2 (2.9)
Skin and subcutaneous tissue disorders						
Pruritus	8 (7.2)	0	27 (10.2)	0	12 (17.6)	0
Investigations						
Weight decreased	3 (2.7)	0	23 (8.7)	0	12 (17.6)	0
Blood and lymphatic system disorders						
Anaemia	3 (2.7)	0	45 (17.0)	17 (6.4)	10 (14.7)	4 (5.9)

*: Patients with unresectable, advanced/recurrent NSCLC were enrolled in the study:
Patients in Cohort 1 had PD-L1 positive tumors (TPS ≥25%) with *EGFR* mutations or *ALK* rearrangements.
Patients in Cohort 2 had PD-L1 positive tumors (TPS ≥25%) with wild-type or unknown status for *EGFR* and *ALK*.
Patients in Cohort 3 had PD-L1 positive tumors (TPS ≥90%) with wild-type or unknown status for *EGFR* and *ALK*.

Serious adverse events occurred in 18 of 111 subjects (16.2%) in Cohort 1, 77 of 265 subjects (29.1%) in Cohort 2, and 21 of 68 subjects (30.9%) in Cohort 3. Those reported by ≥2 subjects in Cohort 1 were dyspnoea (3 subjects [2.7%]) and metastases to central nervous system (2 subjects [1.8%]), those reported by ≥2 subjects in Cohort 2 were pneumonia (8 subjects [3.0%]); dyspnoea (7 subjects [2.6%]); pleural effusion (5 subjects [1.9%]); pneumonitis (4 subjects [1.5%]); fatigue; abdominal pain; sepsis; and anaemia (3 subjects each [1.1%]); general physical condition decreased; pulmonary embolism; respiratory failure; diarrhoea; respiratory tract infection; infectious pleural effusion; adrenal insufficiency; and atrial fibrillation (2 subjects each [0.8%]), and those reported by ≥2 subjects in Cohort 3 were pulmonary embolism (2 subjects [2.9%]) and anaemia (2 subjects [2.9%]). A causal relationship to study drug could not be ruled out for pneumonitis (4 subjects), fatigue (2 subjects), abdominal pain (1 subject), and adrenal insufficiency (1 subject) in Cohort 2, and anaemia (1 subject) in Cohort 3.

Adverse events leading to study drug discontinuation occurred in 2 of 111 subjects (1.8%) in Cohort 1, 24 of 265 subjects (9.1%) in Cohort 2, and 3 of 68 subjects (4.4%) in Cohort 3. The observed adverse events leading to study drug discontinuation were as follows:

Cohort 1: Central nervous system infection (1 subject [0.9%]) and infusion related reaction (1 subject [0.9%]).

Cohort 2: Dyspnoea; and pneumonitis (3 subjects each [1.1%]); pneumonia; and anaemia (2 subjects each [0.8%]); sudden death; abdominal pain; dysphagia; gastrointestinal haemorrhage; sepsis; septic shock; transaminases increased; hepatic enzyme increased; cerebral ischaemia; haemolytic anaemia; hypercalcaemia of malignancy; hypovolaemic shock; cardio-respiratory arrest; and nephritis (1 subject each [0.4%]).

Cohort 3: Diarrhoea; pulmonary embolism; and cardiac failure (1 subject each [1.5%]).

A causal relationship to study drug could not be ruled out for infusion related reaction (1 subject) in Cohort 1, pneumonitis (3 subjects); hepatic enzyme increased; transaminases increased; anaemia; hypovolaemic shock; and nephritis (1 subject each) in Cohort 2, and diarrhoea (1 subject) in Cohort 3.

7.3.4 Foreign phase I/II study (Study 1108): NSCLC cohort

Adverse events occurred in 298 of 304 subjects (98.0%), and those for which a causal relationship to study drug could not be ruled out occurred in 174 of 304 subjects (57.2%). Adverse events reported in ≥15% of subjects are shown in Table 54.

