Report on the Deliberation Results

November 20, 2017
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Tecentriq Intravenous Infusion 1200 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	February 17, 2017

Results of Deliberation

In its meeting held on November 6, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, and the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

In response to the instruction at the Second Committee on New Drugs, layout and scaling of some figures in the Review Report have been revised. There will be no change to the review results associated with this revision.

**Japanese Accepted Name (modified INN)*

Review Report

October 23, 2017
Pharmaceuticals and Medical Devices Agency

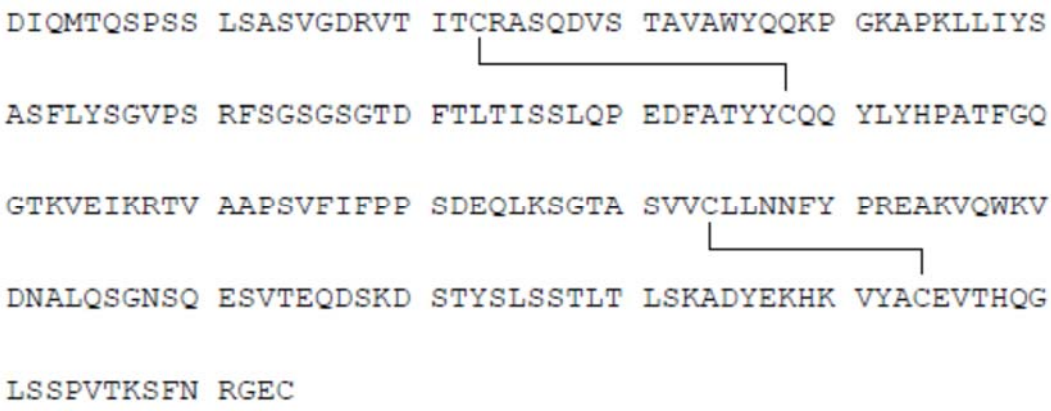
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Tecentriq Intravenous Infusion 1200 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	February 17, 2017
Dosage Form/Strength	Injection: Each vial (20.0 mL) contains 1200 mg of Atezolizumab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Atezolizumab is a recombinant humanized monoclonal antibody against human programmed cell death-ligand 1 (PD-L1) composed of complementarity-determining regions derived from human and mouse antibodies and framework regions and constant regions derived from human IgG1, whose amino acid residue at position 298 in the H-chain is substituted by Ala. Atezolizumab is produced in Chinese hamster ovary cells. Atezolizumab is a protein composed of 2 H-chains (γ1-chains) consisting of 448 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

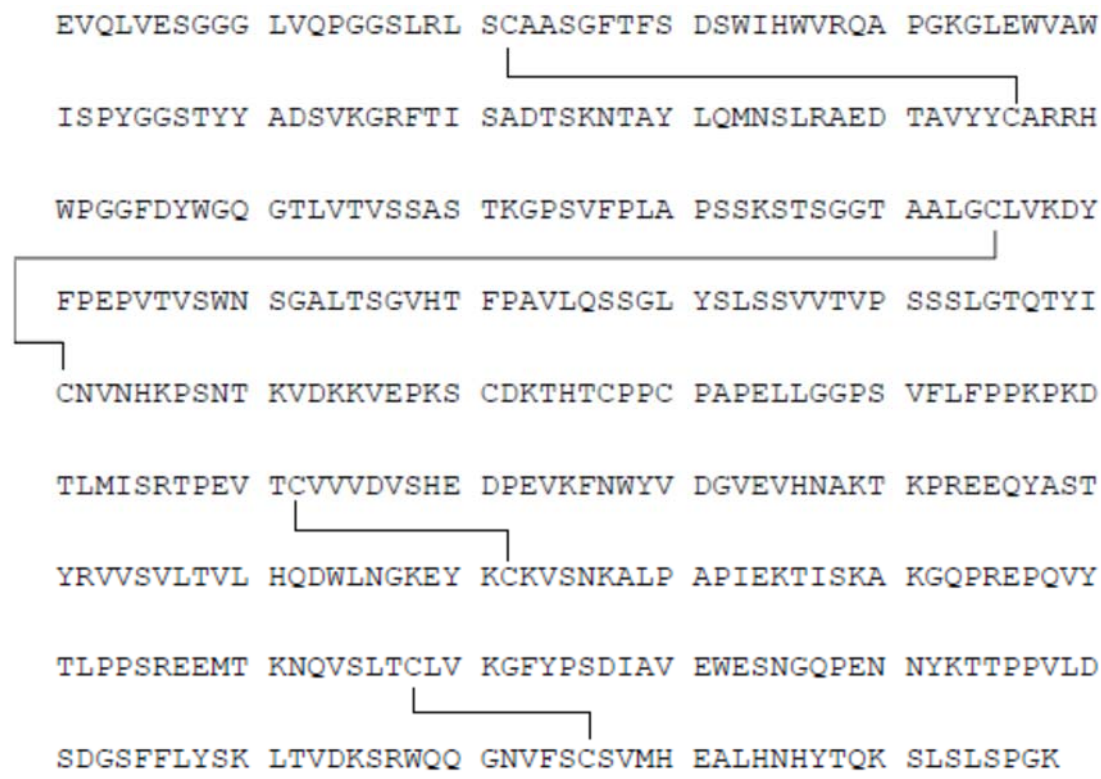
Structure

Amino acid sequence

L-chain



H-chain



Intra-chain disulfide bonds: Solid line

Inter-chain disulfide bonds:

L-chain C214–H-chain C221, H-chain C227–H-chain C227, H-chain C230–H-chain C230

Pyroglutamic acid (partial): H-chain E1

Partial processing: H-chain K448

Molecular formula: $C_{6446}H_{9902}N_{1706}O_{1998}S_{42}$

Molecular weight: 144,610.56

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 product has efficacy in the treatment of unresectable advanced or recurrent non-small cell lung cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Reports of interstitial lung disease, hepatic dysfunction, colitis/severe diarrhea, pancreatitis, type 1 diabetes mellitus, endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction), neuropathies (including Guillain-Barre syndrome), myasthenia gravis, encephalitis/meningitis, infusion reaction, myositis/rhabdomyolysis, renal dysfunction (tubulointerstitial nephritis, etc.), severe skin disorders, myocarditis, hemolytic anemia, and immune thrombocytopenic purpura, embryo-fetal toxicity, and use in organ transplant recipients (including hematopoietic stem cell transplant recipients) should be further investigated via post-marketing surveillance.

Indication

Unresectable advanced or recurrent non-small cell lung cancer

Dosage and Administration

The usual adult dosage is 1200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

September 7, 2017

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

Product Submitted for Approval

Brand Name	Tecentriq Intravenous Infusion 1200 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	February 17, 2017
Dosage Form/Strength	Injection: Each vial (20.0 mL) contains 1200 mg of Atezolizumab (Genetical Recombination).
Proposed Indication	Unresectable advanced or recurrent non-small cell lung cancer

Proposed Dosage and Administration

The usual adult dosage is 1200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

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 [NK] T cells) etc. (*Immunity*. 2007;27:111-22, *Int Immunol*. 2007;19:813-24). Various tumor cells also express PD-L1 (*Cancer Immunol Immunother*. 2007;56:739-45), and the PD-L1/PD-1 pathway is considered a mechanism by which tumor cells evade antigen-specific T-cell attack, etc.

Atezolizumab is a humanized IgG1 monoclonal antibody against human PD-L1 discovered by Genentech (the US). It binds to the extracellular domain of PD-L1, thereby blocking the binding of PD-L1 to PD-1, etc., resulting in enhanced tumor antigen-specific cytotoxic T cell activity and inhibition of tumor growth.

1.2 Development history etc.

Outside Japan, Roche and Genentech initiated a phase I study in patients with advanced solid tumors or hematologic malignancies (Study PCD4989g) in June 2011. Then, Roche undertook a foreign phase II study (POPLAR study) and a global phase III study (OAK study), involving patients with advanced or recurrent non-small cell lung cancer (NSCLC) previously treated with platinum-containing chemotherapy, in August 2013 and March 2014, respectively.

US and EU applications for atezolizumab for NSCLC were filed based mainly on the results from the POPLAR study etc. in February 2016 and April 2016, respectively. In the US, atezolizumab was approved for the following indication in October 2016: "TECENTRIQ is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for theses aberrations prior to receiving TECENTRIQ." The EU application is under review.

As of July 2017, atezolizumab has been approved for the indication of NSCLC in 13 countries or regions.

In Japan, the applicant initiated a phase I study in patients with advanced solid tumors (Study JO28944) in August 2013. The above OAK study initiated patient enrollment in Japan in May 2014.

The applicant has submitted a marketing application for atezolizumab based mainly on the results from the OAK study.

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

Multiple variable region sequences with high affinity for PD-L1 were selected by [redacted]. DNA segments encoding heavy and light chains were prepared by fusing the sequences encoding the obtained variable regions to the sequences encoding human IgG1 heavy and light chain constant regions containing a mutation in the Fc domain that prevents N-linked glycosylation at that site. [redacted]. These DNA segments encoding heavy and light chains were inserted into an expression vector to generate the expression construct for the production of atezolizumab. This expression construct was transfected into Chinese hamster ovary (CHO) cells, and a clone most suitable for the manufacture of atezolizumab was selected from the CHO cell line and 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. Genetic stability during the production of atezolizumab 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 liquid nitrogen. [redacted] a new WCB will be generated as necessary.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of seed train, inoculum train, production culture, harvest, [redacted] chromatography, [redacted] virus inactivation, [redacted], [redacted], virus removal [redacted], [redacted] filtration, filtration, and storage/testing. The obtained drug substance is stored in [redacted] tank at ≤[redacted]°C.

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

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

2.1.3 Safety evaluation of adventitious agents

As raw materials of biological origin etc. other than the host CHO cells, [redacted] for the preparation of the WCB are used in the drug substance manufacturing process. Information on their conformance to the Standard for Biological Ingredients is being requested.

The MCB, WCB, EPC, and CAL were subjected to purity tests [see Section 2.1.1]. Pre-harvest unprocessed bulk was subjected to tests for bioburden and mycoplasma, [redacted], *in vitro* test for adventitious viruses, and [redacted] test. None of the tests revealed contamination with viral or nonviral adventitious agents. Tests for bioburden and mycoplasma, *in vitro* test for adventitious viruses, and [redacted] test are included 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	Minute virus of mice	SV-40
[redacted] virus inactivation	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Virus removal [redacted]	[redacted]*	[redacted]	[redacted]*
Overall reduction factor	≥17.37	≥13.52	≥9.77

*: When the virus reduction factor of the virus removal [redacted] step for [redacted] is used as an estimated value, the overall reduction factors are [redacted] for xenotropic murine leukemia virus and [redacted] for SV-40.

2.1.4 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process A, Process B, Process C, and Process D [the proposed commercial process]).

- Process A→Process B: changes in [redacted] ([redacted]), [redacted], [redacted] condition, etc.
- Process B→Process C: changes in [redacted] ([redacted], [redacted]), [redacted] condition, [redacted], formulation, etc.
- Process C→the proposed commercial process: changes in [redacted] and [redacted], [redacted], etc.

The drug product produced from the drug substance manufactured by Process A or B was used in phase I and II studies, and the drug product produced from the drug substance manufactured by Process C or the proposed commercial process was used in phase I, II, and III studies.

For process changes, comparability of quality attributes between pre-change and post-change drug substances has been demonstrated.

A quality by design (QbD) approach was used to develop the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization was performed as 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, [redacted]
Physicochemical properties	molecular weight, isoelectric point, extinction coefficient, molecular variants ([redacted])
Carbohydrate structure	[redacted]
Biological properties	inhibitory activity against PD-L1/PD-1 binding, inhibitory activity against PD-L1/B7-1 binding
	FcγR-binding activity ([redacted]), [redacted]
	neutralization of inhibition of T-cell activation
	ADCC activity

Biological properties were determined as follows:

- Atezolizumab blocked PD-L1 binding to PD-1 and B7-1, as determined by a competitive enzyme-linked immunosorbent assay (ELISA).
- A PD-1-expressing Jurkat cell line derived from an acute T cell leukaemia patient was co-cultured with a WIL2-S cell line, i.e. PD-L1-expressing human B lymphoblast cells, in the presence of atezolizumab, to measure [redacted]. In this test system, atezolizumab neutralized the PD-L1/PD-1-mediated inhibition of T-cell activation.
- Atezolizumab was engineered to reduce the Fc-effector function via an amino acid substitution (asparagine [Asn] to alanine [Ala]) at position 298 in the heavy chain to prevent N-linked glycosylation in the Fc domain. Thus, assays to assess effector function were performed, and the results are as follows.
  - The binding activity of atezolizumab to FcγR was assessed by ELISA, which showed reduced binding of atezolizumab to FcγR, relative to positive control, trastuzumab.
  - The antibody-dependent cell-mediated cytotoxicity (ADCC) activity of atezolizumab was evaluated using NK cells as effector cells and an anti-PD-L1 antibody obtained by substituting amino acid 298 in the heavy chain of atezolizumab to Asn, as positive control. Atezolizumab showed no ADCC activity.

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization in Section "2.1.5.1 Structure and properties," Variant A, Acidic Variant B, Acidic Variant C, and Acidic Variant D were considered product-related impurities. Among the product-related impurities, Variant A is controlled by the drug substance and drug product specifications for [redacted] and [redacted], respectively, and Acidic Variant B, Acidic Variant C, and Acidic Variant D have been demonstrated to be adequately removed by the manufacturing process.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell DNA, [redacted], and [redacted] were considered process-related impurities. All of the process-related impurities have been demonstrated to be adequately removed by the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identification (peptide map), osmolality, pH, purity ([redacted], size exclusion chromatography [SEC], and [redacted]), endotoxins, microbial limits, [redacted]20, potency (neutralizing activity), and assay (ultraviolet-visible spectrophotometry).

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

Study	Process	No. of batches	Storage conditions	Testing period	Storage package
Long-term	Process C	3	[redacted] ± [redacted]°C	[redacted] months*	[redacted] container
	Proposed commercial process	4		[redacted] months*	
Accelerated	Proposed commercial process	4	[redacted] ± [redacted]°C	[redacted] months	
Stress	Proposed commercial process	3	[redacted] ± [redacted]°C/[redacted] ± [redacted]%RH	[redacted] months	[redacted]

*: The stability studies will be continued up to [redacted] months.

Under the long-term and accelerated conditions, there were no significant changes in quality attributes, in any of the tests conducted, throughout the testing period.

Under the stress condition, [redacted] of Variant A in [redacted], [redacted] of [redacted] in [redacted], and [redacted] of [redacted] in [redacted], [redacted] of [redacted], and [redacted] of [redacted] were observed.

Based on the above, a shelf life of 36 months has been proposed for the drug substance when stored in [redacted] container at ≤[redacted]°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is presented in vials as a solution for intravenous infusion. Each vial (20.0 mL) contains 1200 mg of atezolizumab and the following excipients: L-histidine, glacial acetic acid, sucrose, polysorbate 20, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of thawing and filtration of drug substance, sterile filtration, filling/stoppering, capping, inspection, storage, secondary packaging, labeling, and storage/testing.

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

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

2.2.3 Manufacturing process development

The following are major changes made to the drug product manufacturing process during development (Process A, Process B, and the proposed commercial process).

- Process A→Process B: changes in [redacted] etc.
- Process B→the proposed commercial process: changes in [redacted], [redacted], etc.

For process changes, comparability of quality attributes between pre-change and post-change drug products has been demonstrated.

A QbD approach was 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 (peptide map), osmolality, pH, purity ([redacted], SEC, and [redacted]), endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, potency (neutralizing activity), 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

Study	Process	No. of batches	Storage conditions	Testing period	Storage package
Long-term	Process B*1	3	5 ± 3°C	[redacted] months*3	A glass vial with a butyl rubber stopper
	Proposed commercial process*2	3		[redacted] months*4	
Accelerated	Proposed commercial process*2	3	[redacted] ± [redacted]°C/[redacted]%RH	[redacted] months	
Stress	Proposed commercial process*2	3	[redacted] ± [redacted]°C/[redacted]%RH	[redacted] months	
Photostability	Process B*1	1	An overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		

*1: Drug substance was manufactured by Process C. *2: Drug substance was manufactured by the proposed commercial process.
*3: The stability study will be continued up to [redacted] months. *4: The stability study will be continued up to [redacted] months.

Under the long-term condition, there were no significant changes in quality attributes, in any of the tests conducted, throughout the testing period.

Under the accelerated condition, [redacted] of Variant A by [redacted], [redacted] of [redacted] and [redacted] of [redacted] by [redacted], and [redacted] of [redacted] and [redacted] of [redacted] by [redacted] were observed.

Under the stress condition, the above changes observed in the accelerated testing were more prominent.

The photostability data showed that the drug product is photosensitive.

Based on the above, a shelf life of 36 months has been proposed for the drug product when packaged in a glass vial with a butyl rubber stopper and stored at 2°C to 8°C in a carton to protect from light.

2.3 QbD

A QbD approach was used to develop the drug substance and the drug product, and a quality control strategy was established based on the following studies etc.

- Identification of critical quality attributes (CQAs):
  Concerning product-related impurities, process-related impurities, and formulation quality attributes, the following CQAs were identified based on the information obtained during the development of atezolizumab, the relevant knowledge, etc.
  - [redacted], adventitious agents (viruses, microbial contamination, and endotoxins), [redacted], sterility, and [redacted]
- Process characterization:
  Process parameters were classified based on their impact on quality, and acceptable parameter ranges etc. were determined.
- Development of method of control:
  Based on process knowledge including the above process characterization, the control method of the quality attributes of atezolizumab was developed through the combination of process parameter controls, in-process controls, and the specifications.

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, except for raw materials of biological origin, etc. mentioned in Section 2.1.3 (the relevant information is being requested). Information on the conformance of these raw materials etc. to the Standards for Biological Ingredients will be presented in the Review Report (2).

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

3.1 Primary pharmacodynamics

3.1.1 Binding to PD-L1 (CTD 4.2.1.1.1, 4.2.1.1.2)

Equilibrium binding studies with ^{125}I-labeled atezolizumab and PRO304397[1)] were performed to determine the binding affinities of atezolizumab and PRO304397 to human and murine PD-L1 expressed on human

[1)] A human/murine chimeric antibody (atezolizumab PD-L1 binding variable region set in a mouse IgG2a framework). It contains 2 mutations in the Fc domain to reduce binding to murine FcγR.

embryonic kidney (HEK) 293 cells. The K_d values of atezolizumab and PRO304397 to human and murine PD-L1 are shown in Table 5.

Table 5. Binding of atezolizumab and PRO304397 to human and murine PD-L1

	K_d (nmol/L)	
	Human PD-L1	Murine PD-L1
Atezolizumab	0.433, 0.400	0.134, 0.120
PRO304397	0.374, 0.336	0.147, 0.188

Individual values, n = 2

Flow cytometry analysis was performed to determine the binding activities of atezolizumab, PRO304397, and PRO314483[2)] to PD-L1 on human and cynomolgus monkey T cells and murine PD-L1 expressed on HEK 293 cells. The EC_{50} values of atezolizumab, PRO304397, and PRO314483 are presented in Table 6.

Table 6. Binding of atezolizumab, PRO304397, and PRO314483 to human, cynomolgus monkey, and murine PD-L1

	EC_{50} (nmol/L)		
	Human PD-L1	Cynomolgus monkey PD-L1	Murine PD-L1
Atezolizumab	0.395 ± 0.030	0.704 ± 0.084	0.519 ± 0.025
PRO304397	ND	ND	0.412 ± 0.071
PRO314483	ND	ND	0.433 ± 0.114

Mean ± SD, n = 3 to 8, ND: Not determined

3.1.2 Binding to FcγR (CTD 4.2.1.1.1)

The ability of atezolizumab to bind to 6 different human FcγRs (FcγRIA, FcγRIIA-R131, FcγRIIA-H131, FcγRIIB, FcγRIIIA-F158, and FcγRIIIA-V158) was assessed by ELISA. Atezolizumab exhibited minimal binding to each of the human FcγRs tested.

3.1.3 Blockade of PD-L1 binding to PD-1 and B7-1 (CTD 4.2.1.1.1)

The blockade of human or murine PD-L1 binding to PD-1 and B7-1 by atezolizumab, PRO304397,[1)] or PRO314483[2)] was assessed by ELISA. The IC_{50} values of atezolizumab, PRO304397, and PRO314483 for the blockade of PD-L1 binding to PD-1 and B7-1 are shown in Table 7.

Table 7. Blockade of PD-L1 binding to PD-1 and B7-1 by atezolizumab, PRO304397, or PRO314483

	IC_{50} (pmol/L)			
	Human PD-L1/PD-1	Human PD-L1/B7-1	Murine PD-L1/PD-1	Murine PD-L1/B7-1
Atezolizumab	82.8 ± 40.3	48.4 ± 25.9	104 ± 38.7	75.6 ± 14.8
PRO304397	77.5 ± 25.2	47.5 ± 26.3	113 ± 31.5	79.4 ± 15.5
PRO314483	78.9 ± 31.0	41.0 ± 15.8	125 ± 16.5	96.6 ± 27.2

Mean ± SD, n = 3

[2)] A human/murine chimeric antibody (atezolizumab PD-L1 binding variable region set in a mouse IgG2a framework) that has reduced binding to murine FcγR due to the absence of N-linked glycans.

3.1.4 Anti-tumor efficacy against malignant tumor cell lines (CTD 4.2.1.1.3, 4.2.1.1.4, 4.2.1.1.5, 4.2.1.1.6, 4.2.1.1.7)

The anti-tumor efficacy of PRO314483[2)] was evaluated in mice implanted subcutaneously with the MC38, MC38.OVA,[3)] or CT26 cell line derived from mouse colorectal cancer or the Cloudman S91 cell line derived from mouse melanoma. Once tumors reached a certain volume[4)] (day 0), mice were trreated with PRO314483 10 mg/kg administered as an intraperitoneal injection 3 times weekly for 1 to 3 weeks, and tumor volumes were calculated.[5)] The results are shown in Table 8.

Table 8. Anti-tumor activity of PRO314483 in mice implanted subcutaneously with malignant tumor cell lines

Cell line	Group	Tumor volume (mm^3)	TGI (%)	TTP5X (day)
MC38	Control (murine IgG1)	>3000	0	16.5
	PRO314483 (1-week administration)	1349	76	23.5
	PRO314483 (2-week administration)	372	98	37
	PRO314483 (3-week administration)	282	103	50
MC38.OVA	Control (murine IgG1)	>3000	0	18
	PRO314483 (1-week administration)	0	118	—
	PRO314483 (2-week administration)	0	116	—
	PRO314483 (3-week administration)	0	119	—
CT26	Control (murine IgG1)	>3000	0	11.5
	PRO314483 (3-week administration)	443	92	27.5
Cloudman S91	Control (murine IgG1)	>3000	0	8
	PRO314483 (3-week administration)	1082	78	14

n = 10
TGI (%) = [1 − (the area under the fitted curve for the PRO314483 group/day)/(the area under the fitted curve for the control group/day)] × 100
TTP5X: Time in days for animal to have tumor progress to 5-fold above starting volume
—: Not applicable

3.2 Secondary pharmacodynamics

3.2.1 Impact of anti-PD-L1 in a mouse model of LCMV (CTD 4.2.1.2.1, 4.2.1.2.2, 4.2.1.2.3, 4.2.1.2.4)

Studies in a mouse model of lymphocytic choriomeningitis virus (LCMV) were conducted, and the results are shown below.

- When PRO314483[2)] 10 mg/kg was administered intraperitoneally 3 times weekly for 1 or 2 weeks, beginning 14 days after the initial infection (Day 14), PRO314483 reduced viral titers in the blood, liver, lung, and kidney, compared with the control (murine IgG1) group. Compared with the control (murine IgG1) group, PRO314483 increased the percentages of CD107a+/CD8+ T cells and IFN-γ-producing CD8+ T cells, which respond to LCMV gp33 peptide, in the spleen.
- Intraperitoneal injection of 10 mg/kg of PRO314483, PRO304397,[1)] or a mouse anti-mouse PD-L1 antibody, PRO304135, on Day 7, resulted in mortalities.
- Intraperitoneal injection of 200 μg of a rat anti-mouse PD-1 antibody, Clone 29F-1A12, on Days 3 and 6, resulted in mortalities. When PD-1-deficient mice were infected with LCMV, mortalities were observed.

[3)] MC38 cell line engineered to express ovalbumin
[4)] MC38, 200 mm^3; MC38.OVA, 150 mm^3; CT26, 200 mm^3; Cloudman S91, 200 mm^3
[5)] MC38, day 25; MC38.OVA, day 29; CT26, day 20; Cloudman S91, calculated on day 28

- After CD8+ T cells were depleted by intraperitoneal injection of 500 μg of an anti-CD8 antibody on Days −2, 0, and 2, intraperitoneal injection of 200 μg of a rat anti-mouse PD-L1 antibody, Clone 10F.9G2, on Day 5, did not induce death.

3.3 Safety pharmacology

In 2-month and 6-month repeated-dose toxicity studies in cynomolgus monkeys, the effects of atezolizumab 50 mg/kg on the central nervous, cardiovascular, and respiratory systems were assessed [see Section 5.2]. There were no atezolizumab-related effects.

3.R Outline of the review conducted by PMDA

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

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

The applicant's explanation about the mechanism of action of atezolizumab 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, NK T cells) etc. (*Immunity*. 2007;27:111-22, *Int Immunol.* 2007;19:813-24). Various tumor cells also express PD-L1 (*Cancer Immunol Immunother*. 2007;56:739-45), and PD-L1 expressed on tumor cells is considered to act to suppress the anti-tumor immune response.

Atezolizumab is a humanized IgG1 monoclonal antibody against human PD-L1. It binds to the extracellular domain of PD-L1, thereby blocking the binding of PD-L1 to PD-1 and B7-1 [see Sections 3.1.1 and 3.1.3], resulting in enhanced tumor antigen-specific cytotoxic T cell activity and inhibition of tumor growth [see Section 3.1.4].

Although the anti-tumor efficacy of atezolizumab against a human NSCLC cell line has not been studied, given the following points in addition to the mechanism of action of atezolizumab, the efficacy of atezolizumab in the treatment of NSCLC is expected.

- As atezolizumab exerts its anti-tumor activity via tumor antigen-specific T cell activation, etc., its anti-tumor activity is considered to depend on the immunogenicity of tumor cells.
- Since human NSCLC is considered to have a high somatic mutation frequency and a high tumor-specific mutational load (*Nature*. 2013;499:214-8, *Science*. 2015;348:69-74), and tumor-specific mutation-derived proteins induce an immune response (*Science*. 2015;348:69-74), human NSCLC should be highly immunogenic.

The applicant's explanation about differences in pharmacological properties between a PD-L1 blocking antibody, atezolizumab, and anti-PD-1 antibodies approved for the indication of NSCLC, nivolumab and pembrolizumab:
All of atezolizumab, nivolumab, and pembrolizumab inhibit tumor growth by blocking the binding of PD-L1 to PD-1 and enhancing the anti-tumor immune response, and show no ADCC activity against tumor cells [see Section 2.1.5.1].

On the other hand, nivolumab and pembrolizumab block the binding of PD-L2 to PD-1 (*Immunotherapy*. 2015;7:777-92), but atezolizumab blocks the binding of PD-L1 to B7-1.

PMDA's discussion:
The applicant's explanation (the efficacy of atezolizumab in the treatment of NSCLC is expected) is understandable from the standpoint of the mechanism of action of atezolizumab. However, (a) the contribution of blocking of the binding of PD-L1 to B7-1 to tumor growth inhibition by atezolizumab, (b) factors affecting the efficacy of atezolizumab, and (c) differences in pharmacological properties between atezolizumab and nivolumab/pembrolizumab are not fully understood at present. Since such information may be beneficial in terms of selecting eligible patients in the clinical use of atezolizumab, an investigation should be continued, and if a new finding is obtained, the information should be provided appropriately to healthcare professionals in clinical practice.

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

The non-clinical pharmacokinetics (PK) of atezolizumab were studied in monkeys and mice.

4.1 Analytical method

4.1.1 Atezolizumab assay

Atezolizumab in monkey and mouse serum was quantified by ELISA using [redacted], [redacted], and [redacted].

4.1.2 Anti-atezolizumab antibody assay

Anti-atezolizumab antibodies in monkey and mouse serum were quantified by ELISA using solid phased streptavidin, atezolizumab labeled with biotin, atezolizumab labeled with digoxigenin, and [redacted].

4.2 Absorption

4.2.1 Single-dose study

Following single intravenous doses of atezolizumab 0.5, 5, or 20 mg/kg in male and female monkeys, serum atezolizumab concentrations were determined (Table 9). Atezolizumab exposure (C_{max} and AUC_{inf}) increased with increasing dose across the dose range tested. There were no clear gender-related differences in exposure.

Anti-atezolizumab antibodies were detected in all animals.

Table 9. PK parameters of atezolizumab (male and female monkeys, single intravenous administration)

Dose (mg/kg)	Sex	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
0.5	M	7.22, 9.73	50.1, 43.3	6.27, 3.47	9.98, 11.5	91.7, 60.4
	F	8.80, 8.43	39.1, 60.5	4.21, 6.16	12.8, 8.27	78.8, 75.1
5	M	130, 130	1310, 580	4.47, 3.01	3.83, 8.62	54.1, 45.6
	F	118, 115	617, 456	1.07, 1.11	8.11, 11.0	34.1, 42.5
20	M	576, 642	2430, 5350	1.43, 11.0	8.22, 3.74	32.8, 57.7
	F	625, 595	5370, 4090	6.77, 1.34	3.73, 4.90	47.9, 40.3

Individual values, n = 2

4.2.2 Repeated-dose studies

Female mice were given intravenous doses of atezolizumab 10 or 50 mg/kg QW for 2 weeks, and serum atezolizumab concentrations were determined (Table 10). Atezolizumab exposure was reduced on Day 14 compared to Day 1. The applicant explained that anti-atezolizumab antibodies formed after administration of atezolizumab may be attributable to increased atezolizumab clearance.

Anti-atezolizumab antibodies were detected in all animals.

Table 10. PK parameters of atezolizumab (female mice, 2-week repeated intravenous administration)

Sampling time (days)	Dose (mg/kg)	AUC_{7day}*1 (μg·day/mL)
0*2	10	537
	50	2250
14	10	230
	50	1150

*1: Calculated based on the mean serum atezolizumab concentration (n = 3) at each time point.
*2: The day of the first dose

Male and female monkeys were given intravenous doses of atezolizumab 5, 15, or 50 mg/kg QW for 26 weeks, and serum atezolizumab concentrations were determined (Table 11). In the 15 and 50 mg/kg groups, atezolizumab exposure was generally dose-proportional, and there were no clear gender-related differences in exposure. The applicant explained that atezolizumab exposure increased with increasing number of doses in the 15 and 50 mg/kg groups, indicating accumulation of atezolizumab following repeated dosing. On the other hand, atezolizumab exposure in the 5 mg/kg group was reduced on Day 182 compared to Day 1. The applicant explained that anti-atezolizumab antibodies formed after administration of atezolizumab may be attributable to increased atezolizumab clearance.

Anti-atezolizumab antibodies were detected in all animals in the 5 mg/kg group, 8 of 10 animals in the 15 mg/kg group, and 3 of 10 animals in the 50 mg/kg group.

Table 11. PK parameters of atezolizumab (male and female monkeys, 26-week repeated intravenous administration)

Sampling time (days)	Sex	Dose (mg/kg)	C_{max} (μg/mL)	AUC_{3day} (μg·day/mL)
0[*1]	M	5	139 ± 12.2	263 ± 28.4
		15	351 ± 81	758 ± 149
		50	1290 ± 109	2880 ± 178
	F	5	107 ± 6.65	224 ± 20.3
		15	251 ± 35.7	629 ± 32.4
		50	1110 ± 71.1	2690 ± 218
182	M	5	7.28 ± 12.1[*2]	—
		15	1220 ± 690	4250 ± 341
		50	4060 ± 754	10,100 ± 1060
	F	5	116 ± 140[*2]	709, 47.3[*3]
		15	1350 ± 1470	2810 ± 2740
		50	3300 ± 515	6740 ± 1370

Mean ± SD (Individual values are listed for n = 2), n = 5,
*1: The day of the first dose, *2: n = 3, *3: n = 2, —: Not calculated

4.3 Distribution

The applicant's explanation:

Given that the volume of distribution of atezolizumab in a single-dose study in monkeys [see Section 4.2.1] was similar to the plasma volume in monkeys (45 mL/kg) (*Pharm Res*. 1993;10:1093-5), atezolizumab is considered to have low tissue distribution and be distributed predominantly into circulation, etc. Thus, a tissue distribution study of atezolizumab was not conducted.

As human IgG is transported across the placenta via neonatal Fc receptor (FcRn) into the fetus (*Birth Defects Res B Dev Reprod Toxicol*. 2013;98:459-85), atezolizumab, which is a humanized IgG1 antibody, also has the potential to cross the placenta into the fetus.

4.4 Metabolism and excretion

The applicant's explanation:

Since atezolizumab is an antibody drug and is considered to be cleared by catabolic pathways etc., no metabolism or excretion studies of atezolizumab were conducted, based on “Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals” (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

Given that human IgG has been reported to be excreted in milk (*Vaccine*. 2003;21:3374-6), atezolizumab has the potential to be excreted in milk.

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 atezolizumab is acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

Unless otherwise specified, [redacted] mmol/L [redacted], [redacted] mmol/L [redacted], and [redacted]% [redacted] were used as vehicle in toxicity studies.

5.1 Single-dose toxicity

Although a single-dose toxicity study of atezolizumab was not conducted, the single-dose toxicity of atezolizumab was assessed based on the findings after the first dose in a 2-week repeated intravenous dose toxicity study in mice and 2-month and 6-month repeated dose toxicity studies in monkeys [see Sections 5.2.1-5.2.3]. There were no deaths considered related to atezolizumab even at the highest dose tested in mice and monkeys, i.e. 50 mg/kg.

Based on the above results, the approximate lethal dose for both mice and monkeys in these studies was determined to be >50 mg/kg.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies of atezolizumab were conducted in mice and monkeys. Since systemic exposure was reduced due to the formation of anti-atezolizumab antibodies in mice [see Section 4.2.2], the mouse was not considered relevant for assessing the chronic toxicity of atezolizumab, and a repeated-dose toxicity study of >2 weeks duration was not conducted in mice.

5.2.1 Two-week repeated intravenous dose toxicity study in mice (non-GLP study, Reference data)

Mice (C57BL/6 and CD-1, 8 females each/group) were given intravenous doses of atezolizumab 0 (vehicle), 10 (C57BL/6 only), or 50 mg/kg QW for 2 weeks (a total of 3 doses). At the end of the dosing period, 4 mice in each group were necropsied, and a 4-week recovery period was scheduled for the remaining 4 mice in each group.

No mortality occurred. Sciatic neuropathy at ≥10 mg/kg in C57BL/6 mice, and increased spleen weight at 50 mg/kg in C57BL/6 and CD-1 mice were observed. The applicant explained that the increased spleen weight is of minimal toxicological significance because this finding was due to enhancement of an immune response to a foreign protein, and did not correlate with histopathological findings, etc.

All findings except for sciatic neuropathy were reversible at the end of the 4-week recovery period.

5.2.2 Two-month repeated intravenous or subcutaneous dose toxicity study in monkeys

Cynomolgus monkeys (5/sex/group) were given intravenous (IV) and subcutaneous (SC) doses of atezolizumab 0 mg/kg (vehicle), intravenous doses of atezolizumab 5, 15, or 50 mg/kg, or subcutaneous doses of atezolizumab 15 or 50 mg/kg QW for 2 months (a total of 9 doses). At the end of the dosing period, 3 males and 3 females in each group were necropsied, and a 3-month recovery period was scheduled for the remaining 2 males and 2 females in each group.

No mortality occurred. Arteritis or periarteritis in multiple organs in the 50 mg/kg IV and ≥15 mg/kg SC groups, elevated serum cytokine levels in the 50 mg/kg IV group, and mononuclear cell infiltrates at the SC injection sites in the ≥15 mg/kg SC groups were observed.

All findings were reversible at the end of the 3-month recovery period.

Based on the above, the no-observed-adverse-effect level (NOAEL) in this study was determined to be 5 mg/kg/week.

5.2.3 Six-month repeated intravenous dose toxicity study in monkeys

Cynomolgus monkeys (5/sex/group) were given intravenous doses of atezolizumab 0 (vehicle control: 20 mmol/L histidine acetate, 120 mmol/L sucrose, 0.04% polysorbate 20), 5, 15, or 50 mg/kg QW for 6 months (a total of 27 doses). At the end of the dosing period, 3 males and 3 females in each group were necropsied, and a 3-month recovery period was scheduled for the remaining 2 males and 2 females in each group.

Arteritis or periarteritis in multiple organs at ≥15 mg/kg, increases in CRP at 50 mg/kg, and an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries in females at 50 mg/kg were observed.

All findings were reversible at the end of the 3-month recovery period.

Based on the above, the NOAEL in this study was determined to be 5 mg/kg/week. The AUC over 3 weeks estimated from the $AUC_{182\text{-}185day}$ at 5 mg/kg/week (378 μg·day/mL) was approximately 0.11-fold the human exposure.[6)]

5.3 Genotoxicity

Since atezolizumab is an antibody drug, and it is not expected that atezolizumab would interact directly with DNA or other chromosomal material, no genotoxicity studies were conducted.

5.4 Carcinogenicity

No carcinogenicity studies were conducted because atezolizumab is a drug intended to treat patients with advanced cancer.

5.5 Reproductive and developmental toxicity

Since atezolizumab is a drug intended to treat patients with advanced cancer, and is anticipated to adversely affect embryo-fetal development, in light of its pharmacological effects, no reproductive and developmental toxicity studies were conducted.

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6) The estimated AUC_{ss} in Japanese patients with PD-L1-positive NSCLC receiving atezolizumab 1200 mg Q3W was 6670 μg·day/mL (BIRCH study).

5.5.1 Effects on fertility

The applicant's explanation about the effects of atezolizumab on male and female fertility:

- Male fertility

  Since semen analysis etc. revealed no atezolizumab-related changes and no histopathological findings in the reproductive organs were noted in males dosed with atezolizumab[7)] in a 6-month repeated intravenous dose toxicity study in monkeys [see Section 5.2.3], atezolizumab is unlikely to affect male fertility.

- Female fertility

  Given the following (a) and (b), the possibility that atezolizumab affects female fertility cannot be ruled out. Thus, information regarding (a) will be provided via package insert.

  (a) An irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries, which were related to atezolizumab, were observed in females[7)] at 50 mg/kg in a 6-month repeated intravenous dose toxicity study in monkeys [see Section 5.2.3].

  (b) Since leukocytes present within the ovary have been suggested to be involved in the modulation of luteal function including menstruation (*Women's Health*. 2013;9:387-95), blockade of the PD-L1/PD-1 pathway may make it difficult to modulate menstrual cycles via the immune system.

5.5.2 Effects on embryo-fetal development and use in pregnant women

The applicant's explanation about the effects of atezolizumab on embryo-fetal development and its use in pregnant women:

Given the following points, administration of atezolizumab during pregnancy can cause fetal harm, including embryonic death.

- Blockade of the PD-L1/PD-1 pathway markedly increases the risk of abortion and stillbirth by impairing fetomaternal tolerance (*J Exp Med*. 2005;202:231-7, etc.).
- Human IgG1 crosses the placenta [see Section 4.3], suggesting a potential risk to newborns due to atezolizumab exposure.

Thus, atezolizumab should not be used in pregnant women, as a rule. However, given that NSCLC is a disease with a poor prognosis etc., the clinical use of atezolizumab should be acceptable if the package insert adequately alerts prescribers to the risk of abortion etc. associated with atezolizumab and then the expected therapeutic benefits are considered to outweigh the possible risks.

5.6 Other toxicity studies

5.6.1 Cytokine release study in human PBMCs (non-GLP study, Reference data)

Human peripheral blood mononuclear cells (PBMCs) were incubated with atezolizumab at concentrations of 0.25 to 250 μg/mL for 24 to 48 hours, and then various cytokines (GM-CSF, TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12) produced by PBMCs were measured. Atezolizumab did not induce cytokine release from human PBMCs.

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7) All animals were sexually mature.

5.6.2 Cross-reactivity study of atezolizumab with normal human and cynomolgus monkey tissues

The cross-reactivity of atezolizumab was evaluated immunohistochemically with cryosections of normal (a) human and (b) cynomolgus monkey tissues. The following results were obtained.

(a) Cytoplasmic staining, indicative of atezolizumab binding, was detected in the placenta, lymph node, tonsil, and thymus. Membranous staining, indicative of atezolizumab binding, was observed in the placenta.
(b) Cytoplasmic staining, indicative of atezolizumab binding, was observed in the lymph node.

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 atezolizumab based on non-clinical toxicological evaluation.

5.R.1 Effects on peripheral nerves

Sciatic neuropathy was observed in a 2-week repeated intravenous dose toxicity study in mice [see Section 5.2.1]. PMDA asked the applicant to explain the potential for atezolizumab to affect peripheral nerves in clinical use.

The applicant's response:

Mice deficient for PD-1 having the same major histocompatibility complex (MHC) haplotype as C57BL/6 mice, developed inflammation in multiple tissues including peripheral nerves (*Proc Natl Acad Sci USA*. 2008;105:3533-8). Thus, the mechanism of development of sciatic neuropathy observed in mice is as follows: Autoreactive T cells that are generated in a specific genetic context were activated by the pharmacologic action of atezolizumab, and these autoreactive T cells damaged peripheral nerve tissues.

Peripheral neuropathy has been reported in clinical studies of atezolizumab [see Section 7.R.3.5]. The package insert will caution about neuropathies as adverse reactions to atezolizumab.

PMDA accepted the applicant's explanation.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical method

6.1.1.1 Atezolizumab assay

Atezolizumab in human serum was quantified by ELISA using [redacted], [redacted] and [redacted], and the lower limit of quantification was 60 ng/mL.

6.1.1.2 Anti-atezolizumab antibody assay

Anti-atezolizumab antibodies in human serum were detected by ELISA using solid phased streptavidin, atezolizumab labeled with biotin, atezolizumab labeled with digoxigenin, and [redacted] (detection sensitivity, 20 ng/mL[8]).

Neutralizing anti-atezolizumab antibodies in human serum were detected by [redacted] method using [redacted], [redacted], [redacted], [redacted], [redacted] (detection sensitivity, [redacted] ng/mL).

The applicant's explanation about the potential interference of atezolizumab in serum samples with anti-atezolizumab antibody assay results:

Up to [redacted] μg/mL of atezolizumab in serum samples did not interfere with the above anti-atezolizumab antibody assay. Given that the atezolizumab concentrations in serum samples collected for the anti-atezolizumab antibody assay were up to [redacted] μg/mL in clinical studies, the presence of atezolizumab in serum may have interfered with anti-atezolizumab antibody assay results.

6.1.2 Changes made to the drug substance and drug product manufacturing processes during development

Changes were made to the drug substance and drug product manufacturing processes during development [see Sections 2.1.4 and 2.2.3]. The formulations used in the clinical studies submitted in the present application are shown in Table 12.

For process changes, comparability of quality attributes between pre-change and post-change drug substances and drug products has been demonstrated [see Sections 2.1.4 and 2.2.3].

Table 12. Formulations used in clinical studies

Drug substance manufacturing process	Study Identity
B	foreign phase I study (Study PCD4989g), Japanese phase I study (Study JO28944), foreign phase II studies (FIR study, POPLAR study)
C	foreign phase I study (Study PCD4989g), Japanese phase I study (Study JO28944), global phase II study (BIRCH study), global phase III study (OAK study)
D (the proposed commercial process)	

6.2 Clinical pharmacology

The PK of atezolizumab when administered alone were studied in patients with cancer.

[8] Samples from Study PCD4989g were analyzed using an assay with a detection sensitivity of 10.7 ng/mL.

6.2.1 Japanese clinical study

6.2.1.1 Japanese phase I study (CTD 5.3.3.2.2, Study JO28944 [ongoing since August 2013 (data cutoff date of November 15, 2014)])

An open-label, uncontrolled study was conducted in 6 patients with advanced solid tumors (6 included in PK analysis) to evaluate the PK etc. of atezolizumab. Atezolizumab 10 or 20 mg/kg Q3W was to be administered intravenously, and serum atezolizumab concentrations were determined.

The PK parameters of atezolizumab after the first dose are shown in Table 13. The C_{max} and AUC_{inf} of atezolizumab were generally dose-proportional. The accumulation ratios based on (1) C_{max} and (2) C_{min}, at the last evaluable time point, in the 10 and 20 mg/kg groups, were (1) 1.47 ± 0.28 and 1.25 ± 0.26, respectively, and (2) 3.06 ± 1.65 and 2.53 ± 0.28, respectively.

Among 6 subjects tested for the presence of anti-atezolizumab antibodies, 1 tested positive for anti-atezolizumab antibodies. The neutralizing antibody assay was not performed.

Table 13. PK parameters of atezolizumab after the first dose

Dose (mg/kg)	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	$AUC_{0\text{-}21day}$ (μg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	V_{ss} (L)
10	220 ± 21.9	2290 ± 101	1670 ± 49.3	11.7 ± 0.969	0.24 ± 0.06	3.72 ± 1.14
20	536 ± 49.4	6630 ± 668	4500 ± 398	13.0 ± 1.32	0.21 ± 0.06	3.82 ± 0.718

Mean ± SD, n = 3

6.2.2 Foreign clinical study

6.2.2.1 Foreign phase I study (CTD 5.3.3.2.1, Study PCD4989g [ongoing since June 2011 (data cutoff date of December 2, 2014)])

An open-label, uncontrolled study was conducted in 483 patients with advanced solid tumors or hematologic malignancies (473 included in PK analysis) to evaluate the PK etc. of atezolizumab. Atezolizumab 0.01, 0.03, 0.1, 0.3, 1, 3, 10, or 20 mg/kg, or 1200 mg/body Q3W was to be administered intravenously, and serum atezolizumab concentrations were determined.

The PK parameters of atezolizumab after the first dose are shown in Table 14. The C_{max} and $AUC_{0\text{-}21day}$ were generally dose-proportional over the dose range of 1 to 20 mg/kg, including 1200 mg/body. Since the accumulation ratios[9)] based on (1) C_{max} and (2) C_{min} were almost constant [(1) 1.21-1.41 and (2) 2.04-2.39] at Cycles 4 to 8, serum atezolizumab concentrations were considered to reach a steady-state by Cycle 4.

Among 439 subjects tested for the presence of anti-atezolizumab antibodies, 139 tested positive for anti-atezolizumab antibodies, including 11 with neutralizing antibodies.

9) Calculated based on the combined data from patients receiving ≥1 mg/kg of atezolizumab.

Table 14. PK parameters of atezolizumab after the first dose

Dose[*1]	n	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	$AUC_{0\text{-}21day}$ (μg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	V_{ss} (L)
0.03 mg/kg	1	0.372	—	—	—	—	—
0.1 mg/kg	1	0.955	1.62	1.62	—	4.23	5.30
0.3 mg/kg	3	6.57 ± 1.33	31.2, 34.8[*2]	31.6 ± 2.59	—	0.54, 0.67[*2]	2.54, 3.07[*2]
1 mg/kg	3	26.0 ± 4.08	221, 230[*2]	202 ± 17.1	26.6[*3]	0.26, 0.34[*2]	1.87, 3.77[*2]
3 mg/kg	3	77.3 ± 19.9	557, 761[*2]	622 ± 192	21.8[*3]	0.39, 0.45[*2]	4.93, 5.48[*2]
10 mg/kg	36	268 ± 41.5	2830 ± 611[*4]	2270 ± 384[*5]	25.8 ± 14.7[*6]	0.34 ± 0.11[*4]	4.54 ± 1.61[*4]
15 mg/kg	232	368 ± 200	3450 ± 1050[*7]	2820 ± 677[*5]	19.3 ± 7.35[*5]	0.37 ± 0.09[*7]	5.00 ± 1.09[*7]
20 mg/kg	145	494 ± 130	4980 ± 1150[*6]	3950 ± 783[*8]	25.2 ± 9.65[*9]	0.30 ± 0.09[*6]	4.03 ± 1.06[*6]
1200 mg/body	40	440 ± 146	—	—	—	—	—

Mean ± SD (Individual values are listed for n = 1 or 2)
*1: No PK parameters were calculated for the 0.01 mg/kg dose group. *2: n = 2, *3: n = 1, *4: n = 9, *5: n = 29, *6: n = 10, *7: n = 17, *8: n = 32, *9: n = 28, —: Not calculated

6.2.3. Analysis of relationship between exposure and change in QT/QTc interval

In a foreign phase I study (Study PCD4989g), an analysis of the relationship between ΔQTcF and serum atezolizumab concentration was performed using a linear mixed-effects model. There was no clear relationship between serum atezolizumab concentration and ΔQTcF. The upper bound of the 90% confidence interval (CI) for the mean change in ΔQTcF at serum atezolizumab concentrations tested was below 10 ms.

The applicant explained that given the above results etc., atezolizumab administered at the proposed dosing regimen is unlikely to prolong the QT/QTc interval.

6.2.4 PPK analyses

PPK analyses were performed by non-linear mixed-effects modeling (software, NONMEM Version 7.3.0), based on atezolizumab PK data from a total of 2 studies, i.e. a Japanese phase I study (Study JO28944) and a foreign phase I study (Study PCD4989g) (4563 PK samples from 472 subjects). The PK of atezolizumab were described by a 2-compartment model with first-order elimination.

Age, body weight, albumin, bilirubin, AST, ALT, estimated glomerular filtration rate (eGFR), creatinine clearance (CrCL), tumor burden, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), race, region, anti-atezolizumab antibody status, PD-L1 status (IC 0, IC 1, IC 2, or IC 3 or TC 0, TC 1, TC 2, or TC 3), formulation, brain metastases, liver metastases, visceral metastases, the number of metastatic sites, and cancer type were tested as potential covariates on the CL, V_1, and V_2 of atezolizumab. (1) Albumin, anti-atezolizumab antibody status, tumor burden, and body weight, (2) albumin, body weight, and sex, and (3) sex were identified as significant covariates for (1) CL, (2) V_1, and (3) V_2.

The applicant's explanation:
Since the extents of the effects of the above factors identified as significant covariates on (1) CL, (2) V_1, and (3) V_2 were similar to inter-individual variabilities of these parameters (29%, 14%, and 34%, respectively), the impact of these covariates on the PK of atezolizumab should be limited.

6.2.5 Exposure-efficacy/safety relationship

6.2.5.1 Exposure-efficacy relationship

Based on the data from a global phase III study (OAK study), a logistic regression analysis was performed to assess the relationship between atezolizumab exposure (AUC_{ss}[10)]) and the response rate. The results showed that the response rate tended to increase with increasing atezolizumab exposure.

6.2.5.2 Exposure-safety relationship

Based on the data from (1) a global phase III study (OAK study) and (2) a foreign phase I study (Study PCD4989g), foreign phase II studies (POPLAR study, FIR study), and a global phase II study (BIRCH study), a logistic regression analysis was performed to assess the relationship between atezolizumab exposure [(1) AUC_{ss}[10)] and (2) AUC_{ss}[11)]] and the incidence of Grade ≥3 adverse events. The results showed no clear relationship between atezolizumab exposure and the incidence of Grade ≥3 adverse events.

6.2.6 Effect of renal or hepatic impairment on PK of atezolizumab

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

- Since atezolizumab is considered to be cleared via a pathway mediated by binding to the target antigen and via the reticuloendothelial system, decreased renal or hepatic function is unlikely to affect the PK of atezolizumab.
- In the PPK analysis, eGFR, CrCL, bilirubin, AST, ALT, or liver metastasis was not identified as a significant covariate on the PK parameters of atezolizumab [see Section 6.2.4].

6.2.7 Differences in PK of atezolizumab between Japanese and non-Japanese populations

The applicant explained that taking account of the following points etc., there were no clear differences in the PK of atezolizumab between Japanese and non-Japanese populations.

- With respect to the PK parameters of atezolizumab administered at 10 and 20 mg/kg in a Japanese phase I study (Study JO28944) and a foreign phase I study (Study PCD4989g), there were no clear differences between Japanese and non-Japanese patients [see Sections 6.2.1.1 and 6.2.2.1].
- With respect to serum atezolizumab concentrations following administration of atezolizumab 1200 mg/body in a global phase II study (BIRCH study) and a global phase III study (OAK study), there were no clear differences between Japanese and non-Japanese patients (Table 15).

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10) The PPK model developed for PPK analyses [see Section 6.2.4] was externally validated using atezolizumab PK data from a global phase III study (OAK study) (2754 samples from 596 subjects), and atezolizumab exposure was estimated with the developed PPK model (software, NONMEM Version 7.3.0).

11) The PPK model developed for PPK analyses [see Section 6.2.4] was externally validated using atezolizumab PK data from foreign phase II studies (POPLAR study, FIR study) and a global phase II study (BIRCH study) (3891 samples from 920 subjects), and atezolizumab exposure was estimated with the developed PPK model (software, NONMEM Version 7.3.0).

Table 15. Serum atezolizumab concentrations following administration of atezolizumab 1200 mg/body (μg/mL)

Time point	BIRCH study				OAK study			
	n	Japanese	n	Non-Japanese	n	Japanese	n	Non-Japanese
After the first dose	27	474 ± 115	597	427 ± 221	56	452 ± 107	505	394 ± 127
Predose Cycle 2	25	92.0 ± 35.4	571	87.6 ± 42.0	46	98.2 ± 32.4	488	81.8 ± 30.6
Predose Cycle 3	21	144 ± 34.8	497	134 ± 58.0	40	162 ± 40.8	405	127 ± 56.1
Predose Cycle 4	20	176 ± 45.5	447	163 ± 71.6	35	188 ± 55.6	370	155 ± 66.7
Predose Cycle 8	11	229 ± 55.6	264	211 ± 89.6	18	224 ± 99.1	204	204 ± 99.5

Mean ± SD

6.R Outline of the review conducted by PMDA

6.R.1 Impact of anti-atezolizumab antibodies on PK of atezolizumab

The incidence of anti-atezolizumab antibodies was determined in a Japanese phase I study (Study JO28944), a foreign phase I study (Study PCD4989g), foreign phase II studies (POPLAR study, FIR study), a global phase II study (BIRCH study), and a global phase III study (OAK study). Of 1898 subjects evaluable for anti-atezolizumab antibodies, 691 (36.4%) developed anti-atezolizumab antibodies in serum after administration of atezolizumab. In the foreign phase I study (Study PCD4989g), the foreign phase II studies (POPLAR study, FIR study), and the global phase II study (BIRCH study) in which the neutralizing antibody assay was performed, neutralizing antibodies were detected in 12 of 1086 subjects (1.1%).

The applicant's explanation about the impact of anti-atezolizumab antibodies on the PK of atezolizumab:
Based on the time-matched PK/anti-atezolizumab antibody assay data from patients treated with the proposed dosing regimen of atezolizumab in the foreign phase I study (Study PCD4989g), the foreign phase II studies (POPLAR study, FIR study), the global phase II study (BIRCH study), and the global phase III study (OAK study), serum atezolizumab concentrations tended to be lower in antibody-positive patients than in antibody-negative patients (Table 16).

Based on the PPK analysis, the CL of atezolizumab was estimated to be 16% higher in antibody-positive patients than in antibody-negative patients, but this change was within the range of inter-individual variability of CL estimated in the PPK analysis (29%) [see Section 6.2.4].

However, since the possibility that the presence of atezolizumab in serum samples affected the results of the anti-atezolizumab antibody assay used in clinical studies cannot be ruled out [see Section 6.1.1.2], it is difficult to draw a definitive conclusion on the impact of anti-atezolizumab antibodies on the PK of atezolizumab.

Table 16. Serum atezolizumab concentrations after administration of atezolizumab 1200 mg/body (μg/mL)

Time point	n	Anti-atezolizumab antibody-positive patients	n	Anti-atezolizumab antibody-negative patients
Predose Cycle 2	416	70.7 ± 37.0	990	89.2 ± 38.5
Predose Cycle 3	257	98.4 ± 52.7	902	137 ± 54.0
Predose Cycle 4	195	126 ± 66.5	873	163 ± 67.0
Predose Cycle 8	92	174 ± 73.8	475	214 ± 94.4

Mean ± SD

PMDA's discussion:

PMDA accepted the applicant's explanation. However, it is necessary to continue to collect information on the impact of anti-atezolizumab antibodies on the PK of atezolizumab and appropriately provide any new finding to healthcare professionals in clinical practice.

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 6 studies presented in Table 17: 1 Japanese phase I study, 1 foreign phase I study, 1 global phase II study, 2 foreign phase II studies, and 1 global phase III study.

Table 17. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study Identity	Phase	Study population	No. of subjects enrolled	Dosing regimen (all via intravenous infusion)	Main endpoints
Evaluation	Japan	JO28944	I	Patients with advanced solid tumors	6	Atezolizumab 10 or 20 mg/kg Q3W	Safety PK
	Global	BIRCH	II	TC2/3 or IC2/3 patients with advanced or recurrent NSCLC Cohort 1: No prior chemotherapy Cohort 2: 1 prior platinum-containing chemotherapy Cohort 3: ≥2 prior chemotherapies including 1 platinum	Cohort 1 142 Cohort 2 271 Cohort 3 254	Atezolizumab 1200 mg/body Q3W	Efficacy Safety
		OAK	III	Patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy	1225 (1) 613 (2) 612	(1) Atezolizumab 1200 mg/body Q3W (2) DOC 75 mg/m^2 Q3W	Efficacy Safety
	Foreign	PCD4989g	I	Patients with advanced solid tumors or hematologic malignancies	483	Atezolizumab 0.01-20 mg/kg or 1200 mg/body Q3W	Safety PK
		FIR	II	TC2/3 or IC2/3 patients with advanced or recurrent NSCLC Cohort 1: No prior chemotherapy Cohort 2: A prior platinum-containing chemotherapy without restriction to the maximum number of prior therapies Cohort 3: A prior platinum-containing chemotherapy without restriction to the maximum number of prior therapies, and previously treated brain metastases	Cohort 1 31 Cohort 2 94 Cohort 3 13	Atezolizumab 1200 mg/body Q3W	Efficacy Safety
		POPLAR	II	Patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy	287 (1) 144 (2) 143	(1) Atezolizumab 1200 mg/body Q3W (2) DOC 75 mg/m^2 Q3W	Efficacy Safety

The clinical studies are summarized below. The main adverse events other than deaths observed in the clinical studies are described in Section "7.2 Adverse events etc. observed in clinical studies." PK data are described in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase I study (CTD 5.3.3.2.2, Study JO28944 [ongoing since August 2013 (data cutoff date of November 15, 2014)])

An open-label, uncontrolled study was conducted at 2 sites in Japan to evaluate the safety, PK, etc. of

atezolizumab in patients with advanced solid tumors (target sample size, 6-12 subjects).