Table 54. Adverse events reported in ≥15% of subjects

SOC PT (MedDRA/J ver.19.1)	n (%) N = 304	
	All Grades	Grade 3 or higher
Any adverse event	298 (98.0)	173 (56.9)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	86 (28.3)	37 (12.2)
Cough	79 (26.0)	3 (1.0)
General disorders and administration site conditions		
Fatigue	117 (38.5)	10 (3.3)
Gastrointestinal disorders		
Nausea	67 (22.0)	1 (0.3)
Diarrhoea	53 (17.4)	1 (0.3)
Constipation	49 (16.1)	1 (0.3)
Metabolism and nutrition disorders		
Decreased appetite	80 (26.3)	5 (1.6)
Musculoskeletal and connective tissue disorders		
Back pain	52 (17.1)	10 (3.3)
Blood and lymphatic system disorders		
Anaemia	46 (15.1)	15 (4.9)

Serious adverse events occurred in 142 of 302 subjects (46.7%). Those reported by ≥3 subjects were dyspnoea (23 subjects [7.6%]); pneumonia (17 subjects [5.6%]); pleural effusion (9 subjects [3.0%]); respiratory failure (8 subjects [2.6%]); sepsis (6 subjects [2.0%]); chronic obstructive pulmonary disease (5 subjects [1.6%]); pneumonitis; pneumonia aspiration; fatigue; colitis; back pain; lung infection; and embolism (4 subjects each [1.3%]); pulmonary embolism; acute respiratory failure; pleuritic pain; pyrexia; non-cardiac chest pain; general physical condition decreased; abdominal pain; dysphagia; dehydration; hypercalcaemia; hypotension; atrial fibrillation; pericardial effusion; and atrial flutter (3 subjects each [1.0%]). A causal relationship to study drug could not be ruled out for pneumonitis; and colitis (3 subjects each); chronic obstructive pulmonary disease; pleural effusion; fatigue; pneumonia; and atrial flutter (1 subject each).

Adverse events leading to study drug discontinuation occurred in 32 of 304 subjects (10.5%). Those reported by ≥2 subjects were colitis (3 subjects [1.0%]); pneumonitis; general physical condition decreased; diarrhoea; and pneumonia (2 subjects each [0.7%]). A causal relationship to study drug could not be ruled out for colitis (3 subjects), pneumonitis (2 subjects), and diarrhoea (2 subjects).

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

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

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion are reported in the Review Report (2).

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

The inspection is currently ongoing, and its results and PMDA's conclusion are reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that durvalumab has efficacy in the maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy, and that durvalumab has acceptable safety in view of its benefits. Durvalumab is a drug with a new active ingredient. It binds to the extracellular domain of PD-L1, thereby blocking the binding of PD-L1 to PD-1, resulting in enhanced tumor antigen-specific cytotoxic T cell activity and inhibition of tumor growth. Durvalumab is clinically meaningful because it offers a new maintenance treatment option for locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy. PMDA will further discuss efficacy, safety, indication, dosage and administration, post-marketing investigations, etc. at the Expert Discussion.

PMDA has concluded that durvalumab may be approved if durvalumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 5, 2018

Products Submitted for Approval

Brand Name	Imfinzi Injection 120 mg, Imfinzi Injection 500 mg
Non-proprietary Name	Durvalumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	August 30, 2017

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the products submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's conclusion:

Based on the considerations in Section "7.R.2 Efficacy" in the Review Report (1), PMDA has concluded that durvalumab was shown to have efficacy in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT, because a global phase III study (the PACIFIC study) demonstrated the superiority of durvalumab over placebo in the co-primary endpoint of PFS and the clinically significant magnitude of the effects of durvalumab in this patient population.

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

1.2 Safety

PMDA's conclusion:

Based on the considerations in Section "7.R.3 Safety" in the Review Report (1), PMDA has concluded that attention should be paid to the possible occurrence of the following adverse events when using durvalumab in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT:

ILD, hepatic dysfunction, renal disorders, IRR, and endocrine dysfunction (thyroid dysfunction, adrenal dysfunction)

Although attention should be paid to the possible occurrence of the above adverse events during the use of durvalumab, durvalumab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures (e.g. monitoring of adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and durvalumab dose delay).

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA. The expert advisors made the following comment.

- Deaths occurred relatively early after the initiation of durvalumab in the PACIFIC study. Therefore healthcare professionals in clinical practice should be advised to perform chest CT scans, etc. prior to and during treatment with durvalumab to determine if patients have concurrent ILD.

PMDA's discussion:
Patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive CRT often have prior or concurrent ILD associated with CRT. Therefore, prior to the use of durvalumab, physicians should determine if patients have concurrent ILD and decide carefully whether to use durvalumab. Thus, healthcare professionals in clinical practice should appropriately be informed of how ILD was monitored prior to and during treatment with durvalumab in the PACIFIC study, via information materials.

Based on the above, PMDA instructed the applicant to take appropriate action, and the applicant agreed to take such action.