Atezolizumab 10 or 20 mg/kg Q3W was to be administered intravenously, and subjects were allowed to continue treatment until disease progression or a criterion for discontinuation was met.

All of 6 subjects enrolled in the study received atezolizumab and were included in safety analyses.

The dose-limiting toxicity (DLT) evaluation period was until Day 21 of Cycle 1, and no DLTs were observed.

Regarding safety, there were no deaths during the atezolizumab treatment period or within 30 days after the last dose of atezolizumab.

7.1.2 Global studies

7.1.2.1 Global phase II study (CTD 5.3.5.2.1, BIRCH study [ongoing since January 2014 (data cutoff date of May 28, 2015)])

An open-label, uncontrolled study was conducted at 106 sites in 19 countries including Japan to evaluate the efficacy and safety of atezolizumab in TC2/3 or IC2/3 patients with advanced or recurrent NSCLC. The BIRCH study comprised three patient cohorts: Cohort 1 (no prior chemotherapy[12)]) (target sample size, approximately 127 subjects), Cohort 2 (1 prior platinum-containing chemotherapy[13)]) (target sample size, approximately 254 subjects), and Cohort 3 (≥2 prior chemotherapies including 1 platinum[13)]) (target sample size, ≥254 subjects).

Atezolizumab 1200 mg/body Q3W was to be administered intravenously, and subjects were allowed to continue treatment until disease progression or a criterion for discontinuation was met.

Of 667 subjects enrolled in the study (142 in Cohort 1, 271 in Cohort 2, 254 in Cohort 3), 659 subjects (139 in Cohort 1, 267 in Cohort 2, 253 in Cohort 3) after excluding 8 subjects who did not receive atezolizumab were included in the efficacy analysis population. The same population was used as the safety population.

The primary endpoint for the study was the independent review facility (IRF)-assessed response rate per Response Evaluation Criteria in Solid Tumors (RECIST) ver1.1. Seven subgroups (1) to (7) presented in Table 18 were prespecified according to cohort and PD-L1 status. Efficacy analyses were to be performed in these subgroups. In order to control the overall type I error rate at a two-sided alfa-level of 0.05, the analysis of the response rate was to follow a hierarchical fixed-sequence procedure [(1)→(7)]. Each test was performed at a two-sided alfa of 0.05, with subsequent testing in the sequence being performed if the preceding test was statistically significant.

[12)] Patients with an *EGFR* mutation or an *ALK* rearrangement must have been previously treated with an EGFR or ALK tyrosine kinase inhibitor, respectively.

[13)] Patients with an *EGFR* mutation or an *ALK* rearrangement must have been previously treated with a platinum-based therapy plus an EGFR or ALK tyrosine kinase inhibitor, respectively.

The results of the primary efficacy endpoint of the IRF-assessed response rate per RECIST ver1.1[14)] are shown in Table 18.

Table 18. Best overall response and response rate
(RECIST v1.1, IRF, Efficacy analysis population, data cutoff date of May 28, 2015)

Best overall response	n (%)			
	(1)	(2)	(3)	(4)
	Cohort 3 TC3 or IC3 N = 115	Cohorts 2 and 3 TC3 or IC3 N = 237	Cohort 3 TC3 or IC2/3 N = 236	Cohort 3 TC2/3 or IC2/3 N = 253
CR	2 (1.7)	3 (1.3)	4 (1.7)	4 (1.6)
PR	29 (25.2)	57 (24.1)	39 (16.5)	40 (15.8)
SD	46 (40.0)	83 (35.0)	91 (38.6)	97 (38.3)
PD	31 (27.0)	77 (32.5)	79 (33.5)	86 (34.0)
NE	7 (6.1)	17 (7.2)	23 (9.7)	26 (10.3)
Response (CR+PR) (Response rate [95% CI*] (%))	31 (27.0 [19.1, 36.0])	60 (25.3 [19.9, 31.4])	43 (18.2 [13.5, 23.7])	44 (17.4 [12.9, 22.6])
P-value (two-sided)	<0.0001	<0.0001	<0.0001	<0.0001

Best overall response	n (%)		
	(5)	(6)	(7)
	Cohorts 2 and 3 TC3 or IC2/3 N = 483	Cohorts 2 and 3 TC2/3 or IC2/3 N = 520	Cohorts 1, 2, and 3 TC3 or IC3 N = 302
CR	5 (1.0)	5 (1.0)	4 (1.3)
PR	81 (16.8)	85 (16.3)	73 (24.2)
SD	169 (35.0)	179 (34.4)	104 (34.4)
PD	182 (37.7)	197 (37.9)	94 (31.1)
NE	46 (9.5)	54 (10.4)	27 (8.9)
Response (CR+PR) (Response rate [95% CI*] (%))	86 (17.8 [14.5, 21.5])	90 (17.3 [14.2, 20.8])	77 (25.5 [20.7, 30.8])
P-value (two-sided)	<0.0001	<0.0001	<0.0001

*: Clopper-Pearson method

Regarding safety, 11 of 139 subjects (7.9%) in Cohort 1, 23 of 267 subjects (8.6%) in Cohort 2, and 29 of 253 subjects (11.5%) in Cohort 3 died during the atezolizumab treatment period or within 30 days after the last dose of atezolizumab. The causes of deaths other than disease progression (9 in Cohort 1, 14 in Cohort 2, 21 in Cohort 3) were respiratory failure; and cerebral infarction (1 subject each) in Cohort 1, pneumonia; pneumonia aspiration; pneumonitis; lung infection; cardiopulmonary failure; cardiac arrest; septic shock; hepatic failure; and sudden death (1 subject each) in Cohort 2, and pneumonia (3 subjects); and respiratory distress; acute coronary syndrome; internal haemorrhage; sudden death; and death (1 subject each) in Cohort 3. A causal relationship to atezolizumab could not be ruled out for 1 case of pneumonia in Cohort 3.

14) The historical control response rates for (1) Cohort 3, (2) Cohorts 2 and 3, and (3) Cohorts 1, 2, and 3 were determined to be (1) 5%, (2) 7%, and (3) 15%, based on the following information.
(1) The results from a clinical study in patients with advanced or recurrent NSCLC who have received ≥2 prior chemotherapy regimens (*Lung Cancer*. 2003;39:55-61, etc.).
(2) The results from a clinical study in patients with advanced or recurrent NSCLC who have received ≥1 prior chemotherapy regimen (*J Clin Oncol.* 2004;22:1589-97, etc.), and patients were planned to be enrolled in a 1:1 ratio to Cohort 2 or 3.
(3) The results from a clinical study in chemotherapy-naïve patients with advanced or recurrent NSCLC (*Ann Oncol.* 2010;21:1804-9, etc.), and patients were planned to be enrolled in a 1:4 ratio to Cohort 1 or Cohorts 2 and 3.

7.1.2.2 Global phase III study (CTD 5.3.5.1.1, OAK study [ongoing since March 2014 (data cutoff date of July 7, 2016)])

An open-label, randomized, controlled study was conducted at 194 sites in 31 countries including Japan to evaluate the efficacy and safety of atezolizumab compared with docetaxel hydrate (DOC) in patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy[13] (target sample size, 1100 subjects[15]).

Subjects in the atezolizumab group were to receive atezolizumab 1200 mg/body Q3W intravenously and subjects in the DOC group were to receive DOC 75 mg/m^2 Q3W intravenously. Subjects were allowed to continue treatment until disease progression or a criterion for discontinuation was met.

The intention-to-treat (ITT) population consisted of 1225 subjects who were enrolled in the study and randomized (613 in the atezolizumab group, 612 in the DOC group). Among the ITT population, the first 850 randomized subjects (425 in the atezolizumab group, 425 in the DOC group) were included in the Primary Population (PP), which was used as the efficacy analysis population. Among the ITT population, 1187 subjects (609 in the atezolizumab group, 578 in the DOC group) after excluding 38 subjects who did not receive study drug (5 in the atezolizumab group, 33 in the DOC group) were included in the safety population (1 subject who was assigned to the DOC group but mistakenly received atezolizumab was handled as the atezolizumab group).

The primary endpoint for the study was overall survival (OS). At the time of initiating the study, the primary analysis was to be performed in "the IC2/3 subgroup," "the IC1/2/3 subgroup," and "the ITT population."

However, since the results of the second interim analysis of the POPLAR study showed that high efficacy is expected in the TC3 or IC3 subgroup and the TC3 or IC2/3 subgroup, the statistical analysis plan was modified to perform the primary analysis of the OAK study in "the TC3 or IC3 subgroup," "the TC3 or IC2/3 subgroup," and "the ITT population" (Protocol Version 4, as of [redacted]). Then, the results of the final analysis of the POPLAR study suggested the efficacy of atezolizumab, regardless of PD-L1 status, and even the first 850 randomized subjects were considered to be sufficient to evaluate the efficacy of atezolizumab. Thus, the statistical analysis plan was modified again to perform the primary analysis in (1) "the TC1/2/3 or IC1/2/3 subgroup" and (2) "the ITT population" when approximately 595 deaths have occurred in the PP (Protocol Version 6, as of [redacted]). In order to control the overall type I error rate in the evaluation of OS in the PP, alpha was split between "the TC1/2/3 or IC1/2/3 subgroup" and "the ITT population" (0.02 and 0.03 [two-sided], respectively).

[15] At the time of initiating the study, the target sample size was 850 subjects in order to have approximately 255 IC2/3 patients and 425 IC1/2/3 patients. Then, since the results of the second interim analysis of the POPLAR study showed that high efficacy is expected in TC3 or IC3 patients, the target sample size for the study was increased to 1100 subjects (up to 1300 subjects) in order to ensure at least 220 TC3 or IC3 patients (Protocol Version 4, as of [redacted]).

Regarding efficacy, the results of the primary OS analysis and the Kaplan-Meier curves for OS in the PP are shown in Table 19 and Figures 1 and 2, respectively (data cutoff date of July 7, 2016), demonstrating the superiority of atezolizumab over DOC.

Table 19. Results of primary OS analysis (PP, data cutoff date of July 7, 2016)

	(1) TC1/2/3 or IC1/2/3 subgroup		(2) ITT population	
	Atezolizumab	DOC	Atezolizumab	DOC
N	241	222	425	425
No. of deaths (%)	151 (62.7)	149 (67.1)	271 (63.8)	298 (70.1)
Median [95% CI] (months)	15.7 [12.6, 18.0]	10.3 [8.8, 12.0]	13.8 [11.8, 15.7]	9.6 [8.6, 11.2]
Hazard ratio [95% CI][*1]	0.74 [0.58, 0.93]		0.73 [0.62, 0.87]	
P-value (two-sided)[*2]	0.0102[*3]		0.0003[*4]	

*1: Cox regression stratified by PD-L1 expression (IC0, IC1, IC2, IC3), the number of prior chemotherapy regimens (1, 2), and histology (squamous, non-squamous), *2: Log-rank test stratified by PD-L1 expression (IC0, IC1, IC2, IC3), the number of prior chemotherapy regimens (1, 2), and histology (squamous, non-squamous), *3: A significance level (two-sided) of 0.02, *4: A significance level (two-sided) of 0.03

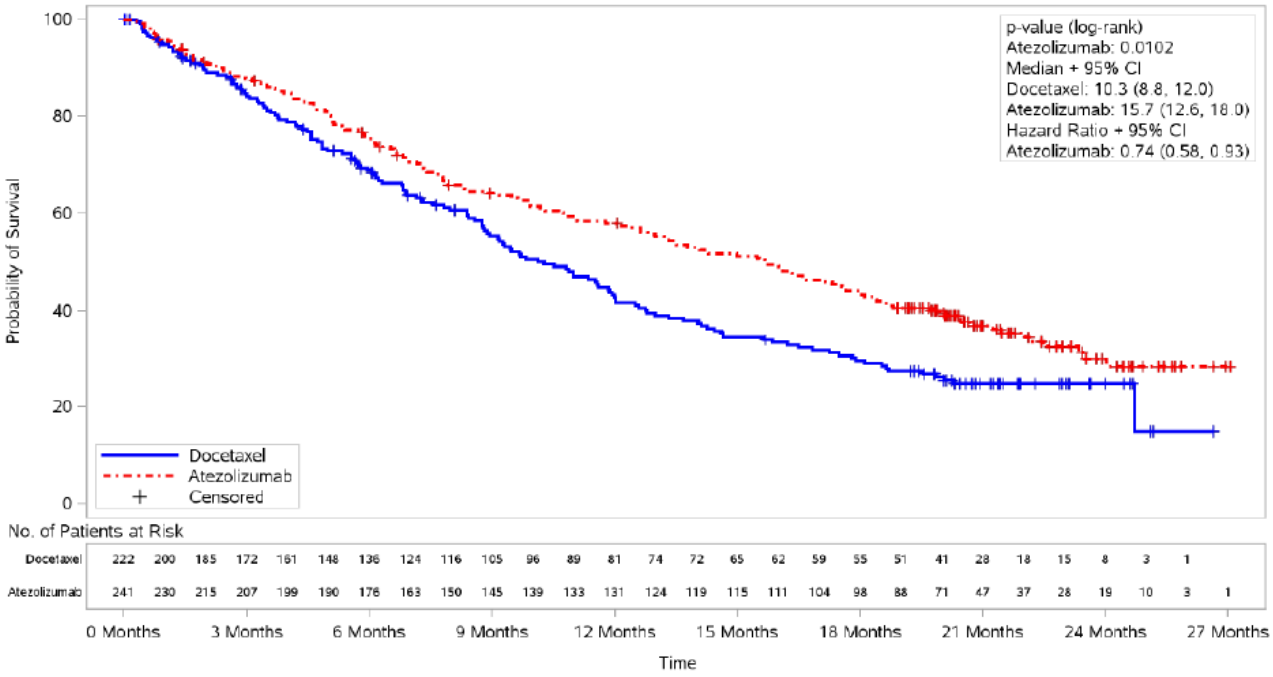


Figure 1. Kaplan-Meier curves for OS at the time of primary analysis [(1) TC1/2/3 or IC1/2/3 subgroup, data cutoff date of July 7, 2016]

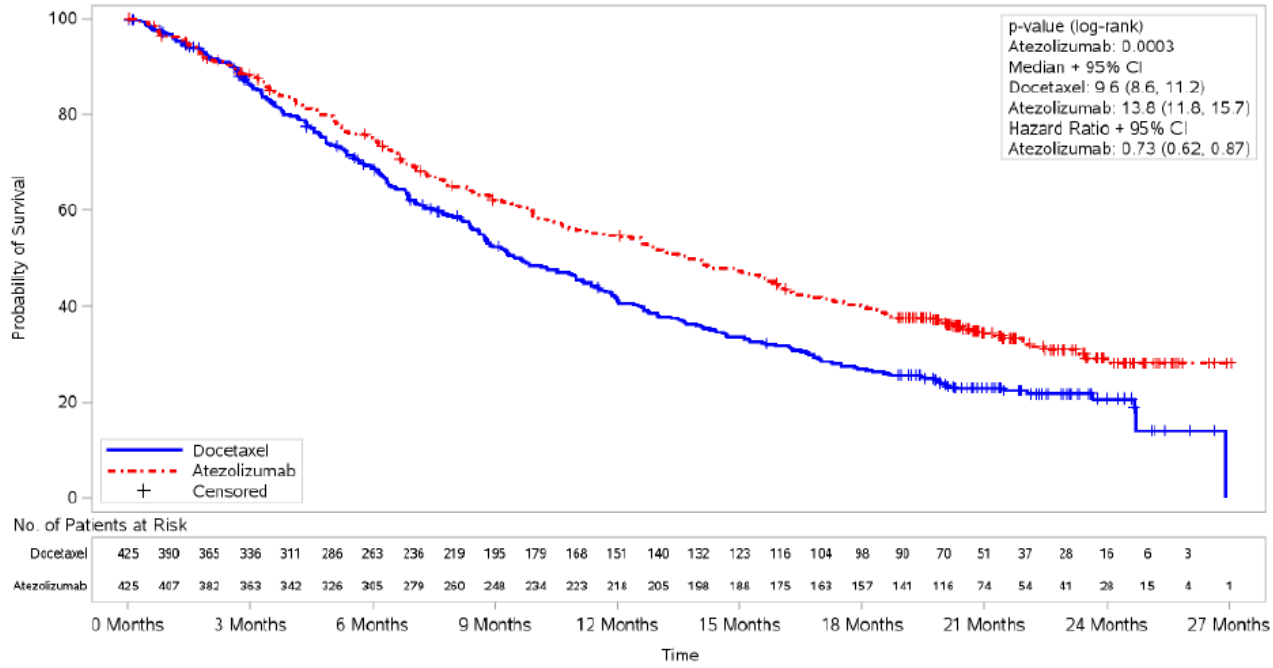


Figure 2. Kaplan-Meier curves for OS at the time of primary analysis [(2) ITT population, data cutoff date of July 7, 2016]

Regarding safety, 62 of 609 subjects (10.2%) in the atezolizumab group and 42 of 578 subjects (7.3%) in the DOC group died during the study treatment period or within 30 days after the last dose of study drug. The causes of deaths other than disease progression (51 in the atezolizumab group, 28 in the DOC group) were sepsis (2 subjects); and pneumonia; septic shock; dyspnoea; pulmonary haemorrhage; sudden death; death; myocardial ischaemia; renal failure; and unknown (1 subject each) in the atezolizumab group and pneumonia;

respiratory tract infection; and sudden death (2 subjects each); and sepsis; dyspnoea; pulmonary haemorrhage; haemoptysis; pneumothorax spontaneous; pulmonary embolism; respiratory distress; and lower gastrointestinal haemorrhage (1 subject each) in the DOC group. A causal relationship to study drug could not be ruled out for 1 case of respiratory tract infection in the DOC group.

7.1.3 Foreign clinical studies

7.1.3.1 Foreign phase I study (CTD 5.3.3.2.1, Study PCD4989g [ongoing since June 2011 (data cutoff date of December 2, 2014)])

An open-label, uncontrolled study was conducted at 20 sites outside Japan to evaluate the safety, PK, etc. of atezolizumab in patients with advanced solid tumors or hematologic malignancies (target sample size, 656-689 subjects).

Atezolizumab 0.01 to 20 mg/kg or 1200 mg/body Q3W was to be administered intravenously. Subjects were allowed to continue treatment until disease progression or a criterion for discontinuation was met.

Among 483 subjects enrolled in the study, 481 subjects who received atezolizumab were included in the safety population.

The DLT evaluation period was until Day 21 of Cycle 1, and the tolerability of atezolizumab was evaluated. No DLTs were observed.

Regarding safety, 46 of 481 subjects (9.6%) died during the atezolizumab treatment period or within 30 days after the last dose of atezolizumab. The causes of deaths other than disease progression (1 in the 10 mg/kg group, 16 in the 15 mg/kg group, 11 in the 20 mg/kg group, 2 in the 1200 mg/body group) were pneumonia (1 subject) in the 10 mg/kg group, acute respiratory failure; alcohol abuse; fall; obstructive airways disorder; sepsis; systemic inflammatory response syndrome; and unknown (1 subject each) in the 15 mg/kg group, acute respiratory failure; cardiac tamponade; cardio-respiratory arrest; and unknown (1 subject each) in the 20 mg/kg group, and dyspnoea; hepatic haematoma; pulmonary hypertension; and unknown (1 subject each) in the 1200 mg/body group. A causal relationship to atezolizumab could not be ruled out for 1 case of cardio-respiratory arrest in the 20 mg/kg group and 1 case of pulmonary hypertension and 1 case of unknown in the 1200 mg/body group.

7.1.3.2 Foreign phase II study (CTD 5.3.5.2.2, FIR study [ongoing since May 2013 (data cutoff date of January 7, 2015)])

An open-label, uncontrolled study was conducted at 28 sites outside Japan to evaluate the efficacy and safety of atezolizumab in TC2/3 or IC2/3 patients with advanced or recurrent NSCLC. The FIR study comprised three patient cohorts: Cohort 1 (no prior chemotherapy) (target sample size, 45 subjects), Cohort 2 (a prior platinum-containing chemotherapy without restriction to the maximum number of prior therapies[5)]) (target sample size, 75 subjects), and Cohort 3 (a prior platinum-containing chemotherapy without restriction to the

maximum number of prior therapies,[5)] and previously treated brain metastases) (target sample size, 10 subjects).

Atezolizumab 1200 mg/body Q3W was to be administered intravenously. Subjects were allowed to continue treatment until disease progression or a criterion for discontinuation was met.

The efficacy analysis population consisted of 137 subjects who were enrolled in the study and received atezolizumab (31 in Cohort 1, 93 in Cohort 2, 13 in Cohort 3). The same population was used as the safety population.

The results of the primary efficacy endpoint of the investigator-assessed response rate per modified RECIST (*Clin Can Res*. 2009;15:7412-20, etc.) are shown in Table 20.

Table 20. Best overall response and response rate
(modified RECIST, Investigator assessment, Efficacy analysis population, data cutoff date of January 7, 2015)

Best overall response	n (%)		
	Cohort 1 N = 31	Cohort 2 N = 93	Cohort 3 N = 13
CR	1 (3.2)	2 (2.2)	0
PR	8 (25.8)	14 (15.1)	3 (23.1)
SD	15 (48.4)	34 (36.6)	4 (30.8)
PD	4 (12.9)	21 (22.6)	3 (23.1)
NE	3 (9.7)	22 (23.7)	3 (23.1)
Response (CR+PR)	9	16	3
(Response rate [95% CI*] (%))	(29.0 [14.2, 48.0])	(17.2 [10.2, 26.4])	(23.1 [5.0, 53.8])

*: Clopper-Pearson method

Regarding safety, 2 of 31 subjects (6.5%) in Cohort 1, 10 of 93 subjects (10.8%) in Cohort 2, and 2 of 13 subjects (15.4%) in Cohort 3 died during the atezolizumab treatment period or within 30 days after the last dose of atezolizumab. The causes of deaths other than disease progression (8 in Cohort 2, 2 in Cohort 3) were cardiac tamponade; and cardiac arrest (1 subject each) in Cohort 1 and constrictive pericarditis; and respiratory disorder (1 subject each) in Cohort 2. A causal relationship to study drug could not be ruled out for 1 case of constrictive pericarditis in Cohort 2.

7.1.3.3 Foreign phase II study (CTD 5.3.5.1.2, POPLAR study [ongoing since August 2013 (data cutoff date of May 8, 2015)])

An open-label, randomized, controlled study was conducted at 61 sites outside Japan to evaluate the efficacy and safety of atezolizumab in patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy[13)] (target sample size, approximately 300 subjects[16)]).

Subjects in the atezolizumab group were to receive atezolizumab 1200 mg/body Q3W intravenously and subjects in the DOC group were to receive DOC 75 mg/m^2 Q3W intravenously. Subjects were allowed to continue treatment until disease progression or a criterion for discontinuation was met.

[16)] Enrollment of patients was to be continued until a minimum of approximately 54 IC2 or IC3 patients were accrued. In the case that the IC2/3 prevalence was lower than 18%, up to a maximum of approximately 300 total patients could be enrolled.

All of 287 subjects who were enrolled in the study and randomized (144 in the atezolizumab group, 143 in the DOC group) were included in the ITT population, which was used as the efficacy analysis population. Among the ITT population, 277 subjects (142 in the atezolizumab group, 135 in the DOC group) after excluding 10 subjects who did not receive study drug were included in the safety population.

The primary endpoint for the study was OS. At the time of initiating the study, the final analysis was to be performed in "the IC2/3 subgroup" and "the ITT population." Three interim analyses (when approximately 30, 100, and 150 OS events have occurred, respectively) for safety data evaluation were to be performed prior to the final analysis (approximately 180 events), and an alfa of 0.0001, 0.0001, and 0.001 was spent for the first, second, and third planned interim analysis of OS, respectively. The final analysis was performed at a two-sided significance level of 0.0488. For evaluation of the results of the interim analyses of the study, an independent data monitoring committee was not established, and an internal monitoring committee constituted by the sponsor evaluated the efficacy and safety data.

However, the protocol was amended to allow for subgroup analyses based on PD-L1 expression on tumor cells, in addition to the efficacy analyses based on PD-L1 expression on tumor-infiltrating immune cells as specified in the protocol, and the statistical analysis plan (Version 1, as of [redacted]) prepared after the third interim analysis stated that the final analysis would be performed in (1) the TC2/3 or IC2/3 subgroup, (2) the TC1/2/3 or IC1/2/3 subgroup, (3) the ITT population, and (4) the TC3 or IC3 subgroup. In order to control the overall type I error rate at a two-sided significance level of 0.0488, the analysis of OS was to follow a hierarchical closed testing procedure [(1)→(2)→(3)→(4)]. Each test was performed at a two-sided alfa of 0.0488, with subsequent testing in the sequence being performed if the preceding test was statistically significant.

The results of the final analysis of the primary efficacy endpoint of OS and the Kaplan-Meier curves are shown in Table 21 and Figure 3, respectively.

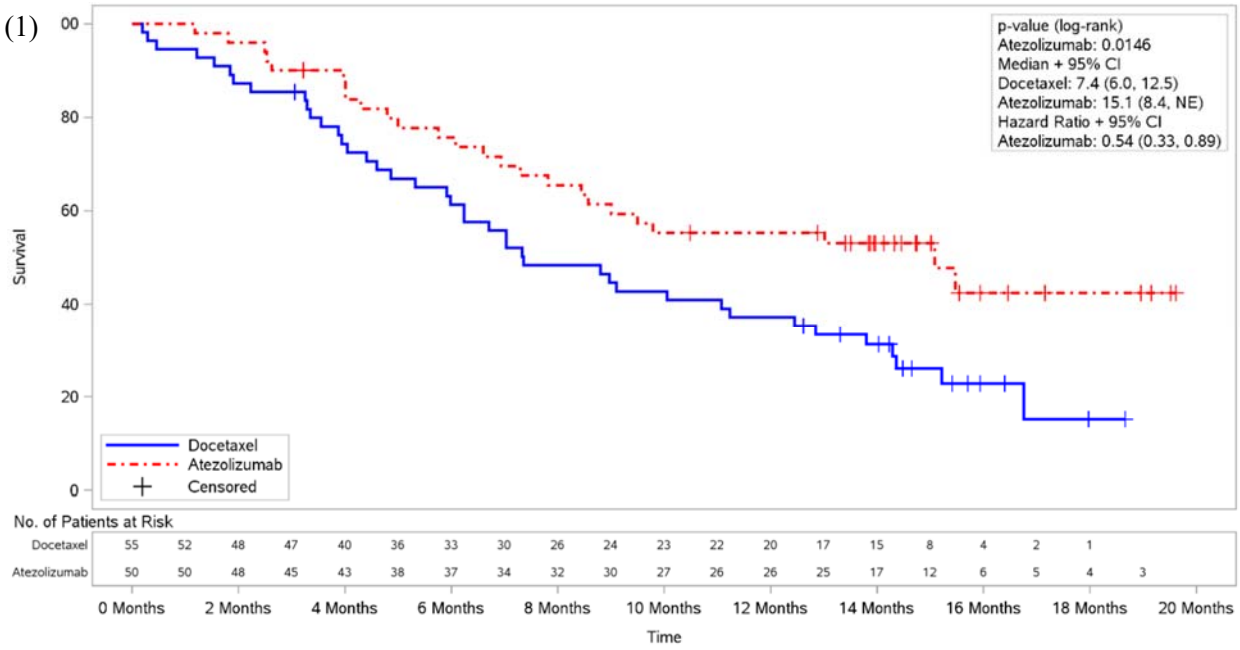
Table 21. Results of final analysis of OS (Final analysis population, data cutoff date of May 8, 2015)

	(1) TC2/3 or IC2/3 subgroup		(2) TC1/2/3 or IC1/2/3 subgroup	
	Atezolizumab	DOC	Atezolizumab	DOC
N	50	55	93	102
No. of deaths (%)	25 (50.0)	41 (74.5)	45 (48.4)	69 (67.6)
Median [95% CI] (months)	15.1 [8.4, NE]	7.4 [6.0, 12.5]	15.5 [11.0, NE]	9.2 [7.3, 12.8]
Hazard ratio [95% CI]	0.54 [0.33, 0.89]*1		0.59 [0.40, 0.85]*1	
P-value (two-sided)	0.0146*2		0.0050*2	

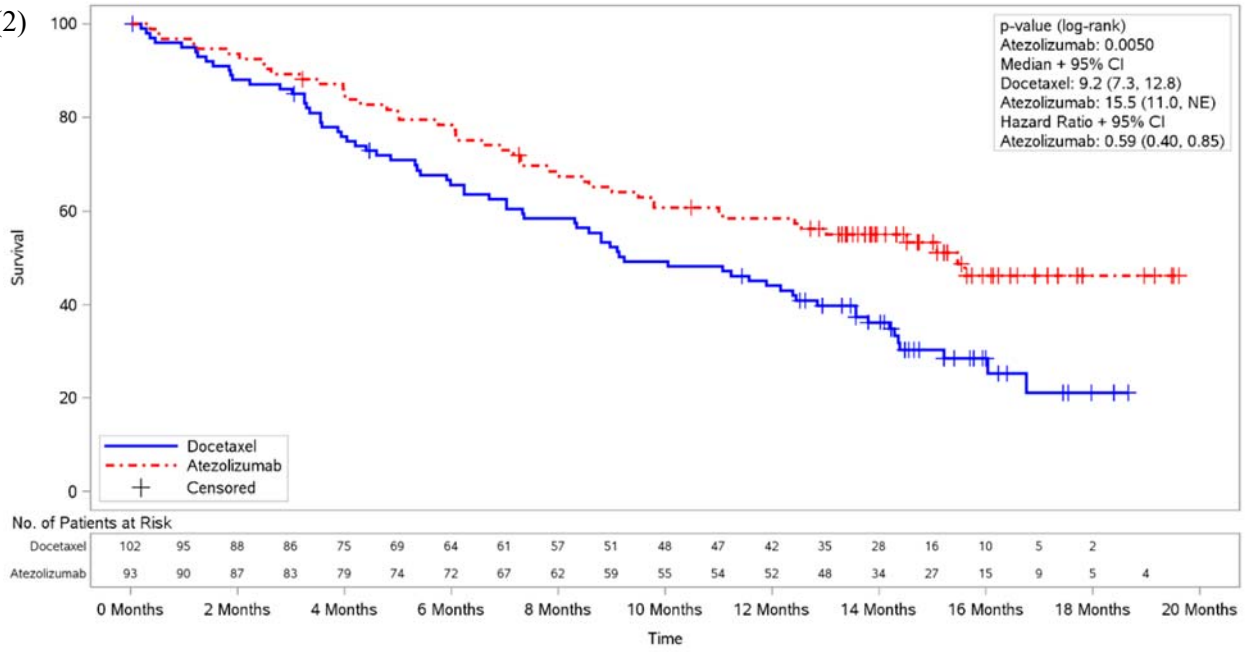
	(3) ITT population		(4) TC3 or IC3 subgroup	
	Atezolizumab	DOC	Atezolizumab	DOC
N	144	143	24	23
No. of deaths (%)	78 (54.2)	95 (66.4)	10 (41.7)	16 (69.6)
Median [95% CI] (months)	12.6 [9.7, 16.4]	9.7 [8.6, 12.0]	15.5 [9.8, NE]	11.1 [6.7, 14.4]
Hazard ratio [95% CI]	0.73 [0.53, 0.99]*3		0.49 [0.22, 1.07]*1	
P-value (two-sided)	0.0404*4		0.0684*2	

*1: Unstratified Cox regression, *2: Unstratified log-rank test, *3: Cox regression stratified by PD-L1expression (IC0, IC1, IC2, IC3), the number of prior lines of therapy (1, 2), and histology (squamous, non-squamous), *4: Log-rank test stratified by PD-L1 expression (IC0, IC1, IC2, IC3), the number of prior lines of therapy (1, 2), and histology (squamous, non-squamous)

(1)



(2)

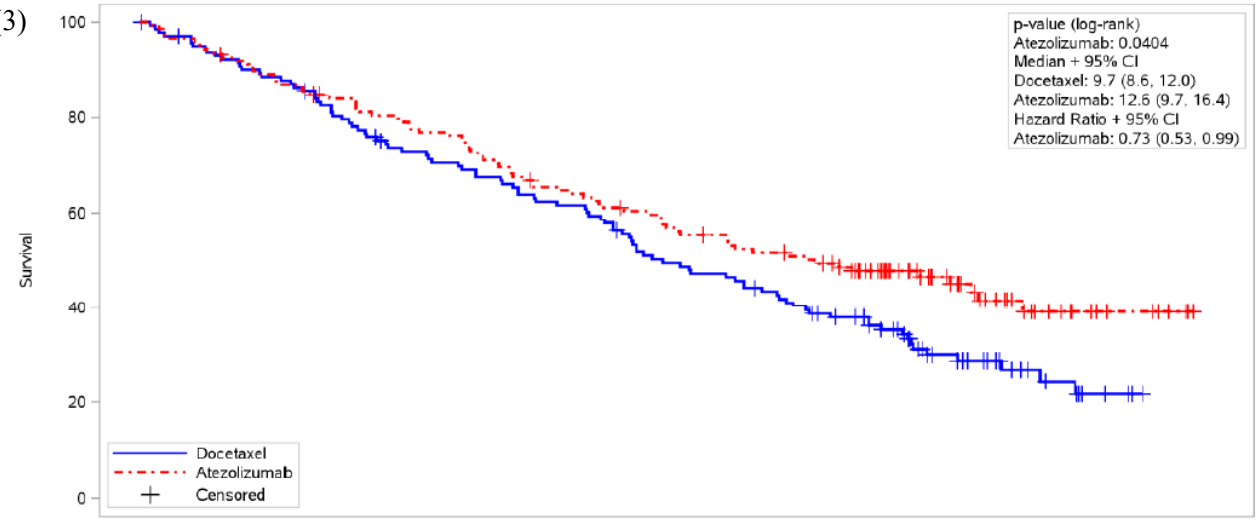


No. of Patients at Risk

	0 Months	2 Months	4 Months	6 Months	8 Months	10 Months	12 Months	14 Months	16 Months	18 Months	20 Months
Docetaxel	102	88	75	64	57	48	42	28	16	5	2
Atezolizumab	93	87	79	72	62	55	52	34	27	15	5

Time

(3)



No. of Patients at Risk

	0 Months	2 Months	4 Months	6 Months	8 Months	10 Months	12 Months	14 Months	16 Months	18 Months	20 Months
Docetaxel	143	123	106	92	82	65	54	30	17	3	
Atezolizumab	144	131	117	106	90	78	69	42	20	7	4

Time

(4)

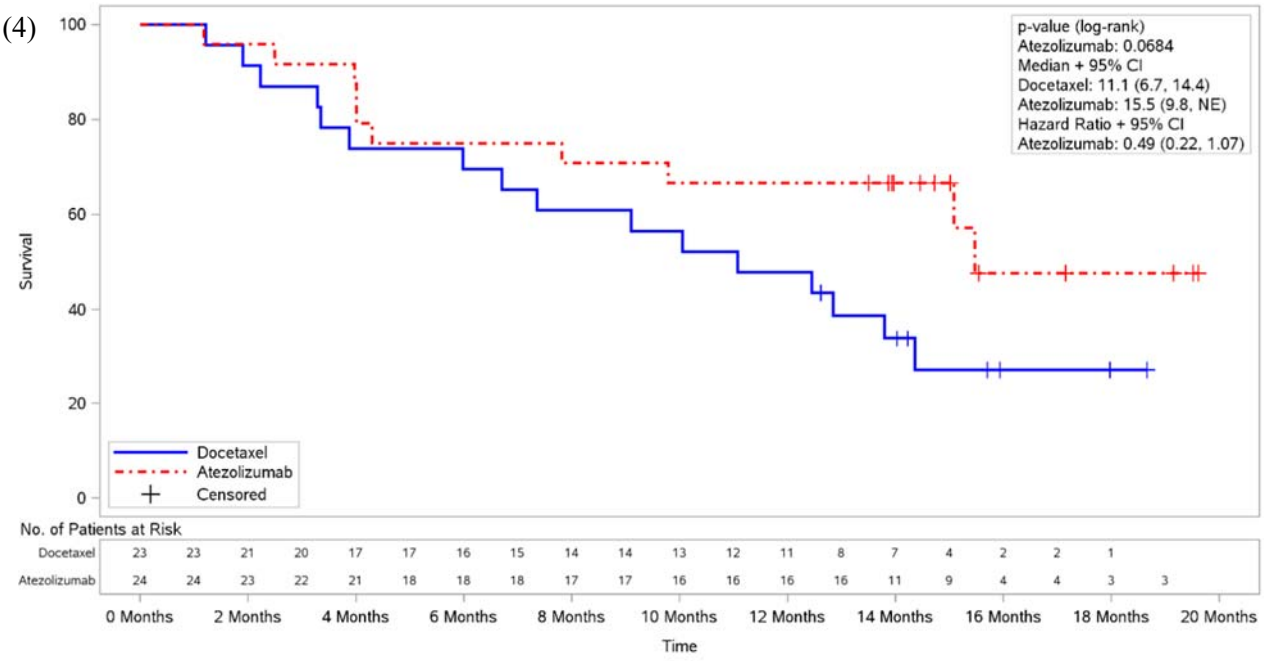


Figure 3. Kaplan-Meier curves for OS at the time of final analysis
[data cutoff date of May 8, 2015, (1) TC2/3 or IC2/3 subgroup, (2) TC1/2/3 or IC1/2/3 subgroup, (3) ITT population, (4) TC3 or IC3 subgroup]

Regarding safety, 16 of 142 subjects (11.3%) in the atezolizumab group and 10 of 135 subjects (7.4%) in the DOC group died during the study treatment period or within 30 days after the last dose of study drug. The causes of deaths other than disease progression (10 in the atezolizumab group, 5 in the DOC group) were cardiac failure; pneumothorax; embolism; ulcer haemorrhage; pneumonia; and pulmonary embolism (1 subject each) in the atezolizumab group and death; and sepsis (2 subjects each); and acute respiratory distress syndrome (1 subject) in the DOC group. A causal relationship to study drug could not be ruled out for 1 case of cardiac failure in the atezolizumab group and death; sepsis; and respiratory distress syndrome (1 subject each) in the DOC group.

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 atezolizumab is a global phase III study (OAK study) that evaluated the efficacy and safety of atezolizumab in patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy. PMDA decided to focus its review on this study. The efficacy of atezolizumab in Japanese patients is evaluated in terms of the consistency of the results between the overall population and the Japanese subgroup in the OAK 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 the efficacy of atezolizumab in patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy was demonstrated.

7.R.2.1 Control group and efficacy endpoint/results of evaluation

The applicant's explanation about the OAK study:

At the time of planning the OAK study, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer (NCCN guidelines) (v.1.2014) etc. recommended DOC based on a report that the efficacy of DOC versus best supportive care was demonstrated in patients with NSCLC previously treated with platinum-based chemotherapy (the study population for the OAK study) (*J Clin Oncol*. 2000;18:2095-103), etc. Thus, patients receiving DOC were selected as a control group. The OAK study demonstrated the superiority of atezolizumab over DOC in the primary endpoint of OS [see Section 7.1.2.2].

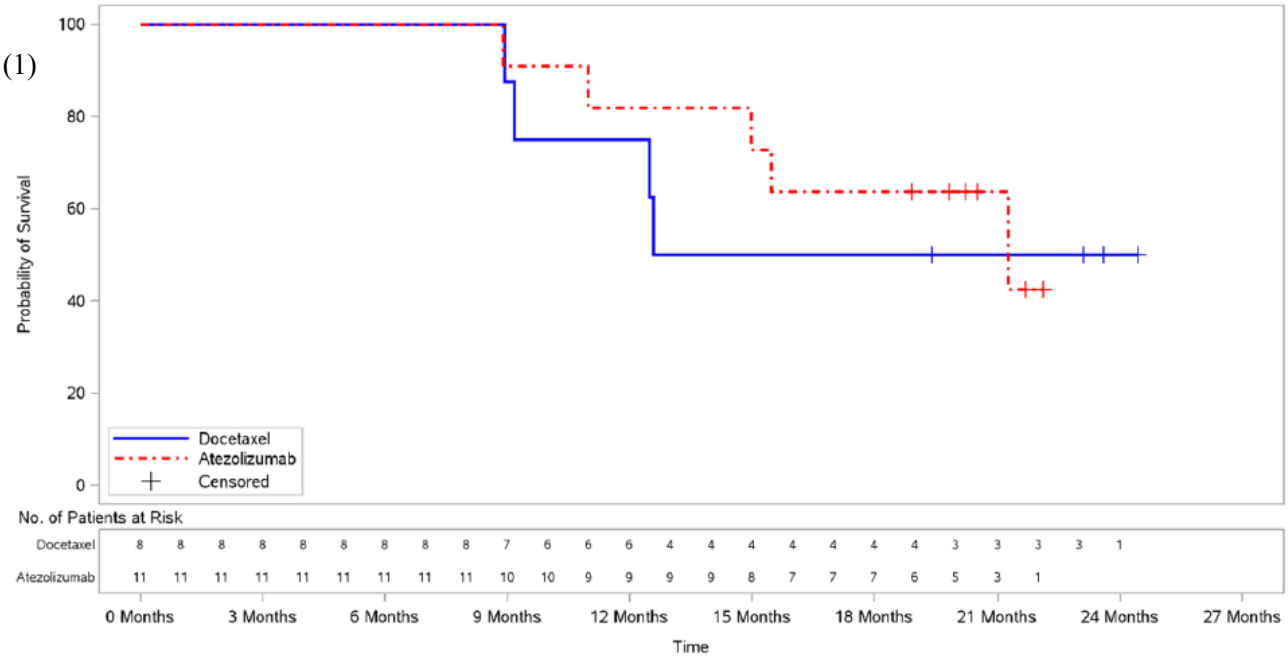
The results of the primary OS analysis in Japanese patients from the OAK study (the primary population [PP]) and the Kaplan-Meier curves are shown in Table 22 and Figure 4, respectively.

Table 22. The results of primary OS analysis in Japanese patients (PP, data cutoff date of July 7, 2016)

	(1) TC1/2/3 or IC1/2/3 subgroup		(2) ITT population	
	Atezolizumab	DOC	Atezolizumab	DOC
N	11	8	36	28
No. of events (%)	5 (45.5)	4 (50.0)	17 (47.2)	17 (60.7)
Median [95% CI] (months)	21.3 [15.0, NE]	NE [9.2, NE]	21.3 [11.0, NE]	17.0 [12.5, NE]
Hazard ratio [95% CI]*1	0.65 [0.05, 7.94]		0.78 [0.36, 1.66]	
P-value (two-sided)*2	0.7364		0.5110	

*1: Cox regression stratified by PD-L1 expression (IC0, IC1, IC2, IC3), the number of prior chemotherapy regimens (1, 2), and histology (squamous, non-squamous), *2: Log-rank test stratified by PD-L1 expression (IC0, IC1, IC2, IC3), the number of prior chemotherapy regimens (1, 2), and histology (squamous, non-squamous)

(1)



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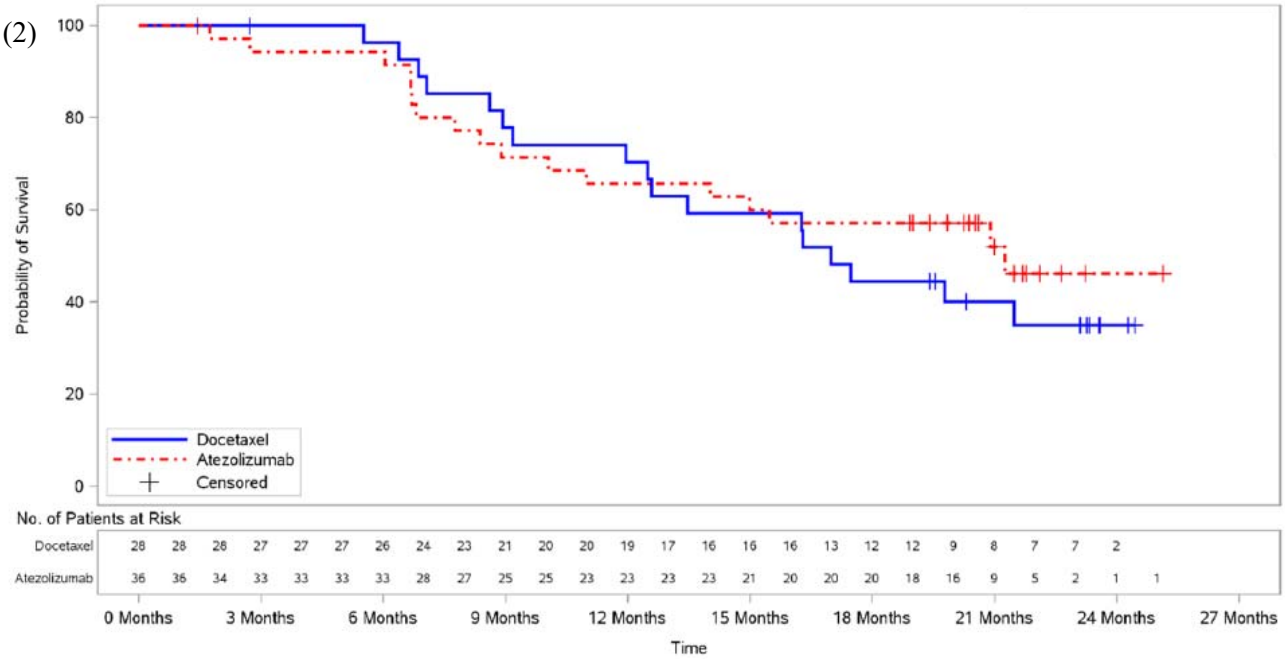


Figure 4. Kaplan-Meier curves for OS in Japanese patients at the time of primary analysis [data cutoff date of July 7, 2016, (1) TC1/2/3 or IC1/2/3 subgroup, (2) ITT population]

PMDA's discussion:

For the following reasons etc., PMDA concluded that the efficacy of atezolizumab was demonstrated in the study population for the OAK study.

- The OAK study demonstrated the superiority of atezolizumab over the control group in the primary endpoint of OS in the ITT population.
- Although the number of Japanese patients and the number of events in Japanese patients in the OAK study were limited, and there were limitations to efficacy evaluation, there was no trend towards clear differences in the results of analyses between the Japanese subgroup and the overall population.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events etc. observed in clinical studies"]

PMDA's conclusion:

Based on the following considerations, adverse events that require particular attention following administration of atezolizumab in patients with unresectable advanced or recurrent NSCLC are gastrointestinal disorders, skin disorders, hepatic dysfunction, neuropathies, thyroid dysfunction, adrenal dysfunction, pituitary dysfunction, diabetes mellitus (especially, type 1 diabetes mellitus), interstitial lung disease (ILD), infusion related reaction (IRR), encephalitis/meningitis, pancreatitis, renal dysfunction, myositis/dermatomyositis/rhabdomyolysis, and myasthenia gravis. Attention should be paid to the possible occurrence of these adverse events during treatment with atezolizumab.

However, atezolizumab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and interruption of atezolizumab, during treatment with atezolizumab.

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

The applicant's explanation about the safety profile of atezolizumab based on atezolizumab safety information from the OAK study.

Safety data from the OAK study are summarized in Table 23.

Table 23. Summary of safety data (OAK study)

	n (%)	
	Atezolizumab N = 609	DOC N = 578
All adverse events	573 (94.1)	555 (96.0)
Grade ≥3 adverse events	237 (38.9)	324 (56.1)
Adverse events leading to death	10 (1.6)	14 (2.4)
Serious adverse events	194 (31.9)	181 (31.3)
Adverse events leading to treatment discontinuation	46 (7.6)	108 (18.7)
Adverse events leading to dose interruption	151 (24.8)	116 (20.1)

In the OAK study, adverse events of any grade reported at a ≥5% higher incidence in the atezolizumab group than in the DOC group were cough (141 subjects [23.2%] in the atezolizumab group, 105 subjects [18.2%] in the DOC group), musculoskeletal pain (64 subjects [10.5%], 25 subjects [4.3%]), and pruritus (50 subjects [8.2%], 18 subjects [3.1%]). There were no Grade ≥3 adverse events, adverse events leading to death, serious adverse events, adverse events leading to treatment discontinuation, or adverse events leading to dose interruption that were reported at a ≥2% higher incidence in the atezolizumab group than in the DOC group.

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

Safety data from Japanese and non-Japanese patients in the atezolizumab group of the OAK study are summarized in Table 24.

Table 24. Summary of safety data (atezolizumab group of OAK study)

	n (%)	
	Japanese patients N = 56	Non-Japanese patients N = 553
All adverse events	52 (92.9)	521 (94.2)
Grade ≥3 adverse events	15 (26.8)	222 (40.1)
Adverse events leading to death	0	10 (1.8)
Serious adverse events	11 (19.6)	183 (33.1)
Adverse events leading to treatment discontinuation	10 (17.9)	36 (6.5)
Adverse events leading to dose interruption	12 (21.4)	139 (25.1)

In the OAK study, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were pyrexia (20 subjects [35.7%] in the Japanese subgroup, 88 subjects [15.9%] in the non-Japanese subgroup), stomatitis (7 subjects [12.5%], 12 subjects [2.2%]), and nasopharyngitis (11 subjects [19.6%], 20 subjects [3.6%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were lymphocyte count decreased (4

subjects [7.1%], 0 subjects). Serious adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were meningitis (3 subjects [5.4%], 0 subjects). Adverse events leading to treatment discontinuation reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were meningitis (3 subjects [5.4%], 0 subjects). There were no adverse events leading to death or dose interruption reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

PMDA's discussion:
Although there were adverse events reported at a higher incidence in the atezolizumab group than in the DOC group in the OAK study, most events were of Grade 2 or lower severity, etc. Thus, atezolizumab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and interruption of atezolizumab. However, particular attention should be paid to the possible occurrence of those events reported at a higher incidence in the atezolizumab group than in the DOC group during treatment with atezolizumab, and it is necessary to appropriately provide information on the incidences of those events to healthcare professionals in clinical practice, using information materials etc.

Although there is limited clinical experience with atezolizumab in Japanese patients with NSCLC, attention should be paid to the possible occurrence of events reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup (e.g., pyrexia), and it is necessary to appropriately provide information to healthcare professionals in clinical practice, using information materials etc.

In the following sections, based mainly on the atezolizumab safety results from the OAK study, PMDA conducted its safety review, focusing on adverse events reported at a higher incidence in the atezolizumab group than in the DOC group, adverse events that require attention following administration of other drugs with a similar mechanism of action to atezolizumab, etc.

7.R.3.2 Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders associated with atezolizumab:
As adverse events of gastrointestinal disorders, events in the MedDRA SOC "gastrointestinal disorders" were counted.

The incidence of gastrointestinal disorders in the OAK study is shown in Table 25.

Table 25. Gastrointestinal disorders reported by ≥5% of subjects in either group (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorders	303 (49.8)	25 (4.1)	326 (56.4)	43 (7.4)
Nausea	109 (17.9)	4 (0.7)	132 (22.8)	2 (0.3)
Constipation	108 (17.7)	2 (0.3)	82 (14.2)	1 (0.2)
Diarrhoea	94 (15.4)	4 (0.7)	141 (24.4)	11 (1.9)
Vomiting	74 (12.2)	2 (0.3)	63 (10.9)	5 (0.9)
Abdominal pain	20 (3.3)	1 (0.2)	38 (6.6)	5 (0.9)
Stomatitis	19 (3.1)	1 (0.2)	63 (10.9)	11 (1.9)

In the OAK study, there were no gastrointestinal disorders leading to death in the atezolizumab group. Gastrointestinal disorder leading to death occurred in 1 of 578 subjects (0.2%) in the DOC group (lower gastrointestinal haemorrhage [1 subject]), and its causal relationship to study drug was denied. Serious gastrointestinal disorders occurred in 17 of 609 subjects (2.8%) in the atezolizumab group (nausea; and abdominal pain lower [2 subjects each]; and diarrhoea; vomiting; abdominal pain; colitis; subileus; small intestinal obstruction; abdominal pain upper; dysphagia; gastritis erosive; melaena; oesophageal obstruction; intestinal obstruction; faeces discoloured; constipation; and pancreatitis [1 subject each] [some subjects had more than 1 event]) and 27 of 578 subjects (4.7%) in the DOC group (diarrhoea [7 subjects]; vomiting [6 subjects]; abdominal pain [4 subjects]; colitis [2 subjects]; and nausea; subileus; small intestinal obstruction; abdominal pain upper; dysphagia; ileus; lower gastrointestinal haemorrhage; haematochezia; stomatitis; duodenal perforation; upper gastrointestinal haemorrhage; oesophageal varices haemorrhage; oesophageal fistula; and intestinal prolapse [1 subject each] [some subjects had more than 1 event]). A causal relationship to study drug could not be ruled out for those events reported by 3 subjects (0.5%) in the atezolizumab group (intestinal obstruction; abdominal pain upper; nausea; and colitis [1 subject each] [1 subject had more than 1 event]) and those events reported by 16 subjects (2.8%) in the DOC group (diarrhoea [6 subjects]; vomiting [3 subjects]; colitis [2 subjects]; and ileus; upper gastrointestinal haemorrhage; duodenal perforation; dysphagia; abdominal pain; stomatitis; and oesophageal varices haemorrhage [1 subject each] [some subjects had more than 1 event]). No gastrointestinal disorders leading to treatment discontinuation were reported in the atezolizumab group. Gastrointestinal disorders leading to treatment discontinuation occurred in 7 of 578 subjects (1.2%) in the DOC group (gastritis; lower gastrointestinal haemorrhage; small intestinal obstruction; upper gastrointestinal haemorrhage; oesophageal varices haemorrhage; abdominal pain; and dysphagia [1 subject each]). Gastrointestinal disorders leading to dose interruption occurred in 15 of 609 subjects (2.5%) in the atezolizumab group (diarrhoea [5 subjects]; stomatitis [2 subjects]; and vomiting; gastritis erosive; melaena; subileus; colitis; intestinal obstruction; pancreatitis; inguinal hernia; and dental caries [1 subject each] [1 subject had more than 1 event]) and 5 of 578 subjects (0.9%) in the DOC group (diarrhoea; vomiting; duodenal perforation; oesophageal fistula; large intestine perforation; and abdominal discomfort [1 subject each] [1 subject had more than 1 event]).

The details of patients with serious colitis or diarrhoea associated with atezolizumab in all clinical studies submitted in the present application are shown in Table 26.

Table 26. Listing of patients with serious colitis or diarrhoea

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	6[redacted]	M	1200 mg/body Q3W	Colitis	2	79	Yes	Resolved
	6[redacted]	F	1200 mg/body Q3W	Diarrhoea	2	117	No	Resolved
BIRCH	6[redacted]	M	1200 mg/body Q3W	Colitis	3	196	Yes	Resolved
				Colitis	3	230	Yes	Resolved
	8[redacted]	F	1200 mg/body Q3W	Diarrhoea	3	26	Yes	Resolved
	7[redacted]	M	1200 mg/body Q3W	Diarrhoea	2	43	No	Resolved
	6[redacted]	M	1200 mg/body Q3W	Colitis	3	88	Yes	Resolved
	5[redacted]	F	1200 mg/body Q3W	Diarrhoea	2	133	Yes	Resolved
	7[redacted]	M	1200 mg/body Q3W	Diarrhoea	3	62	Yes	Resolved
	7[redacted]	F	1200 mg/body Q3W	Colitis	3	33	Yes	Resolved
	7[redacted]	M	1200 mg/body Q3W	Diarrhoea	1	21	Yes	Resolved
FIR	6[redacted]	F	1200 mg/body Q3W	Diarrhoea	1	26	No	Resolved
	4[redacted]	F	1200 mg/body Q3W	Diarrhoea	2	46	Yes	Unresolved
	7[redacted]	M	1200 mg/body Q3W	Diarrhoea	2	69	Yes	Resolved
POPLAR	7[redacted]	M	1200 mg/body Q3W	Colitis	2	21	Yes	Resolved
	7[redacted]	M	1200 mg/body Q3W	Diarrhoea	3	14	Yes	Resolved
PCD4989g	6[redacted]	M	10 mg/kg Q3W	Colitis	3	292	Yes	Resolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for other studies

PMDA's discussion:

Since serious gastrointestinal disorders for which a causal relationship to atezolizumab could not be ruled out were reported in clinical studies, etc., attention should be paid to the possible occurrence of gastrointestinal disorders during treatment with atezolizumab. Among gastrointestinal disorders, colitis and diarrhoea were reported as serious adverse events in the OAK study etc., and serious adverse events of colitis and diarrhoea have been reported also with nivolumab and pembrolizumab that block PD-L1/PD-1 binding, as does atezolizumab. Thus, particular attention should be paid to the possible occurrence of colitis and diarrhoea during treatment with atezolizumab. Based on the above, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management etc. of gastrointestinal disorders in the clinical studies, using the package insert etc.

7.R.3.3 Skin disorders

The applicant's explanation about skin disorders associated with atezolizumab:

As adverse events of skin disorders, events in the MedDRA HLGT "epidermal and dermal conditions" were counted.

The incidence of skin disorders in the OAK study is shown in Table 27.

Table 27. Skin disorders reported by ≥1% of subjects in either group (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorders	159 (26.1)	12 (2.0)	120 (20.8)	1 (0.2)
Rash	59 (9.7)	2 (0.3)	49 (8.5)	0
Pruritus	50 (8.2)	3 (0.5)	18 (3.1)	0
Dry skin	27 (4.4)	0	34 (5.9)	1 (0.2)
Erythema	13 (2.1)	0	11 (1.9)	0
Rash maculo-papular	9 (1.5)	1 (0.2)	5 (0.9)	0
Eczema	7 (1.1)	0	3 (0.5)	0

In the OAK study, no skin disorders leading to death were reported. Serious skin disorders occurred in 5 of 609 subjects (0.8%) in the atezolizumab group (pruritus; dermatitis bullous; pruritus generalised; rash; and pemphigoid [1 subject each]), but not in the DOC group. A causal relationship to study drug could not be ruled out for those events reported by 4 subjects (0.7%) in the atezolizumab group (dermatitis bullous; pruritus generalised; rash; and pemphigoid [1 subject each]). Skin disorders leading to treatment discontinuation occurred in 4 of 609 subjects (0.7%) in the atezolizumab group (dermatitis bullous [2 subjects]; and erythema multiforme; and pemphigoid [1 subject each]), but not in the DOC group. Skin disorders leading to dose interruption occurred in 10 of 609 subjects (1.6%) in the atezolizumab group (pruritus [4 subjects]; rash [3 subjects]; erythema multiforme; and rash maculo-papular [2 subject each]; and dermatitis bullous; rash pustular; eczema asteatotic; dermatitis; skin induration; and drug eruption [1 subject each] [some subjects had more than 1 event]) and 3 of 578 subjects (0.5%) in the DOC group (rash; infusion site rash; and skin reaction [1 subject each]).