1.3 Clinical positioning and indication

Based on the considerations in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), PMDA concluded that the following statement should be included in the precautions concerning indication section, and that the indication should be "maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy."

Precautions Concerning Indication

- The efficacy and safety of durvalumab in adjuvant chemotherapy have not been established.

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

Based on the above, PMDA instructed the applicant to modify the proposed indication and precautions concerning indication sections, and the applicant agreed to take such action.

1.4 Dosage and administration

Based on the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA concluded that the following statements should be included in the precautions concerning dosage and administration section, and that the dosage and administration should be "the usual adult dosage is 10 mg/kg

(body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks for a maximum of 12 months."

Precautions Concerning Dosage and Administration

- The efficacy and safety of durvalumab in combination with other anti-cancer agents have not been established.
- In the event of adverse reactions to durvalumab, durvalumab treatment modification should be considered based on the table below.

Recommended treatment modifications for adverse reactions

Adverse reaction	Severity*	Durvalumab treatment modification
ILD	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hepatic dysfunction	● AST or ALT 3-5 × ULN or total bilirubin 1.5-3 × ULN ● AST or ALT ≤8 × ULN or total bilirubin ≤5 × ULN	Withhold dose until resolution to Grade ≤1
	● AST or ALT >8 × ULN or total bilirubin >5 × ULN ● Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN with no other cause	Permanently discontinue
Colitis or diarrhea	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hyperthyroidism, Adrenal insufficiency, Hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Type 1 diabetes mellitus	Grade 2-4	Withhold dose until clinically stable
Renal dysfunction	Serum creatinine 1.5-3 × ULN or baseline	Withhold dose until resolution to Grade ≤1
	Serum creatinine >3 × ULN or baseline	Permanently discontinue
Skin disorder	● Grade 2 for ≥1 week ● Grade 3	Withhold dose until resolution to Grade ≤1.
	Grade 4	Permanently discontinue
IRR	Grade 1 or 2	Interrupt or decrease the rate of infusion by 50%
	Grade 3 or 4	Permanently discontinue
Other adverse reactions	Grade 2 or 3	Withhold dose until resolution to Grade ≤1
	Grade 4	Permanently discontinue

*: Severity grade based on NCI-CTCAE v4.03

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

Based on the above, PMDA instructed the applicant to modify the proposed dosage and administration and precautions concerning dosage and administration sections, and the applicant agreed to take such action.

1.5 Risk management plan (draft)

The applicant has included ILD in the safety specification and plans to conduct post-marketing surveillance with a target sample size of 500 patients and a 1-year observation period to assess the association between patient characteristics (e.g., the presence/absence and severity of prior radiation pneumonitis) and the occurrence of ILD following administration of durvalumab. Since there is limited safety information from Japanese patients treated with durvalumab, etc., the applicant will conduct post-marketing surveillance, covering all patients treated with durvalumab, in order to obtain information on the characteristics of patients treated with durvalumab, safety information, etc.

Based on the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA has reached the following conclusion:

As it is important to determine the risk factors for ILD including radiation pneumonitis associated with durvalumab, the surveillance plan proposed by the applicant is acceptable. Given the following points, there is little need to promptly and unbiasedly collect information on the characteristics of patients treated with durvalumab or safety information. Thus, all-case surveillance is not necessary.

- As there are many patients eligible for durvalumab therapy, the surveillance can enroll many patients promptly even if it is not designed as “all-case” surveillance.
- Safety information from a certain number of Japanese patients treated with durvalumab has been obtained.
- Other anti-cancer agents that block PD-L1/PD-1 binding, as does durvalumab, have already been approved in Japan, and there is some clinical experience with these agents.

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

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for durvalumab should include the safety specification presented in Table 55, and that the applicant should conduct additional pharmacovigilance activities, surveillance/study for efficacy, and additional risk minimization activities presented in Table 56 and Table 57.