The details of patients with erythema multiforme, pemphigoid, toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome (SJS) associated with atezolizumab in atezolizumab clinical studies and overseas marketing experience are shown in Table 28.

Table 28. Listing of patients with erythema multiforme, pemphigoid, TEN, or SJS

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	5[redacted]	F	1200 mg/body Q3W	Erythema multiforme	2	Non-serious	108	Yes	Unresolved
	5[redacted]	M	1200 mg/body Q3W	Erythema multiforme	2	Non-serious	10	Yes	Resolved
				Erythema multiforme	3	Non-serious	40	Yes	Resolved
	5[redacted]	M	1200 mg/body Q3W	Pemphigoid	3	Serious	347	Yes	Resolved
BIRCH	4[redacted]	F	1200 mg/body Q3W	Erythema multiforme	1	Non-serious	191	Yes	Resolved
	7[redacted]	F	1200 mg/body Q3W	Erythema multiforme	1	Non-serious	221	Yes	Unresolved
PCD4989g	6[redacted]	M	15 mg/kg Q3W	Erythema multiforme	2	Non-serious	4	Yes	Resolved
JO28944	4[redacted]	F	10 mg/kg Q3W	Erythema multiforme	1	Non-serious	6	Yes	Resolved
[redacted]	6[redacted]	M	1200 mg/body Q3W	TEN	3	Serious	249	Yes	Resolved
	7[redacted]	F	1200 mg/body Q3W	TEN	5	Serious	198	Yes	Fatal
[redacted]	6[redacted]	M	800 mg/body Q2W	SJS	3	Serious	30	Yes	Unresolved
[redacted]	5[redacted]	M	1200 mg/body Q3W	Erythema multiforme	2	Non-serious	11	Yes	Resolved
	6[redacted]	F	1200 mg/body Q3W	Erythema multiforme	3	Serious	11	Yes	Resolved
	6[redacted]	M	1200 mg/body Q3W	Erythema multiforme	3	Serious	10	Yes	Resolved
	6[redacted]	F	1200 mg/body Q3W	Erythema multiforme	3	Serious	6	Yes	Resolved
[redacted]	5[redacted]	F	1200 mg/body Q3W	TEN	4	Serious	189	Yes	Resolved
[redacted]	7[redacted]	M	1200 mg/body Q3W	Erythema multiforme	3	Serious	295	Yes	Resolved
[redacted]	4[redacted]	F	1200 mg/body Q3W	Erythema multiforme	3	Serious	247	Yes	Resolved
[redacted]	7[redacted]	M	1200 mg/body Q3W	Erythema multiforme	4	Serious	53	Yes	Unresolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for the BIRCH study and Study PCD4989g, MedDRA ver.16.1 for Study JO28944, MedDRA ver.20.0 for other clinical studies

PMDA's discussion:

Since serious skin disorders such as erythema multiforme associated with atezolizumab were reported in clinical studies of atezolizumab, attention should be paid to the possible occurrence of skin disorders during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management etc. of skin disorders in the clinical studies, using the package insert etc.

7.R.3.4 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with atezolizumab:

As adverse events of hepatic dysfunction, events in the MedDRA SMQs "hepatitis, non-infectious (narrow)," "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow)," and "liver related investigations, signs and symptoms (narrow)" were counted.

The incidence of hepatic dysfunction in the OAK study is shown in Table 29.

Table 29. Incidence of hepatic dysfunction (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction	67 (11.0)	18 (3.0)	22 (3.8)	5 (0.9)
AST increased	38 (6.2)	5 (0.8)	12 (2.1)	2 (0.3)
ALT increased	35 (5.7)	6 (1.0)	14 (2.4)	2 (0.3)
GGT increased	7 (1.1)	3 (0.5)	2 (0.3)	1 (0.2)
Blood bilirubin increased	7 (1.1)	1 (0.2)	2 (0.3)	2 (0.3)
Hepatic function abnormal	3 (0.5)	1 (0.2)	2 (0.3)	0
Ascites	3 (0.5)	0	0	0
Transaminases increased	2 (0.3)	2 (0.3)	0	0
Hepatitis	2 (0.3)	2 (0.3)	0	0
Hepatic pain	1 (0.2)	0	1 (0.2)	0
Hepatic enzyme increased	1 (0.2)	0	0	0
Hepatocellular injury	1 (0.2)	0	0	0
Liver disorder	1 (0.2)	0	0	0
Hepatic lesion	1 (0.2)	0	0	0
Acute hepatitis	1 (0.2)	1 (0.2)	0	0
Hyperbilirubinaemia	1 (0.2)	0	0	0
Hepatic steatosis	1 (0.2)	0	0	0
Drug-induced liver injury	1 (0.2)	1 (0.2)	0	0
Acute hepatic failure	0	0	1 (0.2)	1 (0.2)
Varices oesophageal	0	0	1 (0.2)	0
Oesophageal varices haemorrhage	0	0	1 (0.2)	0

In the OAK study, no hepatic dysfunction leading to death was reported. Serious hepatic dysfunction occurred in 5 of 609 subjects (0.8%) in the atezolizumab group (hepatitis [2 subjects]; and acute hepatitis; drug-induced liver injury; AST increased; and ALT increased [1 subject each] [1 subject had more than 1 event]) and 2 of 578 subjects (0.3%) in the DOC group (oesophageal varices haemorrhage; and acute hepatic failure [1 subject each]). A causal relationship to study drug could not be ruled out for those events reported by 5 subjects (0.8%) in the atezolizumab group (hepatitis [2 subjects]; and acute hepatitis; drug-induced liver injury; AST increased; and ALT increased [1 subject each] [1 subject had more than 1 event]) and the event reported by 1 subject (0.2%) in the DOC group (oesophageal varices haemorrhage [1 subject]). Hepatic dysfunction leading to treatment discontinuation occurred in 5 of 609 subjects (0.8%) in the atezolizumab group (AST increased; and hepatitis [2 subjects each]; and ALT increased; and drug-induced liver injury [1 subject each] [1 subject had more than 1 event]) and 1 of 578 subjects (0.2%) in the DOC group (oesophageal varices haemorrhage [1 subject]). Hepatic dysfunction leading to dose interruption occurred in 10 of 609 subjects (1.6%) in the atezolizumab group (AST increased; and ALT increased [5 subjects each]; blood bilirubin increased; transaminases increased; and GGT increased [2 subjects each]; and acute hepatitis [1 subject] [some subjects had more than 1 event]) and 2 of 578 subjects (0.3%) in the DOC group (AST increased; and blood bilirubin increased [2 subjects each]; and ALT increased [1 subject] [both subjects had more than 1 event]).

There was 1 case (0.2%) 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) in the atezolizumab group of the OAK study. This patient had hepatic dysfunction meeting Hy's law laboratory criteria (AST >3 times the upper limit

of normal [ULN], ALT >3 times ULN, total bilirubin >2 times ULN) on Day 83, and its causal relationship to atezolizumab could not be ruled out. Atezolizumab was discontinued, and the patient's liver function tests returned to normal on Day 174.

PMDA's discussion:
Since serious hepatic dysfunction associated with atezolizumab was reported in the OAK study, attention should be paid to the possible occurrence of hepatic dysfunction during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management etc. of hepatic dysfunction in the clinical studies, using the package insert etc.

7.R.3.5 Neuropathies

The applicant's explanation about neuropathies associated with atezolizumab:
As adverse events of neuropathies, events in the MedDRA SMQs "Guillain-Barre syndrome (narrow)" and "peripheral neuropathy (narrow)" were counted.

The incidence of neuropathies in the OAK study is shown in Table 30.

Table 30. Incidence of neuropathies (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Neuropathies	39 (6.4)	5 (0.8)	112 (19.4)	11 (1.9)
Peripheral neuropathy	24 (3.9)	0	65 (11.2)	7 (1.2)
Peripheral sensory neuropathy	6 (1.0)	0	43 (7.4)	5 (0.9)
Neuralgia	5 (0.8)	2 (0.3)	1 (0.2)	0
Guillain-Barre syndrome	3 (0.5)	3 (0.5)	0	0
Peripheral motor neuropathy	1 (0.2)	0	2 (0.3)	0
Demyelinating polyneuropathy	1 (0.2)	0	0	0
Polyneuropathy	0	0	3 (0.5)	0
Peripheral sensorimotor neuropathy	0	0	1 (0.2)	0

In the OAK study, no neuropathies leading to death were reported. Serious neuropathies occurred in 4 of 609 subjects (0.7%) in the atezolizumab group (Guillain-Barre syndrome [2 subjects]; and neuralgia; and peripheral sensory neuropathy [1 subject each]), but not in the DOC group. A causal relationship to study drug could not be ruled out for those events reported by 2 subjects (0.3%) in the atezolizumab group (Guillain-Barre syndrome [2 subjects]). No neuropathies leading to treatment discontinuation were reported in the atezolizumab group. Neuropathies leading to treatment discontinuation occurred in 14 of 578 subjects (2.4%) in the DOC group (peripheral neuropathy [10 subjects]; and peripheral sensory neuropathy [4 subjects]). Neuropathies leading to dose interruption occurred in 2 of 609 subjects (0.3%) in the atezolizumab group (peripheral neuropathy; and Guillain-Barre syndrome [1 subject each]) and 4 of 578 subjects (0.7%) in the DOC group (peripheral sensory neuropathy [3 subjects]; and peripheral neuropathy [1 subject]).

The details of patients with serious neuropathies in the atezolizumab group of the OAK study are shown in

Table 31.

Table 31. Listing of patients with serious neuropathies (atezolizumab group of OAK study)

Age	Sex	Atezolizumab dosing regimen	PT (MedDRA ver.19.0)	Grade	Time to onset (days)	Causality to atezolizumab	Outcome
5[redacted]	M	1200 mg/body Q3W	Peripheral sensory neuropathy	2	90	No	Unresolved
5[redacted]	M	1200 mg/body Q3W	Guillain-Barre syndrome	3	212	Yes	Resolved
7[redacted]	F	1200 mg/body Q3W	Neuralgia	3	6	No	Unresolved
6[redacted]	M	1200 mg/body Q3W	Guillain-Barre syndrome	3	20	Yes	Unresolved

PMDA's discussion:

Since serious neuropathies such as Guillain-Barre syndrome associated with atezolizumab were reported in the OAK study, attention should be paid to the possible occurrence of neuropathies during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management etc. of neuropathies in the clinical studies, using the package insert etc.

7.R.3.6 Endocrinopathies

The applicant's explanation about endocrinopathies [(a) thyroid dysfunction, (b) adrenal dysfunction, (c) pituitary dysfunction, and (d) diabetes mellitus] associated with atezolizumab:

(a) Thyroid dysfunction

As adverse events of thyroid dysfunction, events in the MedDRA SMQs "hyperthyroidism (broad)" and "hypothyroidism (broad)" were counted.

The incidence of thyroid dysfunction in the OAK study is shown in Table 32.

Table 32. Incidence of thyroid dysfunction (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Thyroid dysfunction	34 (5.6)	0	2 (0.3)	0
Hypothyroidism	18 (3.0)	0	1 (0.2)	0
Hyperthyroidism	7 (1.1)	0	0	0
Blood thyroid stimulating hormone increased	6 (1.0)	0	1 (0.2)	0
Exophthalmos	1 (0.2)	0	0	0
Blood thyroid stimulating hormone decreased	1 (0.2)	0	0	0
Thyroiditis	1 (0.2)	0	0	0
Thyroid function test abnormal	1 (0.2)	0	0	0
Endocrine ophthalmopathy	1 (0.2)	0	0	0

In the OAK study, there was no thyroid dysfunction leading to death or serious thyroid dysfunction. Thyroid dysfunction leading to dose interruption occurred in 5 of 609 subjects (0.8%) in the atezolizumab group (hypothyroidism [4 subjects]; and endocrine ophthalmopathy [1 subject]), but not in the DOC group. No thyroid dysfunction leading to treatment discontinuation was reported in either group.

The details of patients with serious thyroid dysfunction associated with atezolizumab in all clinical studies

submitted in the present application are shown in Table 33.

Table 33. Listing of patients with serious thyroid dysfunction

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT (MedDRA ver.18.0)	Grade	Time to onset (days)	Causality to atezolizumab	Outcome
BIRCH	6[redacted]	M	1200 mg/body Q3W	Hypothyroidism	3	236	Yes	Resolved
	5[redacted]	M	1200 mg/body Q3W	Hypothyroidism	3	217	Yes	Resolved
FIR	6[redacted]	M	1200 mg/body Q3W	Acute thyroiditis	2	43	Yes	Unresolved
	6[redacted]	M	1200 mg/body Q3W	Hypothyroidism	2	337	Yes	Resolved
PCD4989g	7[redacted]	F	20 mg/kg Q3W	Hypothyroidism	2	130	Yes	Resolved

(b) Adrenal dysfunction

As adverse events of adrenal dysfunction, MedDRA PTs "ACTH stimulation test abnormal," "Addison's disease," "adrenal androgen deficiency," "adrenal atrophy," "adrenal insufficiency," "adrenal insufficiency neonatal," "adrenal suppression," "adrenalitis," "adrenocortical insufficiency acute," "adrenocortical insufficiency neonatal," "adrenocorticotropic hormone deficiency," "adrenogenital syndrome," "aldosterone urine abnormal," "aldosterone urine decreased," "apituitarism," "biopsy adrenal gland abnormal," "blood aldosterone abnormal," "blood aldosterone decreased," "blood corticosterone abnormal," "blood corticosterone decreased," "blood corticotrophin abnormal," "blood corticotrophin decreased," "blood corticotrophin increased," "blood cortisol abnormal," "blood cortisol decreased," "corticotropin-releasing hormone stimulation test," "cortisol free urine decreased," "dexamethasone suppression test," "dexamethasone suppression test positive," "glucocorticoid deficiency," "glucocorticoids abnormal," "glucocorticoids decreased," "hydroxycorticosteroids urine abnormal," "hydroxycorticosteroids urine decreased," "hypoaldosteronism," "hypothalamic pituitary adrenal axis suppression," "mineralocorticoid deficiency," "primary adrenal insufficiency," "scan adrenal gland abnormal," "secondary adrenocortical insufficiency," "steroid withdrawal syndrome," "triple A syndrome," "urine cortisol/creatinine ratio abnormal," and "urine cortisol/creatinine ratio decreased" were counted.

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

Table 34. Listing of patients with adrenal dysfunction

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	5[redacted]	F	1200 mg/body Q3W	Adrenal insufficiency	2	Non-serious	407	No	Unresolved
	7[redacted]	M	1200 mg/body Q3W	Adrenal insufficiency	2	Non-serious	96	Yes	Resolved
	4[redacted]	F	1200 mg/body Q3W	Primary adrenal insufficiency	1	Non-serious	174	No	Resolved
BIRCH	7[redacted]	M	1200 mg/body Q3W	Adrenal insufficiency	1	Serious	2	No	Unresolved
	7[redacted]	M	1200 mg/body Q3W	Adrenal insufficiency	2	Serious	158	Yes	Unresolved
PCD4989g	7[redacted]	M	15 mg/kg Q3W	Adrenal insufficiency	3	Serious	13	No	Resolved
	4[redacted]	F	15 mg/kg Q3W	Adrenal insufficiency	3	Non-serious	5	Yes	Unresolved
	8[redacted]	F	15 mg/kg Q3W	Adrenal insufficiency	2	Non-serious	205	Yes	Resolved
	7[redacted]	M	20 mg/kg Q3W	Adrenal insufficiency	2	Non-serious	183	Yes	Unresolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for other studies

(c) Pituitary dysfunction

As adverse events of pituitary dysfunction, events in the MedDRA HLT "hypothalamic and pituitary disorders NEC" were counted.

The details of patients with pituitary dysfunction associated with atezolizumab in all clinical studies submitted in the present application are shown in Table 35.

Table 35. Listing of patients with pituitary dysfunction

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	6[redacted]	M	1200 mg/body Q3W	Hypophysitis	2	Non-serious	418	Yes	Unresolved
PCD4989g	7[redacted]	F	15 mg/kg Q3W	Hypophysitis	3	Serious	273	Yes	Unresolved
				Hypothalamo-pituitary disorder	1	Serious	328	Yes	Unresolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for Study PCD4989g

(d) Diabetes mellitus

As adverse events of diabetes mellitus, events in the MedDRA SMQ "hyperglycaemia/new onset diabetes mellitus (narrow)" were counted.

The incidence of diabetes mellitus in the OAK study is shown in Table 36.

Table 36. Incidence of diabetes mellitus (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diabetes mellitus	20 (3.3)	7 (1.1)	32 (5.5)	7 (1.2)
Hyperglycaemia	18 (3.0)	7 (1.1)	26 (4.5)	5 (0.9)
Type 2 diabetes mellitus	1 (0.2)	1 (0.2)	1 (0.2)	0
Type 1 diabetes mellitus	1 (0.2)	0	0	0
Glucose tolerance impaired	1 (0.2)	0	0	0
Blood glucose increased	0	0	2 (0.3)	1 (0.2)
Diabetes mellitus	0	0	2 (0.3)	1 (0.2)
Glucose urine present	0	0	1 (0.2)	0

In the OAK study, no diabetes mellitus leading to death was reported. Serious diabetes mellitus occurred in 3 of 609 subjects (0.5%) in the atezolizumab group (hyperglycaemia [3 subjects]), but not in the DOC group. A causal relationship to study drug could not be ruled out for the event reported by 1 of 609 subjects (0.2%) in the atezolizumab group (hyperglycaemia [1 subject]). Diabetes mellitus leading to dose interruption occurred in 2 of 609 subjects (0.3%) in the atezolizumab group (hyperglycaemia [2 subjects]) and 1 of 578 subjects (0.2%) in the DOC group (diabetes mellitus [1 subject]). No diabetes mellitus leading to treatment discontinuation was reported in either group.

The details of patients with serious diabetes mellitus or type 1 diabetes mellitus associated with atezolizumab in all clinical studies submitted in the present application are shown in Table 37.

Table 37. Listing of patients with serious diabetes mellitus or type 1 diabetes mellitus

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	6[redacted]	M	1200 mg/body Q3W	Hyperglycaemia	4	Serious	153	No	Resolved
	6[redacted]	F	1200 mg/body Q3W	Hyperglycaemia	3	Serious	124	No	Resolved
	6[redacted]	F	1200 mg/body Q3W	Hyperglycaemia	4	Serious	64	Yes	Resolved
	5[redacted]	F	1200 mg/body Q3W	Type 1 diabetes mellitus	1	Non-serious	Unknown	Yes	Unresolved
BIRCH	6[redacted]	M	1200 mg/body Q3W	Type 1 diabetes mellitus	3	Non-serious	50	Yes	Resolved
FIR	7[redacted]	M	1200 mg/body Q3W	Diabetes mellitus	3	Serious	106	Yes	Resolved
PCD4989g	7[redacted]	F	15 mg/kg Q3W	Diabetes mellitus	3	Serious	198	Yes	Resolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for the FIR study and Study PCD4989g

Furthermore, in atezolizumab clinical studies other than the above studies and overseas marketing experience, 3 cases of type 1 diabetes mellitus for which a causal relationship to atezolizumab could not be ruled out have been reported.

PMDA's discussion:
As serious thyroid dysfunction, adrenal dysfunction, pituitary dysfunction, and diabetes mellitus associated with atezolizumab were reported in clinical studies, attention should be paid to the possible occurrence of these adverse events during treatment with atezolizumab. Since serious adverse events of type 1 diabetes mellitus have been reported also with nivolumab and pembrolizumab that block PD-L1/PD-1 binding, as does atezolizumab, and multiple cases of serious adverse events of type 1 diabetes mellitus have been reported in atezolizumab clinical studies and overseas marketing experience, particular attention should be paid to the possible occurrence of type 1 diabetes mellitus during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidences and management etc. of these adverse events in the clinical studies, using the package insert etc.

7.R.3.7 ILD

The applicant's explanation about ILD associated with atezolizumab:
As adverse events of ILD, events in the MedDRA SMQ "interstitial lung disease (narrow)" were counted.

The incidence of ILD in the OAK study is shown in Table 38.

Table 38. Incidence of ILD (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD	14 (2.3)	5 (0.8)	4 (0.7)	2 (0.3)
Pneumonitis	6 (1.0)	4 (0.7)	4 (0.7)	2 (0.3)
ILD	3 (0.5)	0	0	0
Lung infiltration	2 (0.3)	1 (0.2)	0	0
Radiation pneumonitis	2 (0.3)	0	0	0
Bronchiolitis	1 (0.2)	0	0	0

In the OAK study, no ILD leading to death was reported. Serious ILD occurred in 7 of 609 subjects (1.1%) in

the atezolizumab group (pneumonitis [6 subjects]; and ILD [1 subject]) and 1 of 578 subjects (0.2%) in the DOC group (pneumonitis [1 subject]), and a causal relationship to study drug could not be ruled out for all those events. ILD leading to treatment discontinuation occurred in 3 of 609 subjects (0.5%) in the atezolizumab group (pneumonitis; ILD; and lung infiltration [1 subject each]) and 1 of 578 subjects (0.2%) in the DOC group (pneumonitis [1 subject]). ILD leading to dose interruption occurred in 5 of 609 subjects (0.8%) in the atezolizumab group (lung infiltration; and pneumonitis [2 subjects each]; and radiation pneumonitis [1 subject]) and 1 of 578 subjects (0.2%) in the DOC group (pneumonitis [1 subject]).

The median time to the first onset of ILD (range) in the atezolizumab group of the OAK study was 96 (6-526) days.

The details of patients with serious ILD in the atezolizumab group of the OAK study are shown in Table 39.

Table 39. Listing of patients with serious ILD (atezolizumab group of the OAK study)

Age	Sex	PT (MedDRA ver.19.0)	Grade	Time to onset (days)	Causality to atezolizumab	Outcome
5[redacted]	F	Pneumonitis	2	526	Yes	Resolved
6[redacted]	M	Pneumonitis	3	345	Yes	Resolved
5[redacted]	F	Pneumonitis	3	31	Yes	Resolved
6[redacted]	M	Pneumonitis	2	6	Yes	Resolved
6[redacted]	M	Pneumonitis	3	7	Yes	Resolved
6[redacted]	M	ILD	2	126	Yes	Resolved
6[redacted]	M	Pneumonitis	3	194	Yes	Unresolved

In addition, the details of patients with ILD leading to death associated with atezolizumab in atezolizumab clinical studies are shown in Table 40.

Table 40. Listing of patients with ILD leading to death

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Time to onset (days)	Causality to atezolizumab
BIRCH	7[redacted]	M	1200 mg/body Q3W	Pneumonitis	15	No
[redacted]	6[redacted]	M	Unknown	Pneumonitis	131	Yes
[redacted]	6[redacted]	M	1200 mg/body Q3W	Pneumonitis	248	Yes
[redacted]	5[redacted]	F	1200 mg/body Q3W	Pneumonitis	15	Yes
[redacted]	5[redacted]	M	1200 mg/body Q3W	Pneumonitis	2	No
[redacted]	6[redacted]	M	1200 mg/body Q3W	ILD	177	Yes
[redacted]	7[redacted]	M	1200 mg/body Q3W	Pneumonitis	20	Yes
[redacted]	5[redacted]	F	Unknown	Pneumonitis	148	No
[redacted]	7[redacted]	M	1200 mg/body Q3W	ILD	55	Yes
[redacted]	5[redacted]	M	1200 mg/body Q3W	Pneumonitis	60	Yes
[redacted]	7[redacted]	F	Unknown	Pneumonitis	30	Yes
[redacted]	3[redacted]	M	Unknown	Pneumonitis	61	Yes

*: MedDRA ver.18.0 for the BIRCH study, MedDRA ver.20.0 for other studies

In the overseas marketing experience, 2 cases of ILD leading to death associated with atezolizumab have been reported.

PMDA's discussion:
Since events of ILD associated with atezolizumab, including serious cases, were reported in the OAK study, attention should be paid to the possible occurrence of ILD during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the following points, using the package insert etc.: the incidence of ILD in clinical studies; eligible patients must be selected carefully after checking the presence or absence of current or previous ILD, etc.; and continuous attention should be paid to the possible occurrence of ILD during treatment with atezolizumab, and if clinical symptoms etc. suggestive of ILD occur, appropriate measures should be taken. It is also necessary to appropriately advise healthcare professionals in clinical practice about the atezolizumab dosage modification guideline for ILD used in the clinical studies, using the package insert etc.

7.R.3.8 IRR

The applicant's explanation about IRR associated with atezolizumab:
As adverse events of IRR, events in the MedDRA SMQ "anaphylactic reaction (narrow)," and MedDRA PTs "infusion related reaction," "hypersensitivity," and "drug hypersensitivity" were counted.

The incidence of IRR in the OAK study is shown in Table 41.

Table 41. Incidence of IRR (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
IRR	12 (2.0)	2 (0.3)	22 (3.8)	4 (0.7)
Hypersensitivity	6 (1.0)	1 (0.2)	11 (1.9)	0
Infusion related reaction	5 (0.8)	1 (0.2)	6 (1.0)	1 (0.2)
Drug hypersensitivity	3 (0.5)	0	3 (0.5)	2 (0.3)
Anaphylactic reaction	0	0	2 (0.3)	1 (0.2)

In the OAK study, no IRR leading to death was reported. Serious IRR occurred in 3 of 609 subjects (0.5%) in the atezolizumab group (hypersensitivity [3 subjects]; and infusion related reaction [1 subject] [1 subject had more than 1 event]), but not in the DOC group. A causal relationship to study drug could not be ruled out for all those events. IRR leading to treatment discontinuation occurred in 3 of 609 subjects (0.5%) in the atezolizumab group (hypersensitivity [2 subjects]; and infusion related reaction [1 subject]) and 5 of 578 subjects (0.9%) in the DOC group (drug hypersensitivity [3 subjects]; and infusion related reaction; and anaphylactic reaction [1 subject each]). IRR leading to dose interruption occurred in 6 of 609 subjects (1.0%) in the atezolizumab group (infusion related reaction [5 subjects]; and hypersensitivity [1 subject]) and 6 of 578 subjects (1.0%) in the DOC group (infusion related reaction; and hypersensitivity [3 subjects each]).

The median time to the first onset of IRR (range) in the atezolizumab group was 43.0 days (21-242 days).

The OAK study was conducted according to the dosage modification guideline (infusion rate adjustment, discontinuation, etc.) for IRR occurring during infusion of atezolizumab. Information on this guideline will be

provided, using information materials etc.

PMDA's discussion:
Since serious IRR associated with atezolizumab was reported in the OAK study, attention should be paid to the possible occurrence of IRR during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence of IRR and infusion rate adjustment, etc. at the onset of IRR in the clinical studies, using the package insert etc.

7.R.3.9 Encephalitis/meningitis

The applicant's explanation about encephalitis/meningitis associated with atezolizumab:
As adverse events of encephalitis/meningitis, events in the MedDRA SMQs "noninfectious encephalitis (narrow)" and "noninfectious meningitis (narrow)" were counted.

The incidence of encephalitis/meningitis in the OAK study is shown in Table 42.

Table 42. Incidence of encephalitis/meningitis (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Encephalitis/meningitis	5 (0.8)	3 (0.5)	0	0
Meningitis	3 (0.5)	2 (0.3)	0	0
Encephalitis	1 (0.2)	1 (0.2)	0	0
Photophobia	1 (0.2)	0	0	0

Encephalitis/meningitis leading to treatment discontinuation occurred in 4 of 609 subjects (0.7%) in the atezolizumab group (meningitis [3 subjects]; and encephalitis [1 subject]), but not in the DOC group. No encephalitis/meningitis leading to dose interruption was reported in either group.

The details of patients with encephalitis/meningitis associated with atezolizumab in all clinical studies submitted in the present application are shown in Table 43.

Table 43. Listing of patients with encephalitis/meningitis

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	6[redacted]	M	1200 mg/body Q3W	Photophobia	1	Non-serious	20	Yes	Resolved
	6[redacted]	F	1200 mg/body Q3W	Meningitis	3	Serious	15	Yes	Resolved
	6[redacted]	F	1200 mg/body Q3W	Meningitis	2	Serious	16	Yes	Resolved
	6[redacted]	F	1200 mg/body Q3W	Encephalitis	3	Serious	14	Yes	Resolved
	5[redacted]	F	1200 mg/body Q3W	Meningitis	4	Serious	15	Yes	Resolved
BIRCH	5[redacted]	F	1200 mg/body Q3W	Encephalitis	3	Serious	16	No	Resolved
	6[redacted]	M	1200 mg/body Q3W	Photophobia	1	Non-serious	1	Yes	Unresolved
FIR	6[redacted]	F	1200 mg/body Q3W	Photophobia	2	Non-serious	74	No	Resolved
PCD4989g	7[redacted]	F	10 mg/kg Q3W	Photophobia	1	Non-serious	379	No	Resolved
	3[redacted]	M	15 mg/kg Q3W	Photophobia	1	Non-serious	60	No	Unresolved
	7[redacted]	M	1200 mg/body Q3W	Meningitis	3	Serious	16	Yes	Resolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for other studies

PMDA's discussion:

Since serious encephalitis/meningitis associated with atezolizumab was reported in the OAK study, attention should be paid to the possible occurrence of encephalitis/meningitis during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence etc. of encephalitis/meningitis in the clinical studies, using the package insert etc.

7.R.3.10 Pancreatitis

The applicant's explanation about pancreatitis associated with atezolizumab:

As adverse events of pancreatitis, events in the MedDRA SMQ "acute pancreatitis (narrow)," and MedDRA PTs "amylase abnormal," "amylase increased," "autoimmune pancreatitis," "lipase abnormal," and "lipase increased" were counted.

The details of patients with pancreatitis associated with atezolizumab in all clinical studies submitted in the present application are shown in Table 44.

Table 44. Listing of patients with pancreatitis

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	5[redacted]	M	1200 mg/body Q3W	Pancreatitis	3	Serious	353	No	Resolved
BIRCH	6[redacted]	F	1200 mg/body Q3W	Pancreatitis acute	3	Serious	30	No	Resolved
	7[redacted]	M	1200 mg/body Q3W	Lipase increased	3	Non-serious	8	No	Resolved
	6[redacted]	F	1200 mg/body Q3W	Pancreatitis	3	Serious	331	Yes	Resolved
				Pancreatitis	1	Non-serious	384	Yes	Unresolved
	6[redacted]	F	1200 mg/body Q3W	Lipase increased	2	Non-serious	78	Yes	Unresolved
	5[redacted]	F	1200 mg/body Q3W	Amylase increased	3	Non-serious	168	Yes	Resolved
PCD4989g	6[redacted]	M	15 mg/kg Q3W	Amylase increased	2	Non-serious	169	No	Resolved
	6[redacted]	F	15 mg/kg Q3W	Lipase increased	3	Non-serious	14	No	Unresolved
	8[redacted]	F	15 mg/kg Q3W	Amylase increased	3	Non-serious	315	Yes	Unresolved
				Lipase increased	3	Non-serious	275	Yes	Unresolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for the BIRCH study and Study PCD4989g

PMDA's discussion:

Since serious pancreatitis associated with atezolizumab was reported in clinical studies, attention should be paid to the possible occurrence of pancreatitis during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management etc. of pancreatitis in the clinical studies, using the package insert etc.

7.R.3.11 Renal dysfunction

The applicant's explanation about renal dysfunction associated with atezolizumab:

As adverse events of renal dysfunction, events in the MedDRA HLTs "nephritis NEC," "glomerulonephritis and nephrotic syndrome," "renal disorders NEC," and "renal failure and impairment" were counted.

The incidence of renal dysfunction in the OAK study is shown in Table 45.

Table 45. Incidence of renal dysfunction (OAK study)

PT (MedDRA ver.19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal dysfunction	12 (2.0)	4 (0.7)	11 (1.9)	4 (0.7)
Acute kidney injury	7 (1.1)	2 (0.3)	7 (1.2)	2 (0.3)
Renal failure	3 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)
Chronic kidney disease	1 (0.2)	0	1 (0.2)	0
Henoch-Schonlein purpura nephritis	1 (0.2)	1 (0.2)	0	0
Acute prerenal failure	0	0	1 (0.2)	1 (0.2)
Fluid retention	0	0	1 (0.2)	0

In the OAK study, renal dysfunction leading to death occurred in 1 of 609 subjects (0.2%) in the atezolizumab group (renal failure [1 subject]), but not in the DOC group. A causal relationship to study drug was denied for that event reported by 1 of 609 subjects (0.2%) in the atezolizumab group (renal failure [1 subject]). Renal dysfunction leading to treatment discontinuation occurred in 2 of 609 subjects (0.3%) in the atezolizumab group (renal failure; and Henoch-Schonlein purpura nephritis [1 subject each]), but not in the DOC group. Renal dysfunction leading to dose interruption did not occur in the atezolizumab group, but occurred in 2 of 578 subjects (0.3%) in the DOC group (acute kidney injury [2 subjects]).

The details of patients with serious renal dysfunction in the atezolizumab group of the OAK study are shown in Table 46.

Table 46. Listing of patients with serious renal dysfunction (atezolizumab group of OAK study)

Age	Sex	PT (MedDRA ver.19.0)	Grade	Time to onset (days)	Causality to atezolizumab	Outcome
6[redacted]	M	Acute kidney injury	3	43	No	Resolved
7[redacted]	M	Acute kidney injury	4	41	Yes	Unresolved
5[redacted]	M	Renal failure	5	18	No	Fatal
6[redacted]	M	Henoch-Schonlein purpura nephritis	3	400	Yes	Resolved

Furthermore, in clinical studies other than the above study and overseas marketing experience, 6 cases of serious tubulointerstitial nephritis for which a causal relationship to atezolizumab could not be ruled out have been reported.

PMDA's discussion:
As events of serious renal dysfunction associated with atezolizumab, including a fatal case, have been reported, attention should be paid to the possible occurrence of renal dysfunction during treatment with atezolizumab. Since serious adverse events of tubulointerstitial nephritis have been reported also with nivolumab and pembrolizumab that block PD-L1/PD-1 binding, as does atezolizumab, and multiple cases of serious adverse events of tubulointerstitial nephritis have been reported in atezolizumab clinical studies and overseas marketing experience, particular attention should be paid to the possible occurrence of tubulointerstitial nephritis during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence etc. of renal dysfunction in the clinical studies, using the package insert etc.

7.R.3.12 Myositis/dermatomyositis/rhabdomyolysis

The applicant's explanation about myositis/dermatomyositis/rhabdomyolysis associated with atezolizumab:
As adverse events of myositis/dermatomyositis/rhabdomyolysis, events in the MedDRA HLTs "muscle infections and inflammations" and "muscular autoimmune disorders," and MedDRA PT "rhabdomyolysis" were counted.

The details of patients with myositis/dermatomyositis/rhabdomyolysis associated with atezolizumab in all clinical studies submitted in the present application are shown in Table 47.

Table 47. Listing of patients with myositis/dermatomyositis/rhabdomyolysis

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	6[redacted]	F	1200 mg/body Q3W	Rhabdomyolysis	4	Serious	53	Yes	Resolved
	5[redacted]	F	1200 mg/body Q3W	Polymyalgia rheumatica	2	Non-serious	65	Yes	Unknown
BIRCH	6[redacted]	M	1200 mg/body Q3W	Rhabdomyolysis	1	Non-serious	155	Yes	Resolved
	6[redacted]	M	1200 mg/body Q3W	Dermatomyositis	3	Serious	75	Yes	Resolved
				Dermatomyositis	3	Serious	206	Yes	Resolved
FIR	7[redacted]	F	1200 mg/body Q3W	Polymyalgia rheumatica	2	Non-serious	176	Yes	Resolved
				Polymyalgia rheumatica	1	Non-serious	205	Yes	Unresolved
PCD4989g	5[redacted]	M	20 mg/kg Q3W	Myositis	2	Non-serious	262	Yes	Resolved
				Myositis	1	Non-serious	295	Yes	Resolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for other studies

In clinical studies other than the above studies and overseas marketing experience, 6 cases of serious myositis (including polymyositis) for which a causal relationship to atezolizumab could not be ruled out, 1 case of serious dermatomyositis for which a causal relationship to atezolizumab could not be ruled out, and 3 cases of serious rhabdomyolysis for which a causal relationship to atezolizumab could not be ruled out have been

reported.

PMDA's discussion:
Since serious myositis, dermatomyositis, and rhabdomyolysis associated with atezolizumab were reported in clinical studies, and serious adverse events of myositis, dermatomyositis, and rhabdomyolysis have been reported also with nivolumab and pembrolizumab that block PD-L1/PD-1 binding, as does atezolizumab, attention should be paid to the possible occurrence of these adverse events during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence etc. of these adverse events in the clinical studies, using the package insert etc.

7.R.3.13 Myasthenia gravis

The applicant's explanation about myasthenia gravis associated with atezolizumab:
As adverse events of myasthenia gravis, events in the MedDRA HLT "myasthenia gravis and related conditions" were counted.

In all clinical studies submitted in the present application, the details of a patient with myasthenia gravis associated with atezolizumab are shown in Table 48.

Table 48. A patient with myasthenia gravis

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT (MedDRA ver.18.0)	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
PCD4989g	6[redacted]	M	15 mg/kg Q3W	Myasthenia gravis	2	Serious	36	Yes	Unresolved

In clinical studies other than the above studies and overseas marketing experience, 6 cases of serious myasthenia gravis for which a causal relationship to atezolizumab could not be ruled out have been reported.

PMDA's discussion:
Since serious myasthenia gravis associated with atezolizumab was reported in clinical studies, and serious myasthenia gravis has been reported also with nivolumab and pembrolizumab that block PD-L1/PD-1 binding, as does atezolizumab, attention should be paid to the possible occurrence of myasthenia gravis during treatment with atezolizumab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence etc. of myasthenia gravis in the clinical studies, using the package insert etc.

7.R.3.14 Others

Given the mechanism of action of atezolizumab, and adverse events reported with other drugs with a similar mechanism of action, (a) hemolytic anemia, (b) immune thrombocytopenic purpura, (c) myocarditis, and (d) organ transplant rejection are anticipated following administration of atezolizumab. The applicant's explanation about these events:
(a) Hemolytic anemia
As adverse events of hemolytic anemia, events in the MedDRA SMQ "haemolytic disorders (narrow)" were

counted.

The details of patients with hemolytic anemia associated with atezolizumab in all clinical studies submitted in the present application are shown in Table 49.

Table 49. Listing of patients with hemolytic anemia

Study Identity	Age	Sex	Atezolizumab dosing regimen	PT*	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
OAK	8[redacted]	F	1200 mg/body Q3W	Haemoglobinuria	1	Non-serious	295	No	Unresolved
BIRCH	6[redacted]	M	1200 mg/body Q3W	Haemolysis	4	Serious	36	Yes	Unresolved
POPLAR	5[redacted]	M	1200 mg/body Q3W	Haemolysis	3	Non-serious	12	Yes	Resolved
				Haemolysis	2	Non-serious	49	Yes	Resolved
PCD4989g	5[redacted]	F	10 mg/kg Q3W	Haptoglobin decreased	1	Non-serious	15	Yes	Unresolved

*: MedDRA ver.19.0 for the OAK study, MedDRA ver.18.0 for other studies

In clinical studies other than the above studies and overseas marketing experience, 5 cases of serious autoimmune hemolytic anemia for which a causal relationship to atezolizumab could not be ruled out have been reported.

(b) Immune thrombocytopenic purpura

In atezolizumab clinical studies and overseas marketing experience, the details of a patient with immune thrombocytopenic purpura associated with atezolizumab are shown in Table 50.

Table 50. A patient with immune thrombocytopenic purpura

Study Identity	Age	Sex	Primary disease	Atezolizumab dosing regimen	Grade	Seriousness	Time to onset (days)	Causality to atezolizumab	Outcome
[redacted]	4[redacted]	F	Ovarian cancer	1200 mg/body Q3W	4	Serious	14	Yes	Resolved

(c) Myocarditis

In atezolizumab clinical studies and overseas marketing experience, 6 cases of serious myocarditis for which a causal relationship to atezolizumab could not be ruled out have been reported.

(d) Organ transplant rejection

In atezolizumab clinical studies and overseas marketing experience, organ transplant rejection has not been reported in patients treated with atezolizumab at present.

PMDA's discussion:

Although the cases of (a) to (c) for which a causal relationship to atezolizumab could not be ruled out have been reported in clinical studies and overseas marketing experience, as the reported number of cases is limited etc., it is difficult to draw a definitive conclusion on their relationship to atezolizumab from the currently available information. Thus, no special precautionary statements concerning (a) to (c) are required at present, but it is necessary to collect post-marketing information and appropriately provide any new information to healthcare professionals in clinical practice.

With regard to (d), though the foreign labelings for nivolumab and pembrolizumab that block PD-L1/PD-1 binding, as does atezolizumab, advise that solid organ transplant rejection has been reported in patients treated with anti-PD-1 antibodies, as organ transplant rejection has not been reported in patients treated with atezolizumab, it is difficult to draw a definitive conclusion on its relationship to atezolizumab. Thus, no special precautionary statement concerning (d) is required 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 atezolizumab is "unresectable advanced or recurrent non-small cell lung cancer." The following statements are included in the PRECAUTIONS CONCERNING INDICATION section of the proposed package insert.

- The efficacy and safety of atezolizumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of atezolizumab in a post-operative adjuvant setting have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section, and of the efficacy and safety of atezolizumab.

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety," and the following considerations, PMDA concluded that the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section and that the proposed indication of "unresectable advanced or recurrent non-small cell lung cancer" is appropriate.

Precautions Concerning Indication

- The efficacy and safety of atezolizumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of atezolizumab in a post-operative adjuvant chemotherapy setting have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of atezolizumab.

7.R.4.1 Target population

Atezolizumab for patients with unresectable advanced or recurrent NSCLC is described as follows in the foreign clinical practice guidelines and the major textbook of clinical oncology. At present, there is no mention of atezolizumab for patients with NSCLC in the Japanese clinical practice guidelines or New Clinical Oncology, the 4th edition (Nankodo, 2015).

[Clinical practice guidelines]

- NCCN guidelines (v.6.2017)
  Atezolizumab is strongly recommended as second-line therapy for unresectable advanced or recurrent

NSCLC.

- US National Cancer Institute Physician Data Query (NCI PDQ) (Updated: March 31, 2017)
  Compared with DOC, treatment with atezolizumab resulted in improved OS rate in the OAK study.

[Textbook]

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (Lippincott Williams & Wilkins 2015, PA, USA)
  - Clinical trials demonstrated a certain level of efficacy of atezolizumab in patients with NSCLC.

The applicant's explanation about the clinical positioning and indication of atezolizumab:
Based on the results of the OAK study etc., atezolizumab is positioned as a treatment option for patients with unresectable advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy.

The efficacy and safety results of atezolizumab in the OAK study by histology are shown in Table 51 and Table 52, respectively. Since there were no clear differences in the efficacy or safety of atezolizumab according to histology, the efficacy of atezolizumab is expected, irrespective of histology.

Table 51. Efficacy results by histology (OAK study, data cutoff date of July 7, 2016)

Histology	Treatment group	N	OS	
			Median [95% CI] (months)	Hazard ratio* [95% CI]
Non-squamous	Atezolizumab	313	15.6 [13.3, 17.6]	0.73 [0.60, 0.89]
	DOC	315	11.2 [9.3, 12.6]	
Squamous	Atezolizumab	112	8.9 [7.4, 12.8]	0.73 [0.54, 0.98]
	DOC	110	7.7 [6.3, 8.9]	

*: Unstratified Cox regression

Table 52. Summary of safety data by histology (OAK study)

	n (%)			
	Non-squamous		Squamous	
	Atezolizumab N = 449	DOC N = 422	Atezolizumab N = 160	DOC N = 156
All adverse events	427 (95.1)	406 (96.2)	146 (91.3)	149 (95.5)
Grade ≥3 adverse events	167 (37.2)	234 (55.5)	70 (43.8)	90 (57.7)
Adverse events leading to death	3 (0.7)	8 (1.9)	7 (4.4)	6 (3.8)
Serious adverse events	134 (29.8)	120 (28.4)	60 (37.5)	61 (39.1)
Adverse events leading to treatment discontinuation	31 (6.9)	81 (19.2)	15 (9.4)	27 (17.3)
Adverse events leading to dose interruption	113 (25.2)	87 (20.6)	38 (23.8)	29 (18.6)

Based on the above, the indication of "unresectable advanced or recurrent non-small cell lung cancer" was proposed. However, since there are no clinical study data confirming the efficacy and safety of atezolizumab in chemotherapy-naïve patients or candidates for post-operative adjuvant therapy, and the use of atezolizumab in these patients is not recommended, the relevant information will be included in the PRECAUTIONS CONCERNING INDICATION section. Moreover, as the patient population for the OAK study should be made known appropriately, the PRECAUTIONS CONCERNING INDICATION section will advise that eligible patients must be selected by physicians with a full understanding of the information presented in the

CLINICAL STUDIES section, and of the efficacy and safety of atezolizumab.

Nivolumab and pembrolizumab, which block PD-L1/PD-1 binding, as does atezolizumab, have been approved for patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy, i.e. the target population for atezolizumab, but there are no data from a clinical study comparing the efficacy and safety of atezolizumab with those of nivolumab or pembrolizumab, and when to use atezolizumab and when to use nivolumab or pembrolizumab are unknown at present.

PMDA's discussion:
PMDA largely accepted the applicant's explanation. The CLINICAL STUDIES section of the package insert should state that the OAK study was conducted in patients previously treated with platinum-containing chemotherapy, and the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section. Then, the proposed indication of "unresectable advanced or recurrent non-small cell lung cancer" is appropriate.

- The efficacy and safety of atezolizumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of atezolizumab in a post-operative adjuvant chemotherapy setting have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of atezolizumab.

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

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

The applicant's response:
In the OAK study, the Ventana anti-PD-L1 (SP142) assay was used to measure PD-L1 expression in tumor specimens, and the following analyses (a) and (b) were performed.

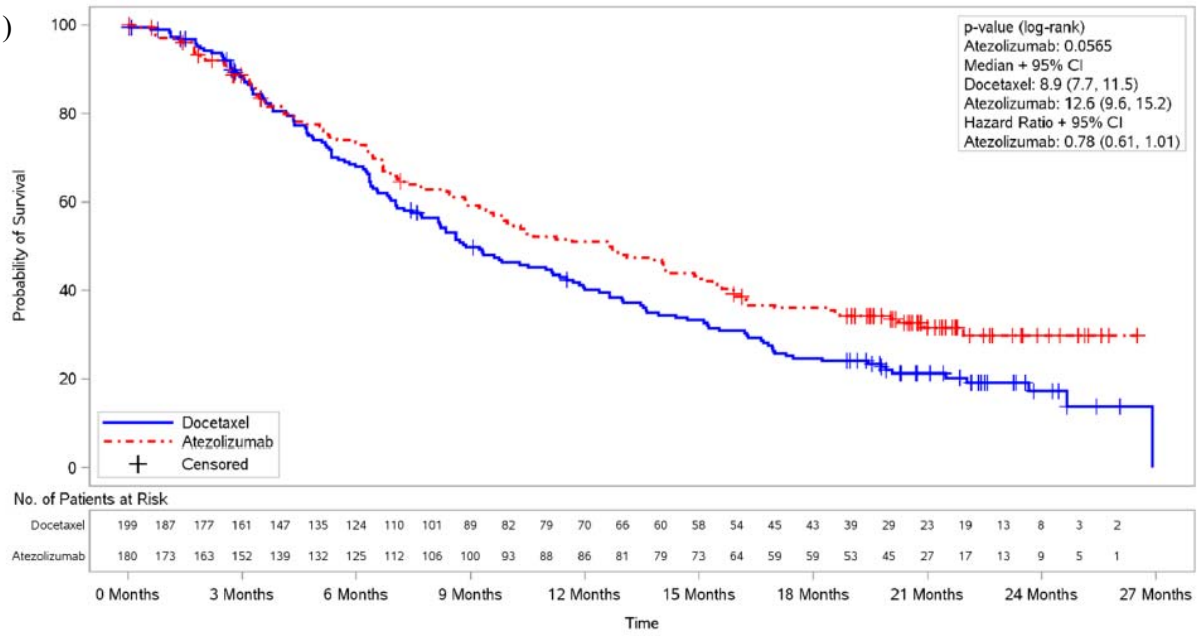
(a) Efficacy
OS by PD-L1 expression status is shown in Table 53 and Figures 5, 6, and 7 (data cutoff date of July 7, 2016). As OS favored the atezolizumab group compared to the DOC group in the TC0/1/2 and IC0/1/2 subgroup, the TC0/1 and IC0/1 subgroup, and the TC0 and IC0 subgroup, etc., it is not concluded that PD-L1 expression status is the best predictive factor for response to atezolizumab in terms of OS, and the efficacy of atezolizumab is expected, irrespective of PD-L1 expression status.

Table 53. Efficacy results by PD-L1 expression status in tumor specimens (OAK study, data cutoff date of July 7, 2016)

PD-L1	Treatment group	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
TC0 and IC0	Atezolizumab	180	12.6 [9.6, 15.2]	0.78 [0.61, 1.01]	0.8454
	DOC	199	8.9 [7.7, 11.5]		
TC1/2/3 or IC1/2/3	Atezolizumab	241	15.7 [12.6, 18.0]	0.74 [0.58, 0.93]	
	DOC	222	10.3 [8.8, 12.0]		
TC0/1 and IC0/1	Atezolizumab	290	12.7 [10.0, 15.0]	0.79 [0.64, 0.96]	0.4479
	DOC	284	9.2 [8.2, 11.1]		
TC2/3 or IC2/3	Atezolizumab	129	16.3 [13.3, 20.1]	0.67 [0.49, 0.92]	
	DOC	136	10.8 [8.8, 12.7]		
TC0/1/2 and IC0/1/2	Atezolizumab	348	12.6 [10.2, 14.2]	0.83 [0.69, 1.00]	0.0031
	DOC	356	9.8 [8.6, 11.8]		
TC3 or IC3	Atezolizumab	72	20.5 [17.5, NE]	0.43 [0.27, 0.69]	
	DOC	65	8.9 [5.6, 11.6]		

*: Cox regression stratified by PD-L1 expression (IC0, IC1, IC2, IC3), the number of prior chemotherapy regimens (1, 2), and histology (squamous, non-squamous)

(1)



(2)

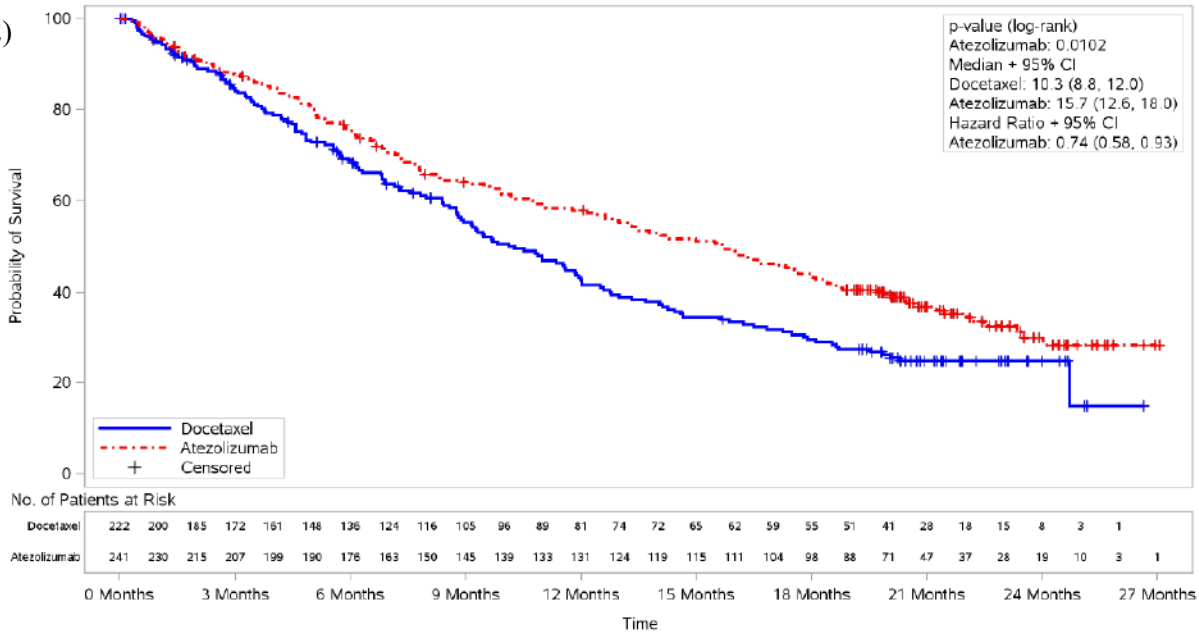


Figure 5. Kaplan-Meier curves for OS by PD-L1 expression status
[(1) TC0 and IC0 subgroup, (2) TC1/2/3 or IC1/2/3 subgroup]

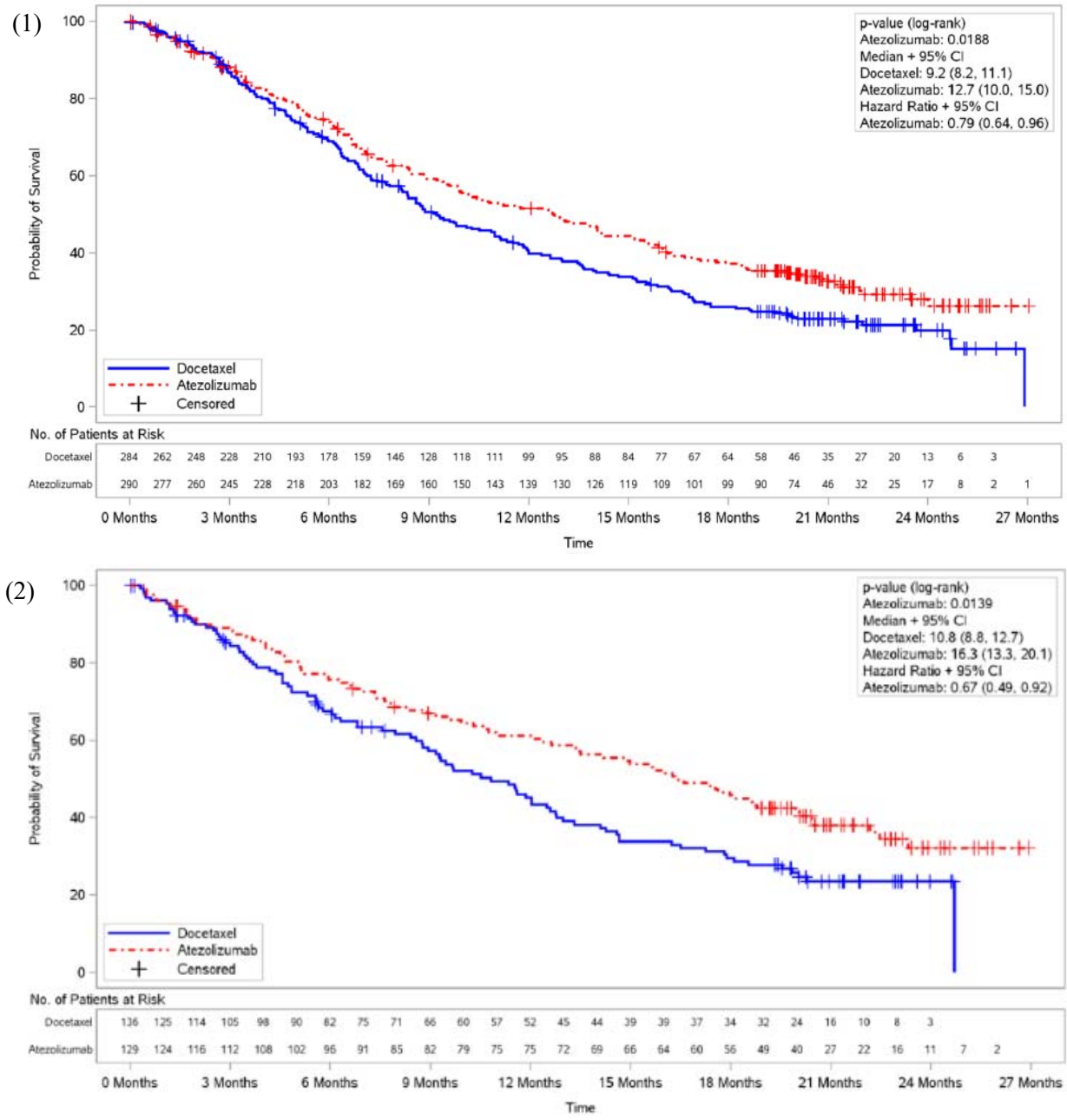


Figure 6. Kaplan-Meier curves for OS by PD-L1 expression status
[(1) TC0/1 and IC0/1 subgroup, (2) TC2/3 or IC2/3 subgroup]

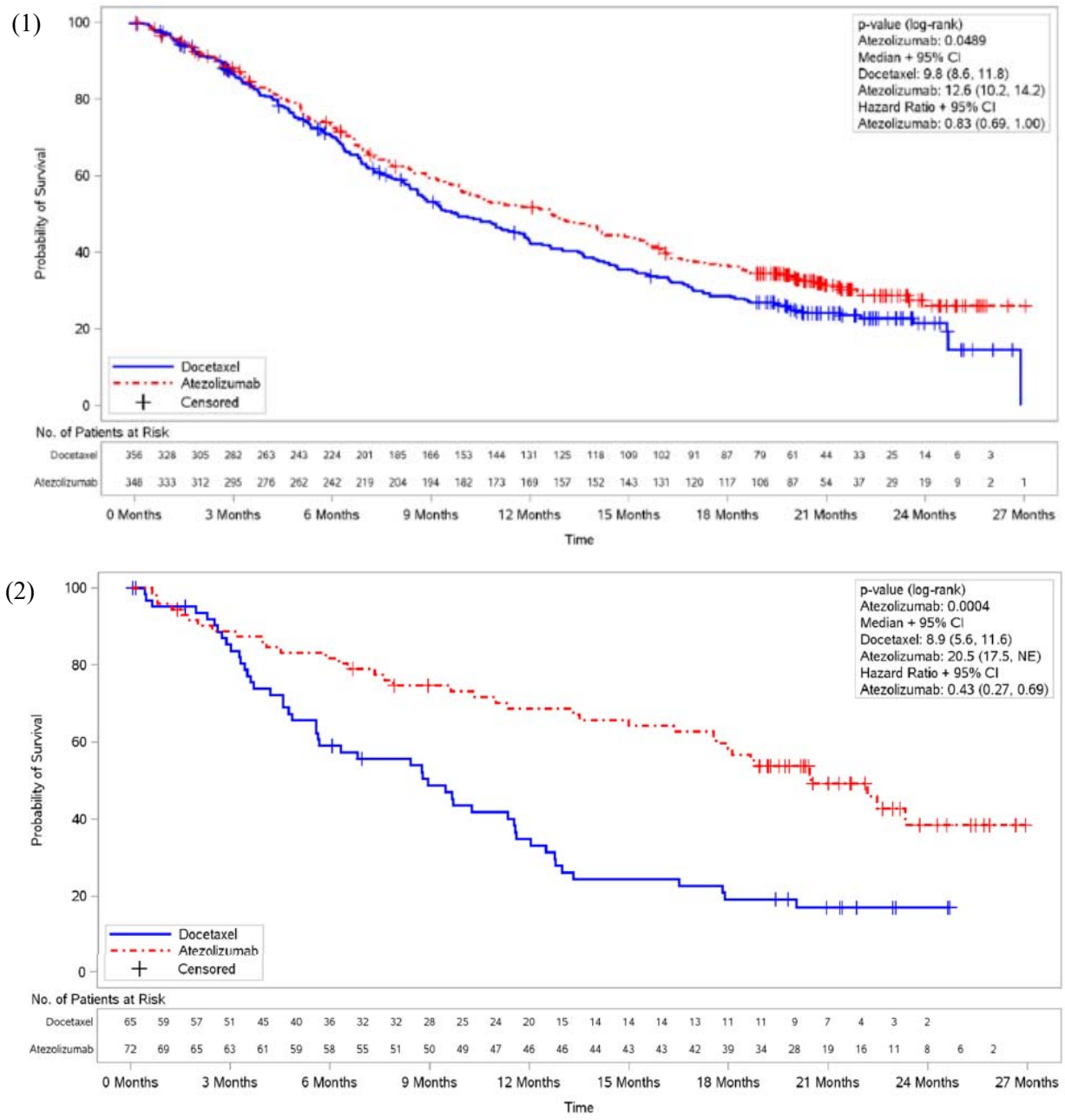


Figure 7. Kaplan-Meier curves for OS by PD-L1 expression status
[(1) TC0/1/2 and IC0/1/2 subgroup, (2) TC3 or IC3 subgroup]

Furthermore, efficacy results by PD-L1 expression status and histology are shown in Table 54.