Table 55. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
● ILD ● Hepatic dysfunction ● Endocrine dysfunction (thyroid dysfunction, adrenal dysfunction) ● Renal disorders (interstitial nephritis, etc.) ● IRR	● Colitis/severe diarrhoea ● Type 1 diabetes mellitus ● Pituitary dysfunction ● Myositis/rhabdomyolysis ● Meningitis ● Immune thrombocytopenic purpura ● Embryo-fetal toxicity ● Use in organ transplant recipients (including hematopoietic stem cell transplant recipients)	None
Efficacy specification		
Efficacy in patients with locally-advanced, unresectable NSCLC whose disease has not progressed following definitive, platinum-based CRT (Overall survival)		

Table 56. Summary of additional pharmacovigilance activities, surveillance/study for efficacy, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillance/study for efficacy	Additional risk minimization activities
● Early post-marketing phase vigilance ● Specified use-results survey of durvalumab as maintenance therapy after definitive CRT in locally-advanced, unresectable NSCLC	● Post-marketing clinical study (an extension study of PACIFIC)	● Disseminate data gathered during early post-marketing phase vigilance ● Develop information materials to be distributed to healthcare professionals ● Develop information materials to be distributed to patients

Table 57. Outline of post-marketing surveillance (draft)

Objective	To assess the association between patient characteristics (e.g., the presence/absence and severity of prior radiation pneumonitis) and the occurrence of ILD following administration of durvalumab.
Survey method	Central registry system
Population	Locally-advanced, unresectable NSCLC patients treated with durvalumab
Observation period	1 year
Planned sample size	500 patients
Main survey items	Safety specification: ILD Other main survey items: patient characteristics (age, sex, PS, smoking habit, the presence/absence and severity of prior ILD [including radiation pneumonitis] following definitive CRT, etc.), the details of CRT, the use of durvalumab, etc.

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

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

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

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

The new drug application data (CTD 5.3.3.2.1, CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection showed that the clinical studies as a whole were conducted in compliance with GCP. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted. Though the outcome of the overall assessment of the studies was not affected significantly, the inspection revealed the following finding at a study site, and the head of the medical institution was notified of this finding requiring improvement.

Finding requiring improvement

Study site

● Protocol deviation (noncompliance with the rules for the dose of study drug)

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved for the following indication and dosage and administration with the condition of approval shown below, provided that necessary precautionary statements are included in the package insert and information on the proper use of the products is properly disseminated after the market launch, and provided that the products are used properly under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can adequately respond to emergencies. As the products are drugs with a new active ingredient, the re-examination period is 8 years. The products are classified as biological products, and the drug products and their drug substance are classified as powerful drugs.

Indication

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy

Dosage and Administration

The usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks for a maximum of 12 months.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warnings

1. Imfinzi should be used only in patients considered eligible to receive Imfinzi, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can adequately respond to emergencies. Prior to initiation of treatment, patients or their families must provide consent after being fully informed of the efficacy of treatment and associated risks.
2. Since cases of interstitial lung disease (including radiation pneumonitis), including fatal cases, have been reported, patients should be closely monitored (e.g. chest X-ray, detection of initial symptoms such as shortness of breath, dyspnoea, cough, pyrexia). If abnormalities are observed, discontinue Imfinzi and take appropriate measures such as administration of corticosteroids.

Contraindication

Patients with a history of hypersensitivity to any of the components of Imfinzi

Precautions Concerning Indication

The efficacy and safety of Imfinzi in adjuvant chemotherapy have not been established.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of Imfinzi in combination with other anti-cancer agents have not been established.

2. In the event of adverse reactions to Imfinzi, Imfinzi treatment modification should be considered based on the table below.

Recommended treatment modifications for adverse reactions

Adverse reaction	Severity*	Imfinzi treatment modification
Interstitial lung disease	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hepatic dysfunction	● AST or ALT 3-5 × ULN or total bilirubin 1.5-3 × ULN ● AST or ALT ≤8 × ULN or total bilirubin ≤5 × ULN	Withhold dose until resolution to Grade ≤1
	● AST or ALT >8 × ULN or total bilirubin >5 × ULN ● Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN with no other cause	Permanently discontinue
Colitis or diarrhea	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hyperthyroidism, Adrenal insufficiency, Hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Type 1 diabetes mellitus	Grade 2-4	Withhold dose until clinically stable
Renal dysfunction	Serum creatinine 1.5-3 × ULN or baseline	Withhold dose until resolution to Grade ≤1
	Serum creatinine >3 × ULN or baseline	Permanently discontinue
Skin disorder	● Grade 2 for ≥1 week ● Grade 3	Withhold dose until resolution to Grade ≤1.
	Grade 4	Permanently discontinue
Infusion reaction	Grade 1 or 2	Interrupt or decrease the rate of infusion by 50%
	Grade 3 or 4	Permanently discontinue
Other adverse reactions	Grade 2 or 3	Withhold dose until resolution to Grade ≤1
	Grade 4	Permanently discontinue