In both non-squamous and squamous histology, OS favored the atezolizumab group compared with the DOC group in the TC0/1/2 and IC0/1/2 subgroup, the TC0/1 and IC0/1 subgroup, and the TC0 and IC0 subgroup, etc. Thus, it is not concluded that histology and PD-L1 expression status are the best predictive factors for response to atezolizumab in terms of OS, and the efficacy of atezolizumab is expected, irrespective of histology and PD-L1 expression status.

Table 54. Efficacy results by histology and PD-L1 expression status in tumor specimens (OAK study, data cutoff date of July 7, 2016)

PD-L1	Treatment group	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
Non-squamous					
TC0 and IC0	Atezolizumab	140	14.0 [10.1, 15.9]	0.75 [0.57, 1.00]	0.8364
	DOC	150	11.2 [8.6, 13.5]		
TC1/2/3 or IC1/2/3	Atezolizumab	171	17.6 [14.2, 20.4]	0.72 [0.55, 0.95]	
	DOC	162	11.3 [9.3, 13.0]		
TC0/1 and IC0/1	Atezolizumab	221	14.1 [11.7, 16.3]	0.79 [0.62, 1.00]	0.2447
	DOC	212	11.3 [8.9, 13.5]		
TC2/3 or IC2/3	Atezolizumab	89	18.7 [15.5, NE]	0.61 [0.42, 0.88]	
	DOC	99	11.3 [8.8, 13.0]		
TC0/1/2 and IC0/1/2	Atezolizumab	262	14.2 [12.1, 16.1]	0.83 [0.67, 1.03]	0.0017
	DOC	265	11.9 [9.8, 13.9]		
TC3 or IC3	Atezolizumab	49	22.5 [18.0, NE]	0.35 [0.21, 0.61]	
	DOC	47	8.7 [4.7, 11.3]		
Squamous					
TC0 and IC0	Atezolizumab	40	7.6 [4.4, 12.9]	0.82 [0.51, 1.32]	0.7207
	DOC	49	7.1 [6.0, 8.6]		
TC1/2/3 or IC1/2/3	Atezolizumab	70	9.9 [7.6, 15.5]	0.71 [0.48, 1.06]	
	DOC	60	8.7 [6.2, 10.9]		
TC0/1 and IC0/1	Atezolizumab	69	7.8 [6.7, 11.2]	0.76 [0.52, 1.11]	0.9299
	DOC	72	7.3 [6.3, 8.6]		
TC2/3 or IC2/3	Atezolizumab	40	10.4 [7.6, 17.5]	0.76 [0.45, 1.29]	
	DOC	37	9.7 [5.6, 17.2]		
TC0/1/2 and IC0/1/2	Atezolizumab	86	7.8 [6.9, 10.6]	0.79 [0.57, 1.11]	0.4902
	DOC	91	7.5 [6.3, 8.7]		
TC3 or IC3	Atezolizumab	23	17.5 [7.9, 23.3]	0.57 [0.27, 1.20]	
	DOC	18	11.6 [5.6, 16.5]		

*: Unstratified Cox regression

(b) Safety

Safety data by PD-L1 expression status are summarized in Table 55. There was no clear association between PD-L1 expression status in tumor specimens and the safety of atezolizumab.

Table 55. Summary of safety data by PD-L1 expression status (OAK study)

	n (%)			
	TC0 and IC0 subgroup		TC1/2/3 or IC1/2/3 subgroup	
	Atezolizumab N = 258	DOC N = 256	Atezolizumab N = 345	DOC N = 319
All adverse events	242 (93.8)	246 (96.1)	325 (94.2)	306 (95.9)
Grade ≥3 adverse events	100 (38.8)	146 (57.0)	134 (38.8)	176 (55.2)
Adverse events leading to death	6 (2.3)	7 (2.7)	3 (0.9)	7 (2.2)
Serious adverse events	71 (27.5)	83 (32.4)	120 (34.8)	98 (30.7)
Adverse events leading to treatment discontinuation	18 (7.0)	52 (20.3)	27 (7.8)	56 (17.6)
Adverse events leading to dose interruption	48 (18.6)	57 (22.3)	102 (29.6)	59 (18.5)

	n (%)			
	TC0/1 and IC0/1 subgroup		TC2/3 or IC2/3 subgroup	
	Atezolizumab N = 433	DOC N = 402	Atezolizumab N = 168	DOC N = 173
All adverse events	402 (92.8)	387 (96.3)	163 (97.0)	165 (95.4)
Grade ≥3 adverse events	171 (39.5)	226 (56.2)	62 (36.9)	96 (55.5)
Adverse events leading to death	7 (1.6)	11 (2.7)	2 (1.2)	3 (1.7)
Serious adverse events	140 (32.3)	125 (31.1)	51 (30.4)	56 (32.4)
Adverse events leading to treatment discontinuation	30 (6.9)	79 (19.7)	14 (8.3)	29 (16.8)
Adverse events leading to dose interruption	99 (22.9)	83 (20.6)	51 (30.4)	33 (19.1)

	n (%)			
	TC0/1/2 and IC0/1/2 subgroup		TC3 or IC3 subgroup	
	Atezolizumab N = 513	DOC N = 494	Atezolizumab N = 89	DOC N = 81
All adverse events	482 (94.0)	476 (96.4)	85 (95.5)	76 (93.8)
Grade ≥3 adverse events	204 (39.8)	277 (56.1)	29 (32.6)	46 (56.8)
Adverse events leading to death	8 (1.6)	12 (2.4)	1 (1.1)	2 (2.5)
Serious adverse events	169 (32.9)	147 (29.8)	22 (24.7)	34 (42.0)
Adverse events leading to treatment discontinuation	36 (7.0)	92 (18.6)	9 (10.1)	15 (18.5)
Adverse events leading to dose interruption	122 (23.8)	103 (20.9)	27 (30.3)	13 (16.0)

Moreover, safety data by PD-L1 expression status and histology are summarized in Tables 56 and 57. Also when analyzed by non-squamous or squamous histology, there was no clear association between PD-L1 expression status in tumor specimens and the safety of atezolizumab.

Table 56. Summary of safety data by PD-L1 expression status (OAK study, non-squamous)

	n (%)			
	TC0 and IC0 subgroup		TC1/2/3 or IC1/2/3 subgroup	
	Atezolizumab N = 198	DOC N = 190	Atezolizumab N = 248	DOC N = 230
All adverse events	186 (93.9)	182 (95.8)	238 (96.0)	222 (96.5)
Grade ≥3 adverse events	74 (37.4)	107 (56.3)	92 (37.1)	125 (54.3)
Adverse events leading to death	1 (0.5)	6 (3.2)	2 (0.8)	2 (0.9)
Serious adverse events	50 (25.3)	54 (28.4)	83 (33.5)	66 (28.7)
Adverse events leading to treatment discontinuation	11 (5.6)	40 (21.1)	20 (8.1)	41 (17.8)
Adverse events leading to dose interruption	38 (19.2)	38 (20.0)	74 (29.8)	49 (21.3)

	n (%)			
	TC0/1 and IC0/1 subgroup		TC2/3 or IC2/3 subgroup	
	Atezolizumab N = 326	DOC N = 291	Atezolizumab N = 119	DOC N = 129
All adverse events	307 (94.2)	280 (96.2)	116 (97.5)	124 (96.1)
Grade ≥3 adverse events	122 (37.4)	162 (55.7)	43 (36.1)	70 (54.3)
Adverse events leading to death	2 (0.6)	7 (2.4)	1 (0.8)	1 (0.8)
Serious adverse events	96 (29.4)	82 (28.2)	37 (31.1)	38 (29.5)
Adverse events leading to treatment discontinuation	20 (6.1)	59 (20.3)	11 (9.2)	22 (17.1)
Adverse events leading to dose interruption	77 (23.6)	60 (20.6)	35 (29.4)	27 (20.9)

	n (%)			
	TC0/1/2 and IC0/1/2 subgroup		TC3 or IC3 subgroup	
	Atezolizumab N = 384	DOC N = 360	Atezolizumab N = 61	DOC N = 60
All adverse events	366 (95.3)	346 (96.1)	57 (93.4)	58 (96.7)
Grade ≥3 adverse events	149 (38.8)	199 (55.3)	16 (26.2)	34 (56.7)
Adverse events leading to death	3 (0.8)	7 (1.9)	0	1 (1.7)
Serious adverse events	119 (31.0)	96 (26.7)	14 (23.0)	24 (40.0)
Adverse events leading to treatment discontinuation	25 (6.5)	71 (19.7)	6 (9.8)	9 (15.0)
Adverse events leading to dose interruption	91 (23.7)	77 (21.4)	20 (32.8)	10 (16.7)

Table 57. Summary of safety data by PD-L1 expression status (OAK study, squamous)

	n (%)			
	TC0 and IC0 subgroup		TC1/2/3 or IC1/2/3 subgroup	
	Atezolizumab N = 60	DOC N = 66	Atezolizumab N = 97	DOC N = 89
All adverse events	56 (93.3)	64 (97.0)	87 (89.7)	84 (94.4)
Grade ≥3 adverse events	26 (43.3)	39 (59.1)	42 (43.3)	51 (57.3)
Adverse events leading to death	5 (8.3)	1 (1.5)	1 (1.0)	5 (5.6)
Serious adverse events	21 (35.0)	29 (43.9)	37 (38.1)	32 (36.0)
Adverse events leading to treatment discontinuation	7 (11.7)	12 (18.2)	7 (7.2)	15 (16.9)
Adverse events leading to dose interruption	10 (16.7)	19 (28.8)	28 (28.9)	10 (11.2)

	n (%)			
	TC0/1 and IC0/1 subgroup		TC2/3 or IC2/3 subgroup	
	Atezolizumab N = 107	DOC N = 111	Atezolizumab N = 49	DOC N = 44
All adverse events	95 (88.8)	107 (96.4)	47 (95.9)	41 (93.2)
Grade ≥3 adverse events	49 (45.8)	64 (57.7)	19 (38.8)	26 (59.1)
Adverse events leading to death	5 (4.7)	4 (3.6)	1 (2.0)	2 (4.5)
Serious adverse events	44 (41.1)	43 (38.7)	14 (28.6)	18 (40.9)
Adverse events leading to treatment discontinuation	10 (9.3)	20 (18.0)	3 (6.1)	7 (15.9)
Adverse events leading to dose interruption	22 (20.6)	23 (20.7)	16 (32.7)	6 (13.6)

	n (%)			
	TC0/1/2 and IC0/1/2 subgroup		TC3 or IC3 subgroup	
	Atezolizumab N = 129	DOC N = 134	Atezolizumab N = 28	DOC N = 21
All adverse events	116 (89.9)	130 (97.0)	27 (96.4)	18 (85.7)
Grade ≥3 adverse events	55 (42.6)	78 (58.2)	13 (46.4)	12 (57.1)
Adverse events leading to death	5 (3.9)	5 (3.7)	1 (3.6)	1 (4.8)
Serious adverse events	50 (38.8)	51 (38.1)	8 (28.6)	10 (47.6)
Adverse events leading to treatment discontinuation	11 (8.5)	21 (15.7)	3 (10.7)	6 (28.6)
Adverse events leading to dose interruption	31 (24.0)	26 (19.4)	7 (25.0)	3 (14.3)

Based on the results of the above analyses (a) and (b), the use of atezolizumab is recommended, irrespective of PD-L1 expression status.

PMDA's discussion:

PMDA accepted the applicant's explanation, but considers that as atezolizumab is an antibody drug directed against PD-L1, etc., it is necessary to provide the above clinical study results by PD-L1 expression status to healthcare professionals in clinical practice, using information materials etc., continue to collect information on the predictive factors for response to atezolizumab, 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 is "The usual adult dosage is 1200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks." The following statements are included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert.

- The efficacy and safety of atezolizumab in combination with other anti-neoplastic drugs have not been established.
- Infusion solution preparation procedure
- Infusion time
  - Administer the initial infusion of atezolizumab over 60 minutes.
  - If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety," and the following considerations, PMDA concluded that the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement should be amended to "The usual adult dosage is 1200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes."

- The efficacy and safety of atezolizumab in combination with other anti-neoplastic drugs have not been established.
- Infusion solution preparation procedure
- Recommended dosage modifications for adverse reactions

7.R.5.1 Dosage and administration for atezolizumab

The applicant's explanation about the dosing rationale for atezolizumab in patients with unresectable advanced or recurrent NSCLC:

A foreign phase I study (Study PCD4989g) demonstrated the safety of atezolizumab 0.03 to 20 mg/kg Q3W. Although serum atezolizumab concentrations tended to be lower in anti-atezolizumab antibody-positive patients than in antibody-negative patients [see Section 6.R.1], there were no clear differences in atezolizumab exposure according to anti-atezolizumab antibody status in the 15 or 20 mg/kg group. Moreover, as there seemed be no clear differences in the C_{min}[17)] of atezolizumab between the 15 and 20 mg/kg groups, the recommended dosage of 15 mg/kg Q3W was selected.

Then, given that compared with body weight-based dosing, fixed dosing can reduce the risk of human errors when preparing the drug solution for infusion, and has its advantages in clinical practice (e.g. there is no need

[17)] The C_{min} values of atezolizumab (mean ± SD) predose of Cycle 4 in the 15 and 20 mg/kg groups were 145 ± 66.1 and 185 ± 68.4 μg/mL, respectively.

to discard unused product remaining in the vials), the dosing regimen of atezolizumab 1200 mg/body Q3W was selected for the OAK study, taking account of the results of preliminary analysis using the PPK model.[18)] Since the OAK study demonstrated the clinical usefulness of atezolizumab in patients with unresectable advanced or recurrent NSCLC, the proposed dosing regimen was selected based on the OAK study. In a Japanese phase I study (Study JO28944), atezolizumab 10 or 20 mg/kg Q3W was administered, and no DLTs were observed at either dose level, demonstrating the tolerability of atezolizumab at doses up to 20 mg/kg also in Japanese patients.

With respect to the infusion time of atezolizumab, based on the infusion time specified in the OAK study, the following statements will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section: Administer the initial infusion of atezolizumab over 60 minutes; and if the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes. Furthermore, as there are no data on the efficacy and safety of atezolizumab in combination with other anti-neoplastic drugs in patients with NSCLC, this information will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

PMDA's discussion:
PMDA largely accepted the applicant's explanation. However, since the infusion time of atezolizumab used in the OAK study should be specified in the DOSAGE AND ADMINISTRATION section, the proposed dosage and administration statement should be amended to "The usual adult dosage is 1200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes."

7.R.5.2 Recommended dosage modifications

The applicant's explanation about the recommended dosage modifications for atezolizumab:
The OAK study was conducted according to the specific dosage modification guidelines, and demonstrated the tolerability and safety of atezolizumab. Thus, information on these dosage modification guidelines will be appropriately provided to healthcare professionals in clinical practice, using information materials etc.

PMDA's discussion:
Given that the OAK study was conducted according to the specific dosage modification guidelines, and demonstrated the tolerability and safety of atezolizumab, and that atezolizumab will be used by physicians with adequate knowledge of and experience in cancer chemotherapy, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section should include a revised version of these dosage modification guidelines as shown below.

- In the event of adverse reactions to atezolizumab, atezolizumab dosage modifications should be considered as per the table below.

[18)] The model was developed based on atezolizumab PK data (1326 samples from 162 subjects) from a foreign phase I study (Study PCD4989g) (software: NONMEM Version 7.2.0).

Recommended dosage modifications for adverse reactions[*1]

Adverse reaction	Severity of adverse reaction	Dosage modifications
Respiratory disorders such as ILD	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3, or recurrent respiratory disorder	Permanently discontinue
Hepatic dysfunction	AST or ALT 3-5 × ULN or total bilirubin 1.5-3 × ULN persists for >5 days	Withhold dose until resolution to the normal range. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	AST or ALT >5 × ULN or total bilirubin >3 × ULN	Permanently discontinue
Colitis/Diarrhoea	Grade 2 or 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4	Permanently discontinue
Endocrinopathies	• Symptomatic hypothyroidism • Symptomatic hyperthyroidism, or asymptomatic hyperthyroidism with thyroid stimulating hormone <0.1 mU/L • Grade ≥2 adrenal insufficiency • Grade ≥3 hyperglycaemia	Withhold dose until resolution. Permanently discontinue if adrenal insufficiency does not improve to Grade ≤1 within 12 weeks.
Ophthalmopathies	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue
IRR	Grade 1	Reduce the infusion rate by 50%. Monitor for 30 minutes after symptoms have improved, and if IRR does not recur, the infusion rate may be increased back to baseline.
	Grade 2	Interrupt infusion, and resume infusion at a 50% reduction in rate after symptoms have improved.
	Grade ≥3	Discontinue infusion immediately
Pancreatitis	• Grade ≥3 amylase or lipase levels increased • Grade 2 or 3 immune-related[*2] pancreatitis	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4 immune-related[*2] pancreatitis or recurrent pancreatitis	Permanently discontinue
Skin toxicities	Grade 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4	Permanently discontinue
Neuropathies	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue

*1: Severity grade based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0
*2: Involvement of autoimmunity cannot be ruled out.

7.R.6 Post-marketing investigations

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

The applicant is planning to conduct post-marketing surveillance, covering all patients treated with atezolizumab, to assess the safety etc. of atezolizumab in clinical practice. In this surveillance, only events considered by the treating physician to be caused by excessive immune response among adverse reactions to atezolizumab, will be collected, taking account of the mechanism of action of atezolizumab.

Given the incidence of adverse events in the OAK study etc. and the mechanism of action of atezolizumab etc., the safety specification for the surveillance includes pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies (diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis),

neuropathies (myasthenia gravis, Guillain-Barre syndrome), meningoencephalitis, myocarditis, myositis, ocular inflammation, nephritis, severe skin disorders, vasculitis, and autoimmune hemolytic anemia.

Taking account of the incidences of individual events included in the safety specification in the OAK study, etc., a planned sample size of 1000 patients has been chosen.

The observation period is 1 year because most of specific events included in the safety specification occurred within 1 year after the start of treatment with atezolizumab in the OAK study, and the incidence of any of those events did not tend to increase beyond 1 year of treatment.

PMDA's discussion:
Since the safety information from Japanese patients treated with atezolizumab is limited, etc., it is necessary to conduct post-marketing surveillance covering all patients treated with atezolizumab over a specified period of time, in order to collect all safety information, including but not limited to events considered by the treating physician to be caused by excessive immune response, in a prompt and unbiased manner, and provide the obtained safety information to healthcare professionals in clinical practice as soon as possible.

Based on the considerations in Sections "5.5.2 Effects on embryo-fetal development and use in pregnant women" and "7.R.3 Safety," the safety specification for the surveillance should include ILD, hepatic dysfunction, colitis/severe diarrhea, pancreatitis, type 1 diabetes mellitus, endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction), neuropathies (including Guillain-Barre syndrome), myasthenia gravis, encephalitis/meningitis, IRR, myositis/rhabdomyolysis, renal dysfunction (tubulointerstitial nephritis, etc.), severe skin disorders, myocarditis, hemolytic anemia, immune thrombocytopenic purpura, embryo-fetal toxicity, and use in organ transplant recipients (including hematopoietic stem cell transplant recipients).

The planned sample size and observation period need to be reconsidered, taking account of the occurrence of individual events included in the safety specification for the surveillance.

7.2 Adverse events etc. observed in clinical studies

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

7.2.1 Japanese phase I study (Study JO28944)

Adverse events occurred in all subjects, and those for which a causal relationship to study drug could not be ruled out also occurred in all subjects. Adverse events reported by ≥2 subjects in each cohort were rash; and headache (2 subjects each) in Cohort 1.

A serious adverse event occurred in 1 of 3 subjects (33.3%) in Cohort 1, which was influenza like illness. Its causal relationship to study drug could not be ruled out.

There were no adverse events leading to study drug discontinuation.

7.2.2 Global phase II study (BIRCH study)

Adverse events occurred in 127 of 139 subjects (91.4%) in Cohort 1, 246 of 267 subjects (92.1%) in Cohort 2, and 244 of 253 subjects (96.4%) in Cohort 3, and those for which a causal relationship to study drug could not be ruled out occurred in 79 of 139 subjects (56.8%) in Cohort 1, 169 of 267 subjects (63.3%) in Cohort 2, and 174 of 253 subjects (68.8%) in Cohort 3. Adverse events reported by ≥20% of subjects in any cohort are shown in Table 58.

Table 58. Adverse events reported by ≥20% of subjects in any cohort

SOC PT (MedDRA ver. 18.0)	n (%)					
	Cohort 1 N = 139		Cohort 2 N = 267		Cohort 3 N = 253	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	127 (91.4)	58 (41.7)	246 (92.1)	108 (40.4)	244 (96.4)	105 (41.5)
General disorders and administration site conditions						
Fatigue	45 (32.4)	3 (2.2)	74 (27.7)	7 (2.6)	84 (33.2)	5 (2.0)
Gastrointestinal disorders						
Nausea	26 (18.7)	3 (2.2)	61 (22.8)	4 (1.5)	54 (21.3)	3 (1.2)
Respiratory, thoracic and mediastinal disorders						
Cough	33 (23.7)	0	45 (16.9)	3 (1.1)	66 (26.1)	2 (0.8)
Dyspnoea	36 (25.9)	5 (3.6)	42 (15.7)	9 (3.4)	65 (25.7)	14 (5.5)
Metabolism and nutrition disorders						
Decreased appetite	32 (23.0)	0	47 (17.6)	3 (1.1)	69 (27.3)	3 (1.2)

Serious adverse events occurred in 43 of 139 subjects (30.9%) in Cohort 1, 96 of 267 subjects (36.0%) in Cohort 2, and 94 of 253 subjects (37.2%) in Cohort 3. Those reported by ≥3 subjects in each cohort were pneumonia; and dyspnoea (3 subjects each [2.2%]) in Cohort 1, pneumonitis; and pyrexia (8 subjects each [3.0%]); pneumonia (7 subjects [2.6%]); hypercalcaemia (5 subjects [1.9%]); dyspnoea; and vomiting (4 subjects each [1.5%]); and nausea; and lung infection (3 subjects each [1.1%]) in Cohort 2, and pneumonia (12 subjects [4.7%]); dyspnoea (11 subjects [4.3%]); pyrexia (7 subjects [2.8%]); pneumonitis (5 subjects [2.0%]); haemoptysis (4 subjects [1.6%]); and vomiting; cerebrovascular accident; and anaemia (3 subjects each [1.2%]) in Cohort 3. A causal relationship to study drug could not be ruled out for pneumonitis (5 subjects); pyrexia; and nausea (2 subjects each); and dyspnoea; vomiting; and hypercalcaemia (1 subject each) in Cohort 2 and pneumonitis; and pyrexia (3 subjects each); anaemia (2 subjects); and pneumonia (1 subject) in Cohort 3.

Adverse events leading to study drug discontinuation occurred in 8 of 139 subjects (5.8%) in Cohort 1, 15 of 267 subjects (5.6%) in Cohort 2, and 11 of 253 subjects (4.3%) in Cohort 3. Those reported by ≥2 subjects in each cohort were pneumonitis (3 subjects [1.1%]) in Cohort 2 and pneumonia (2 subjects [0.8%]) in Cohort 3.

A causal relationship to study drug could not be ruled out for pneumonitis (1 subject) in Cohort 2 and pneumonia (1 subject) in Cohort 3.

7.2.3 Global phase III study (OAK study)

Adverse events occurred in 573 of 609 subjects (94.1%) in the atezolizumab group and 555 of 578 subjects (96.0%) in the DOC group, and those for which a causal relationship to study drug could not be ruled out occurred in 390 of 609 subjects (64.0%) in the atezolizumab group and 496 of 578 subjects (85.8%) in the DOC group. Adverse events reported by ≥20% of subjects in either group are shown in Table 59.

Table 59. Adverse events reported by ≥20% of subjects in either group

SOC PT (MedDRA ver. 19.0)	n (%)			
	Atezolizumab N = 609		DOC N = 578	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	573 (94.1)	237 (38.9)	555 (96.0)	324 (56.1)
General disorders and administration site conditions				
Fatigue	163 (26.8)	17 (2.8)	205 (35.5)	23 (4.0)
Respiratory, thoracic and mediastinal disorders				
Cough	141 (23.2)	2 (0.3)	105 (18.2)	1 (0.2)
Gastrointestinal disorders				
Nausea	108 (17.7)	4 (0.7)	131 (22.7)	2 (0.3)
Diarrhoea	94 (15.4)	4 (0.7)	141 (24.4)	11 (1.9)
Metabolism and nutrition disorders				
Decreased appetite	143 (23.5)	2 (0.3)	136 (23.5)	9 (1.6)
Skin and subcutaneous tissue disorders				
Alopecia	3 (0.5)	0	202 (34.9)	1 (0.2)
Blood and lymphatic system disorders				
Anaemia	70 (11.5)	14 (2.3)	136 (23.5)	33 (5.7)

Serious adverse events occurred in 194 of 609 subjects (31.9%) in the atezolizumab group and 181 of 578 subjects (31.3%) in the DOC group. Those reported by ≥3 subjects in each group were pneumonia (20 subjects [3.3%]); dyspnoea; and pleural effusion (12 subjects each [2.0%]); pyrexia; and pulmonary embolism (9 subjects each [1.5%]); respiratory tract infection (8 subjects [1.3%]); anaemia; haemoptysis; sepsis; and pneumonitis (5 subjects each [0.8%]); pericardial effusion; and bone pain (4 subjects each [0.7%]); and fatigue; lower respiratory tract infection; pneumothorax; hypoxia; respiratory failure; back pain; superior vena cava syndrome; hypotension; hypersensitivity; meningitis; hyperglycaemia; and hip fracture (3 subjects each [0.5%]) in the atezolizumab group and febrile neutropenia (37 subjects [6.4%]); pneumonia (31 subjects [5.4%]); dyspnoea; and pyrexia (8 subjects each [1.4%]); anaemia; and diarrhoea (7 subject each [1.2%]); pleural effusion (6 subjects [1.0%]); haemoptysis; vomiting; and neutrophil count decreased (5 subjects each [0.9%]); respiratory tract infection; fatigue; abdominal pain; and infection (4 subjects each [0.7%]); and lower respiratory tract infection; lung infection; chronic obstructive pulmonary disease; dehydration; acute kidney injury; syncope; asthenia; atrial fibrillation; and neutropenia (3 subjects each [0.5%]) in the DOC group. A causal relationship to study drug could not be ruled out for pneumonitis (5 subjects); pyrexia; hypersensitivity; and meningitis (3 subjects each); pneumonia (2 subjects); and dyspnoea; pleural effusion; respiratory tract infection; sepsis; pericardial effusion; fatigue; pneumothorax; hypoxia; superior vena cava syndrome; and

hyperglycaemia (1 subject each) in the atezolizumab group and febrile neutropenia (36 subjects); pneumonia (10 subjects); diarrhoea (6 subjects); pyrexia; and neutrophil count decreased (5 subjects each); anaemia (4 subjects); pleural effusion; lung infection; vomiting; dehydration; and neutropenia (3 subjects each); lower respiratory tract infection; acute kidney injury; syncope; and asthenia (2 subjects each); and dyspnoea; respiratory tract infection; fatigue; abdominal pain; and atrial fibrillation (1 subject each) in the DOC group.

Adverse events leading to study drug discontinuation occurred in 46 of 609 subjects (7.6%) in the atezolizumab group and 108 of 578 subjects (18.7%) in the DOC group. Those reported by ≥3 subjects in each group were pneumonia; and meningitis (3 subjects each [0.5%]) in the atezolizumab group and fatigue (15 subjects [2.6%]); paraesthesia (11 subjects [1.9%]); peripheral neuropathy; and asthenia (10 subjects each [1.7%]); pneumonia (7 subjects [1.2%]); dyspnoea; and peripheral oedema (6 subjects each [1.0%]); peripheral sensory neuropathy (4 subjects [0.7%]); and pleural effusion; decreased appetite; generalised oedema; and drug hypersensitivity (3 subjects each [0.5%]) in the DOC group. A causal relationship to study drug could not be ruled out for meningitis (3 subjects); and pneumonia (2 subjects) in the atezolizumab group and fatigue (14 subjects); paraesthesia (11 subjects); peripheral neuropathy; and asthenia (10 subjects each); pneumonia; and peripheral oedema (5 subjects each); peripheral sensory neuropathy (4 subjects); decreased appetite; generalised oedema; and drug hypersensitivity (3 subjects each); pleural effusion (2 subjects); and dyspnoea (1 subject) in the DOC group.

7.2.4 Foreign phase I study (Study PCD4989g)

Adverse events occurred in 1 of 1 subject (100%) in the 0.01 mg/kg group, 1 of 1 subject (100%) in the 0.03 mg/kg group, 1 of 1 subject (100%) in the 0.1 mg/kg group, 3 of 3 subjects (100%) in the 0.3 mg/kg group, 3 of 3 subjects (100%) in the 1 mg/kg group, 3 of 3 subjects (100%) in the 3 mg/kg group, 35 of 36 subjects (97.2%) in the 10 mg/kg group, 231 of 236 subjects (97.9%) in the 15 mg/kg group, 145 of 146 subjects (99.3%) in the 20 mg/kg group, and 43 of 51 subjects (84.3%) in the 1200 mg/body group, and those for which a causal relationship to study drug could not be ruled out occurred in 1 of 1 subject (100%) in the 0.03 mg/kg group, 1 of 1 subject (100%) in the 0.1 mg/kg group, 3 of 3 subjects (100%) in the 0.3 mg/kg group, 3 of 3 subjects (100%) in the 1 mg/kg group, 3 of 3 subjects (100%) in the 3 mg/kg group, 31 of 36 subjects (86.1%) in the 10 mg/kg group, 172 of 236 subjects (72.9%) in the 15 mg/kg group, 108 of 146 subjects (74.0%) in the 20 mg/kg group, and 25 of 51 subjects (49.0%) in the 1200 mg/body group. Adverse events reported by ≥25% of subjects in the 10 mg/kg, 15 mg/kg, 20 mg/kg, or 1200 mg/body group are shown in Table 60.

Table 60. Adverse events reported by ≥25% of subjects in the 10 mg/kg, 15 mg/kg, 20 mg/kg, or 1200 mg/body group

SOC PT (MedDRA ver. 18.0)	n (%)							
	10 mg/kg N = 36		15 mg/kg N = 236		20 mg/kg N = 146		1200 mg/body N = 51	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	35 (97.2)	22 (61.1)	231 (97.9)	119 (50.4)	145 (99.3)	61 (41.8)	43 (84.3)	20 (39.2)
General disorders and administration site conditions								
Fatigue	16 (44.4)	1 (2.8)	88 (37.3)	4 (1.7)	52 (35.6)	6 (4.1)	14 (27.5)	1 (2.0)
Gastrointestinal disorders								
Nausea	9 (25.0)	0	51 (21.6)	2 (0.8)	44 (30.1)	2 (1.4)	13 (25.5)	1 (2.0)
Diarrhoea	16 (44.4)	1 (2.8)	43 (18.2)	0	30 (20.5)	0	8 (15.7)	0
Constipation	9 (25.0)	0	50 (21.2)	1 (0.4)	35 (24.0)	1 (0.7)	6 (11.8)	0
Respiratory, thoracic and mediastinal disorders								
Cough	10 (27.8)	0	51 (21.6)	1 (0.4)	31 (21.2)	0	5 (9.8)	0
Dyspnoea	12 (33.3)	2 (5.6)	31 (13.1)	4 (1.7)	45 (30.8)	9 (6.2)	10 (19.6)	3 (5.9)
Musculoskeletal and connective tissue disorders								
Arthralgia	9 (25.0)	1 (2.8)	30 (12.7)	0	26 (17.8)	0	2 (3.9)	0
Metabolism and nutrition disorders								
Decreased appetite	9 (25.0)	0	57 (24.2)	4 (1.7)	43 (29.5)	0	12 (23.5)	0
Skin and subcutaneous tissue disorders								
Pruritus	9 (25.0)	0	31 (13.1)	0	16 (11.0)	0	5 (9.8)	0
Nervous system disorders								
Headache	13 (36.1)	1 (2.8)	31 (13.1)	1 (0.4)	25 (17.1)	0	6 (11.8)	0
Psychiatric disorders								
Insomnia	10 (27.8)	0	25 (10.6)	1 (0.4)	20 (13.7)	0	2 (3.9)	0

Serious adverse events occurred in 1 of 1 subject (100%) in the 0.01 mg/kg group, 15 of 36 subjects (41.7%) in the 10 mg/kg group, 94 of 236 subjects (39.8%) in the 15 mg/kg group, 56 of 146 subjects (38.4%) in the 20 mg/kg group, and 16 of 51 subjects (31.4%) in the 1200 mg/body group. Those reported by ≥3 subjects in each group were pyrexia (9 subjects [3.8%]); abdominal pain; urinary tract infection; and back pain (5 subjects each [2.1%]); dyspnoea; pneumonia; pain; and sepsis (4 subjects each [1.7%]); and fatigue; hypoxia; acute renal failure; dehydration; and renal failure (3 subjects each [1.3%]) in the 15 mg/kg group, dyspnoea (8 subjects [5.5%]); pyrexia; abdominal pain; and pleural effusion (4 subjects each [2.7%]); and fatigue; and bone pain (3 subjects each [2.1%]) in the 20 mg/kg group, and dyspnoea (4 subjects [7.8%]) in the 1200 mg/body group. A causal relationship to study drug could not be ruled out for pyrexia (6 subjects); hypoxia (2 subjects); and pneumonia; and urinary tract infection (1 subject each) in the 15 mg/kg group, dyspnoea (3 subjects); pyrexia; and bone pain (2 subjects each); and abdominal pain; and fatigue (1 subject each) in the 20 mg/kg group, and dyspnoea (1 subject) in the 1200 mg/body group.

Adverse events leading to study drug discontinuation occurred in 2 of 36 subjects (5.6%) in the 10 mg/kg group, 20 of 236 subjects (8.5%) in the 15 mg/kg group, 7 of 146 subjects (4.8%) in the 20 mg/kg group, and 3 of 51 subjects (5.9%) in the 1200 mg/body group. Those reported by ≥2 subjects in each group were AST increased; and ALT increased (2 subjects each [0.8%]) in the 15 mg/kg group, and a causal relationship to study drug could not be ruled out for all those events.

7.2.5 Foreign phase II study (FIR study)

Adverse events occurred in 31 of 31 subjects (100%) in Cohort 1, 92 of 93 subjects (98.9%) in Cohort 2, and 13 of 13 subjects (100%) in Cohort 3, and those for which a causal relationship to study drug could not be ruled out occurred in 23 of 31 subjects (74.2%) in Cohort 1, 61 of 93 subjects (65.6%) in Cohort 2, and 9 of 13 subjects (69.2%) in Cohort 3. Adverse events reported by ≥20% of subjects in any cohort are shown in Table 61.

Table 61. Adverse events reported by ≥20% of subjects in any cohort

SOC PT (MedDRA ver. 18.0)	n (%)					
	Cohort 1 N = 31		Cohort 2 N = 93		Cohort 3 N = 13	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	31 (100)	15 (48.4)	92 (98.9)	49 (52.7)	13 (100)	7 (53.8)
General disorders and administration site conditions						
Fatigue	15 (48.4)	0	36 (38.7)	2 (2.2)	5 (38.5)	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	8 (25.8)	0	28 (30.1)	4 (4.3)	2 (15.4)	0
Cough	4 (12.9)	0	31 (33.3)	1 (1.1)	2 (15.4)	0
Gastrointestinal disorders						
Nausea	9 (29.0)	1 (3.2)	23 (24.7)	0	4 (30.8)	0
Diarrhoea	8 (25.8)	1 (3.2)	16 (17.2)	0	4 (30.8)	1 (7.7)
Constipation	8 (25.8)	0	14 (15.1)	0	4 (30.8)	1 (7.7)
Vomiting	4 (12.9)	2 (6.5)	13 (14.0)	0	3 (23.1)	0
Musculoskeletal and connective tissue disorders						
Back pain	5 (16.1)	0	19 (20.4)	4 (4.3)	2 (15.4)	0
Metabolism and nutrition disorders						
Decreased appetite	6 (19.4)	0	20 (21.5)	0	2 (15.4)	0
Hypokalaemia	2 (6.5)	1 (3.2)	12 (12.9)	2 (2.2)	4 (30.8)	2 (15.4)
Nervous system disorders						
Headache	2 (6.5)	0	8 (8.6)	0	3 (23.1)	0

Serious adverse events occurred in 16 of 31 subjects (51.6%) in Cohort 1, 43 of 93 subjects (46.2%) in Cohort 2, and 6 of 13 subjects (46.2%) in Cohort 3. Those reported by ≥2 subjects in each cohort were pneumonia; haemoptysis; diarrhoea; and upper respiratory tract infection (2 subjects each [6.5%]) in Cohort 1, pneumonia; and dyspnoea (5 subjects each [5.4%]); back pain (3 subjects [3.2%]); and haemoptysis; lower respiratory tract infection; pulmonary embolism; pulmonary haemorrhage; and pain (2 subjects each [2.2%]) in Cohort 2, and chest pain (2 subjects [15.4%]) in Cohort 3. A causal relationship to study drug could not be ruled out for diarrhoea; and upper respiratory tract infection (1 subject each) in Cohort 1.

Adverse events leading to study drug discontinuation occurred in 2 of 31 subjects (6.5%) in Cohort 1, 9 of 93 subjects (9.7%) in Cohort 2, and 2 of 13 subjects (15.4%) in Cohort 3, which were weight decreased; bronchostenosis; pericardial effusion; and dysphagia (1 subject each [3.2%]) in Cohort 1, dyspnoea (2 subjects [2.2%]); and weight decreased; Guillain-Barre syndrome; diabetes mellitus; pulmonary hypertension; hypercalcaemia; tumour pain; pulmonary embolism; anaemia; and haemoptysis (1 subject each [1.1%]) in Cohort 2, and mental status changes; and general physical condition decreased (1 subject each [7.7%]) in Cohort 3. A causal relationship to study drug could not be ruled out for Guillain-Barre syndrome; diabetes mellitus; and pulmonary hypertension (1 subject each) in Cohort 2.

7.2.6 Foreign phase II study (POPLAR study)

Adverse events occurred in 136 of 142 subjects (95.8%) in the atezolizumab group and 130 of 135 subjects (96.3%) in the DOC group, and those for which a causal relationship to study drug could not be ruled out occurred in 95 of 142 subjects (66.9%) in the atezolizumab group and 119 of 135 subjects (88.1%) in the DOC group. Adverse events reported by ≥20% of subjects in either group are shown in Table 62.

Table 62. Adverse events reported by ≥20% of subjects in either group

SOC PT (MedDRA ver. 18.0)	n (%)			
	Atezolizumab N = 142		DOC N = 135	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	136 (95.8)	63 (44.4)	130 (96.3)	76 (56.3)
General disorders and administration site conditions				
Fatigue	55 (38.7)	3 (2.1)	54 (40.0)	10 (7.4)
Gastrointestinal disorders				
Nausea	31 (21.8)	1 (0.7)	45 (33.3)	0
Constipation	29 (20.4)	0	32 (23.7)	1 (0.7)
Diarrhoea	24 (16.9)	1 (0.7)	38 (28.1)	4 (3.0)
Respiratory, thoracic and mediastinal disorders				
Cough	38 (26.8)	0	33 (24.4)	0
Dyspnoea	38 (26.8)	10 (7.0)	27 (20.0)	2 (1.5)
Metabolism and nutrition disorders				
Decreased appetite	49 (34.5)	2 (1.4)	28 (20.7)	0
Skin and subcutaneous tissue disorders				
Alopecia	3 (2.1)	0	52 (38.5)	1 (0.7)

Serious adverse events occurred in 50 of 142 subjects (35.2%) in the atezolizumab group and 46 of 135 subjects (34.1%) in the DOC group. Those reported by ≥2 subjects in each group were pneumonia (8 subjects [5.6%]); dyspnoea (7 subjects [4.9%]); pleural effusion (4 subjects [2.8%]); pyrexia (3 subjects [2.1%]); and pulmonary embolism; AST increased; rash; hypoxia; pneumothorax; cardiac tamponade; and dysphagia (2 subjects each [1.4%]) in the atezolizumab group and febrile neutropenia (7 subjects [5.2%]); pulmonary embolism (6 subjects [4.4%]); pneumonia; haemoptysis; and sepsis (3 subjects each [2.2%]); and neutropenia; death; and chronic obstructive pulmonary disease (2 subjects each [1.5%]) in the DOC group. A causal relationship to study drug could not be ruled out for pneumonia; and pyrexia (3 subjects each); AST increased; and rash (2 subjects each); and hypoxia (1 subject) in the atezolizumab group and febrile neutropenia (7 subjects); pneumonia; sepsis; and neutropenia (2 subjects each); and death (1 subject) in the DOC group.

Adverse events leading to study drug discontinuation occurred in 11 of 142 subjects (7.7%) in the atezolizumab group and 30 of 135 subjects (22.2%) in the DOC group. Those reported by ≥2 subjects in each group were dyspnoea (2 subjects [1.4%]) in the atezolizumab group and peripheral sensory neuropathy; and fatigue (4 subjects each [3.0%]); sepsis (3 subjects [2.2%]); and peripheral neuropathy; and death (2 subjects each [1.5%]) in the DOC group. A causal relationship to study drug could not be ruled out for peripheral sensory neuropathy (4 subjects); fatigue (3 subjects); sepsis; and peripheral neuropathy (2 subjects); and death (1 subject) in the DOC group.

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 will be 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 will be 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 atezolizumab has efficacy in the treatment of unresectable advanced or recurrent NSCLC, and that atezolizumab has acceptable safety in view of its benefits. Atezolizumab is a drug with a new active ingredient, which binds to the extracellular domain of PD-L1, thereby blocking the binding of PD-L1 to PD-1, etc., resulting in enhanced tumor antigen-specific cytotoxic T cell activity and inhibition of tumor growth. Atezolizumab is clinically meaningful because it offers a treatment option for patients with unresectable advanced or recurrent NSCLC. PMDA considers that safety, post-marketing investigations, etc. need to be further discussed.

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

Review Report (2)

October 20, 2017

Product Submitted for Approval

Brand Name	Tecentriq Intravenous Infusion 1200 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	February 17, 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 product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's conclusion:

Based on the considerations in Section "7.R.2 Efficacy" in the Review Report (1), since a global phase III study in patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy (OAK study) demonstrated the superiority of atezolizumab over DOC in the primary endpoint of OS, the efficacy of atezolizumab in these patients was demonstrated.

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), adverse events that require attention following administration of atezolizumab in patients with NSCLC previously treated with platinum-containing chemotherapy are gastrointestinal disorders, skin disorders, hepatic dysfunction, neuropathies, thyroid dysfunction, adrenal dysfunction, pituitary dysfunction, diabetes mellitus (especially, type 1 diabetes mellitus), ILD, IRR, encephalitis/meningitis, pancreatitis, renal dysfunction, myositis/dermatomyositis/rhabdomyolysis, and myasthenia gravis. Particular attention should be paid to the

possible occurrence of these adverse events during treatment with atezolizumab.

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

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

1.3 Clinical positioning and indication

PMDA's conclusion:

Based on the considerations in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), the detailed information on prior therapies of patients enrolled in the OAK study should be included in the CLINICAL STUDIES section of the package insert, and the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section. Then, the proposed indication of "unresectable advanced or recurrent non-small cell lung cancer" is appropriate.

Precautions Concerning Indication

- The efficacy and safety of atezolizumab in chemotherapy-naïve patients have not been established.
- The efficacy and safety of atezolizumab in a post-operative adjuvant chemotherapy setting have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of atezolizumab.

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

Based on the above, PMDA instructed the applicant to handle the INDICATION and PRECAUTIONS CONCERNING INDICATION sections accordingly. The applicant agreed to take such action.

1.4 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement should be amended to "The usual adult dosage is 1200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes."

Precautions Concerning Dosage and Administration

- The efficacy and safety of atezolizumab in combination with other anti-neoplastic drugs have not been established.
- Infusion solution preparation procedure
- In the event of adverse reactions to atezolizumab, atezolizumab dosage modifications should be considered as per the table below.

Adverse reaction	Severity of adverse reaction	Dosage modifications
Respiratory disorders such as ILD	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3, or recurrent respiratory disorder	Permanently discontinue
Hepatic dysfunction	Grade 2 event (AST or ALT 3-5 × ULN or total bilirubin 1.5-3 × ULN) persists for >5 days	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3 (AST or ALT >5 × ULN or total bilirubin >3 × ULN)	Permanently discontinue
Colitis/Diarrhoea	Grade 2 or 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4	Permanently discontinue
Pancreatitis	• Grade ≥3 amylase or lipase levels increased • Grade 2 or 3 pancreatitis	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4 or recurrent pancreatitis	Permanently discontinue
Endocrinopathies	Grade ≥3 hyperglycaemia	Withhold dose until blood glucose levels have stabilized.
	• Symptomatic hypothyroidism • Symptomatic hyperthyroidism, or asymptomatic hyperthyroidism with thyroid stimulating hormone <0.1 mU/L	Withhold dose until resolution.
	Grade ≥2 adrenal insufficiency	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
Encephalitis, Meningitis	All Grades	Permanently discontinue
Neuropathies	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue
	Any grade of Guillain-Barre syndrome	Permanently discontinue
Myasthenia gravis	All Grades	Permanently discontinue
Skin disorders	Grade 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4	Permanently discontinue
Ophthalmopathies	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue
IRR	Grade 1	Reduce the infusion rate by 50%. Monitor for 30 minutes after symptoms have improved, and if IRR does not recur, the infusion rate may be increased back to baseline.
	Grade 2	Interrupt infusion, and resume infusion at a 50% reduction in rate after symptoms have improved.
	Grade ≥3	Discontinue infusion immediately

Severity grade based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0

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

Based on the above, PMDA instructed the applicant to amend the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections accordingly. The applicant agreed to take such action.

1.5 Risk management plan (draft)

The applicant is planning to conduct post-marketing surveillance with a planned sample size of 1000 and an observation period of 1 year, covering all patients treated with atezolizumab, to assess the safety etc. of atezolizumab in clinical practice. In this surveillance, only events considered by the treating physician to be caused by excessive immune response among adverse reactions to atezolizumab, will be collected, taking account of the mechanism of action of atezolizumab.

Based on the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA concluded that it is necessary to conduct post-marketing surveillance covering all patients treated with atezolizumab over a specified period of time, in order to collect all safety information, including but not limited to events considered by the treating physician to be caused by excessive immune response, in a prompt and unbiased manner, and provide the obtained safety information to healthcare professionals in clinical practice as soon as possible.

Concerning the surveillance plan, PMDA concluded as follows:

- The safety specification for the surveillance should include ILD, hepatic dysfunction, colitis/severe diarrhea, pancreatitis, type 1 diabetes mellitus, endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction), neuropathies (including Guillain-Barre syndrome), myasthenia gravis, encephalitis/meningitis, IRR, myositis/rhabdomyolysis, renal dysfunction (tubulointerstitial nephritis, etc.), severe skin disorders, myocarditis, hemolytic anemia, immune thrombocytopenic purpura, embryo-fetal toxicity, and use in organ transplant recipients (including hematopoietic stem cell transplant recipients).
- The planned sample size and observation period need to be reconsidered, taking account of the occurrence of individual events included in the safety specification for the surveillance.

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

Based on the above, PMDA instructed the applicant to reconsider the surveillance plan.

The applicant's response:

- The safety specification will be modified as instructed by PMDA.
- The planned sample size is 1000, taking account of the incidences of individual events included in the

safety specification for the surveillance in the OAK study, etc.

- The observation period is 1 year, taking account of the occurrence of individual events included in the safety specification in the OAK study.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for atezolizumab should include the safety specification presented in Table 63, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 64.

Table 63. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Hepatic dysfunction • Colitis/Severe diarrhea • Pancreatitis • Type 1 diabetes mellitus • Endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction) • Encephalitis/Meningitis • Neuropathies (including Guillain-Barre syndrome) • Myasthenia gravis • Severe skin disorders • Renal dysfunction (tubulointerstitial nephritis, etc.) • Myositis/Rhabdomyolysis • IRR	• Myocarditis • Hemolytic anemia • Immune thrombocytopenic purpura • Embryo-fetal toxicity • Use in organ transplant recipients (including hematopoietic stem cell transplant recipients)	None
Efficacy specification		
None		

Table 64. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey (all-case surveillance) • Post-marketing clinical study (an extension study of OAK) • Post-marketing clinical study (an extension study of BIRCH)	• 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 65. Outline of post-marketing surveillance (draft)

Objective	To assess the safety etc. of atezolizumab in clinical practice after marketing.
Survey method	All-case surveillance by central registry system
Population	All atezolizumab-treated patients with unresectable advanced or recurrent NSCLC
Observation period	1 year
Planned sample size	1000 patients
Main survey items	Safety specification: ILD, hepatic dysfunction, colitis/severe diarrhea, pancreatitis, type 1 diabetes mellitus, endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction), neuropathies (including Guillain-Barre syndrome), myasthenia gravis, encephalitis/meningitis, IRR, myositis/rhabdomyolysis, renal dysfunction (tubulointerstitial nephritis, etc.), severe skin disorders, myocarditis, hemolytic anemia, immune thrombocytopenic purpura, embryo-fetal toxicity, and use in organ transplant recipients (including hematopoietic stem cell transplant recipients) Other main survey items: patient characteristics (age, sex, histology, ECOG performance status, prior therapies for the primary disease, disease stage, medical history, complications, pregnancy, etc.), the use of atezolizumab, adverse events, etc.

1.6 Others

PMDA confirmed that there is no problem with raw materials etc. that are used for the preparation of the WCB [the information was being requested during the preparation of the Review Report (1)], and concluded that all raw materials of biological origin etc. conform to the Standard for Biological Ingredients.

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 5.3.5.1-1, CTD 5.3.5.2-1) 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. On the basis of the inspection, PMDA concluded that since the clinical studies as a whole were performed in compliance with GCP, 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 findings at some of the study sites used by the applicant and at the sponsor, and the heads of the relevant medical institutions and the sponsor were notified of these findings requiring corrective action.

Findings requiring corrective action

Study sites

- Some subjects failed to meet the inclusion criterion as to previous treatment, but were enrolled in the clinical study and received study drug.

Sponsor

- Some subjects failed to meet the inclusion criterion as to previous treatment, but were enrolled in the clinical study and received study drug. These cases were not detected at appropriate timing during monitoring visits.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and provided that the proper use of the product is ensured under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs, and the product is classified as a biological product.

Indication

Unresectable advanced or recurrent non-small cell lung cancer

Dosage and Administration

The usual adult dosage is 1200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Warnings

1. Atezolizumab should be administered only to patients eligible for atezolizumab therapy, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.

2. As cases of interstitial lung disease, including fatal cases, have been reported, patients should be closely monitored, e.g. detection of initial symptoms (dyspnoea, cough, pyrexia, etc.) and chest X-ray. If abnormalities are observed, atezolizumab should be discontinued, and appropriate measures such as administration of corticosteroids, should be taken.

Contraindication

Patients with a history of hypersensitivity to any of the components of atezolizumab.

Precautions Concerning Indication

1. The efficacy and safety of atezolizumab in chemotherapy-naïve patients have not been established.
2. The efficacy and safety of atezolizumab in a post-operative adjuvant chemotherapy setting have not been established.
3. Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of atezolizumab.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of atezolizumab in combination with other anti-neoplastic drugs have not been established.
2. Twenty mL of atezolizumab should be withdrawn from the vial with a syringe and diluted into approximately 250 mL of Isotonic Sodium Chloride Solution (JP). The diluted solution should be administered as an intravenous infusion.
3. In the event of adverse reactions to atezolizumab, atezolizumab dosage modifications should be considered as per the table below.

Adverse reaction	Severity of adverse reaction	Dosage modifications
Respiratory disorders such as interstitial lung disease	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3, or recurrent respiratory disorder	Permanently discontinue
Hepatic dysfunction	Grade 2 event (AST or ALT 3-5 × ULN or total bilirubin 1.5-3 × ULN) persists for >5 days	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3 (AST or ALT >5 × ULN or total bilirubin >3 × ULN)	Permanently discontinue
Colitis/Diarrhoea	Grade 2 or 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4	Permanently discontinue
Pancreatitis	• Grade ≥3 amylase or lipase levels increased • Grade 2 or 3 pancreatitis	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	• Grade 4 or recurrent pancreatitis	Permanently discontinue
Endocrinopathies	Grade ≥3 hyperglycaemia	Withhold dose until blood glucose levels have stabilized.
	• Symptomatic hypothyroidism • Symptomatic hyperthyroidism, or asymptomatic hyperthyroidism with thyroid stimulating hormone <0.1 mU/L	Withhold dose until resolution.
	Grade ≥2 adrenal insufficiency	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
Encephalitis, Meningitis	All Grades	Permanently discontinue
Neuropathies	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue
	Any grade of Guillain-Barre syndrome	Permanently discontinue
Myasthenia gravis	All Grades	Permanently discontinue
Skin disorders	Grade 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4	Permanently discontinue
Ophthalmopathies	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue
Infusion reaction	Grade 1	Reduce the infusion rate by 50%. Monitor for 30 minutes after symptoms have improved, and if the event does not recur, the infusion rate may be increased back to baseline.
	Grade 2	Interrupt infusion, and resume infusion at a 50% reduction in rate after symptoms have improved.
	Grade ≥3	Discontinue infusion immediately

Severity grade based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0

List of Abbreviations

ACTH	adrenocorticotropic hormone
ADCC	antibody dependent cell mediated cytotoxicity
[redacted]	[redacted]
Ala	alanine
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
anti-atezolizumab antibody	antibody against Atezolizumab (Genetical Recombination)
Asn	asparagine
AST	aspartate aminotransferase
atezolizumab	Atezolizumab (Genetical Recombination)
BIRCH study	Study GO28754
CAL	cells at the limit of *in vitro* cell age
CDR	complementarity-determining region
[redacted]	[redacted]
[redacted]	[redacted]
CHO cells	Chinese hamster ovary cells
CI	confidence interval
CQA	critical quality attributes
CR	complete response
CrCL	creatinine clearance
CRP	C reactive protein
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOC	docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EPC	end of production cells
Fab	fragment antigen binding
Fc	fragment crystallizable
FcRn	neonatal Fc Receptor
FcγR	Fcγ receptor
FIR study	Study GO28625
GGT	gamma-glutamyltransferase
Glu	glutamic acid
GM-CSF	granulocyte macrophage colony-stimulating factor
HCP	host cell protein
HLGT	high level group term
HLT	high level term
HRP	horseradish peroxidase
IC0	<1% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC0/1	<5% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC0/1/2	<10% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells

IC1	≥1% and <5% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC1/2/3	≥1% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC2	≥5% and <10% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC2/3	≥5% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC3	≥10% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
[redacted]	[redacted]
IFN-γ	interferon-γ
Ig	immunoglobulin
IL	interleukin
ILD	interstitial lung disease
IRR	infusion related reaction
ITT	intention-to-treat
K_d	dissociation constant
LCMV	lymphocytic choriomeningitis virus
Lys	lysine
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
Met	methionine
MHC	major histocompatibility complex
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NCI-PDQ	National Cancer Institute Physician Data Query
NE	not evaluable
nivolumab	Nivolumab (Genetical Recombination)
NK cell	natural killer cell
NSCLC	non-small cell lung cancer
OAK study	Study GO28915
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PD-1	programmed cell death-1
pembrolizumab	Pembrolizumab (Genetical Recombination)
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
POPLAR study	Study GO28753
PP	primary population
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
QbD	quality by design
QW	quaque 1 week
Q3W	quaque 3 week
RECIST	Response Evaluation Criteria in Solid Tumors
Recombinant PD-L1-Fc fusion protein	a recombinant protein generated by fusing human PD-L1 to the Fc domain of human IgG1

SD	stable disease
SEC	size exclusion chromatography
SJS	Stevens-Johnson syndrome
SMQ	standardised MedDRA queries
SOC	system organ class
TC0	<1% of tumor area occupied by PD-L1-expressing tumor cells
TC0/1	<5% of tumor area occupied by PD-L1-expressing tumor cells
TC0/1/2	<50% of tumor area occupied by PD-L1-expressing tumor cells
TC1	≥1% and <5% of tumor area occupied by PD-L1-expressing tumor cells
TC1/2/3	≥1% of tumor area occupied by PD-L1-expressing tumor cells
TC2	≥5% and <50% of tumor area occupied by PD-L1-expressing tumor cells
TC2/3	≥5% of tumor area occupied by PD-L1-expressing tumor cells
TC3	≥50% of tumor area occupied by PD-L1-expressing tumor cells
TEN	toxic epidermal necrolysis
TNF-α	tumor necrosis factor-α
trastuzumab	Trastuzumab (Genetical Recombination)
ULN	upper limit of normal
V_1	central volume of distribution
V_2	peripheral volume of distribution
V_{ss}	volume of distribution at steady state
WCB	working cell bank
ΔQTcF	change from baseline in QT interval corrected using the Fridericia formula