*: Severity grade based on NCI-CTCAE (Common Terminology Criteria for Adverse Events) v4.03

Appendix

List of Abbreviations

ADCC	Antibody dependent cellular cytotoxicity
[redacted]	[redacted]
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
Anti-durvalumab antibody	Antibody against Durvalumab (Genetical Recombination)
Anti-TM antibody	Antibody against amino acid mutations (L234F, L235E, P331S) introduced into the Fc domain of Durvalumab (Genetical Recombination)
Application	Marketing application
AP-1	Activated protein-1
AST	Aspartate aminotransferase
Atezolizumab	Atezolizumab (Genetical Recombination)
ATLANTIC study	Study D4191C00003
ATP	Adenosine triphosphate
AUC_{ss}	Area under the serum concentration-time curve at steady state
Avelumab	Avelumab (Genetical Recombination)
BICR	Blinded independent central review
CAL	Cells at the limit of *in vitro* cell age
CDC	Complement dependent cytotoxicity
[redacted]	[redacted]
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
cIEF	Capillary isoelectric focusing
$C_{max,ss}$	Maximum serum concentration at steady state
C_{min}	Serum concentration at the end of the dosing interval
$C_{min,ss}$	Minimum serum concentration at steady state
CQA	Critical quality attribute
CR	Complete remission
CrCL	Creatinine clearance
CRT	(Concurrent) chemoradiotherapy
CT	Computed tomography
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
Durvalumab	Durvalumab (Genetical Recombination)
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EPC	End of production cells
Fc	Fragment crystallizable
FcγR	Fc γ receptor
FcRn	Neonatal Fc receptor
HCP	Host cell protein
HRP	Horseradish peroxidase
HTRF	Homogeneous time resolved fluorescence
IDMC	Independent data monitoring committee
IFN-γ	Interferon-γ
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin

ILD	Interstitial lung disease
IRR	Infusion related reaction
ITT	Intention-to-treat
Japanese clinical practice guideline	Evidence-based clinical practice guideline for lung cancer, the Japan Lung Cancer Society ed. 2016
K_D	Dissociation constant
LDH	Lactate dehydrogenase
[redacted]	[redacted]
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Murine minute virus
MYSTIC study	Study D419AC00001
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimated
NFAT	Nuclear factor of activated T-cells
Nivolumab	Nivolumab (Genetical Recombination)
NOD/SCID mouse	Non-obese diabetic/severe combined immunodeficient mouse
NSCLC	Non-small cell lung cancer
OS	Overall survival
PACIFIC study	Study D4191C00001
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed cell death-1
PD-L	Programmed cell death-ligand
PD-L1 negative (TPS <25%)	PD-L1 expression of <25% on tumor cells
PD-L1 positive (TPS ≥25%)	PD-L1 expression of ≥25% on tumor cells
PD-L1 positive (TPS ≥90%)	PD-L1 expression of ≥90% on tumor cells
Pembrolizumab	Pembrolizumab (Genetical Recombination)
PFS	Progression free survival
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PR	Partial response
PRV	Pseudorabies virus
PS	Performance status
PT	Preferred term
QbD	Quality by design
QTcF	QT interval corrected using Fredericia's formula
ΔQTcF	Change from baseline in QTcF
QW	Quaque 1 week
Q2W	Quaque 2 weeks
Q3W	Quaque 3 weeks
Q4W	Quaque 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
Reo-3	Reovirus type 3
[redacted]	[redacted]
SD	Stable disease
[redacted]	[redacted]
[redacted]	[redacted]
SPR	Surface plasmon resonance
Study 1108	Study CD-ON-MEDI4736-1108

Study 02	Study D4190C00002
TNF-α	Tumor necrosis factor-α
TPS	Tumor proportion score
V1	Central volume of distribution
V2	Peripheral volume of distribution
WCB	Working cell bank
X-MuLV	Xenotropic murine leukemia virus
30/15 mg/kg	Durvalumab 30 mg/kg IV on Day 1 followed by durvalumab 15 mg/kg IV QW from Day 8 onward
60/30 mg/kg	Durvalumab 60 mg/kg IV on Day 1 (or gestation day 20) followed by durvalumab 30 mg/kg IV QW from Day 8 onward (or from gestation day 27 until parturition)
200/100 mg/kg	Durvalumab 200 mg/kg IV on Day 1 (or gestation day 20) followed by durvalumab 100 mg/kg IV QW from Day 8 onward (or from gestation day 27 until parturition)