Report on the Deliberation Results

August 15, 2019
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	December 7, 2018

Results of Deliberation

In its meeting held on August 2, 2019, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

July 24, 2019
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	December 7, 2018
Dosage Form/Strength	Injection: Each vial (20.0 mL) contains 1200 mg of Atezolizumab (Genetical Recombination).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage

Items Warranting Special Mention
Orphan drug (Orphan Drug Designation No. 421 of 2018 [*30 yaku*]; PSEHB/PED Notification No. 1206-1 dated December 6, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

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 extensive-stage 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 indications and dosage and administration shown below, with the following condition.

Indications
Unresectable advanced or recurrent non-small cell lung cancer
<u>Extensive-stage small cell lung cancer</u>

(Underline denotes additions.)

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Dosage and Administration

For chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer

Atezolizumab in combination with carboplatin, paclitaxel, and bevacizumab (genetical recombination)

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.

For patients with unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy

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.

For patients with extensive-stage small cell lung cancer

Atezolizumab in combination with carboplatin and etoposide

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.

(Single underline denotes new additions. Double underline denotes additions made as of December 21, 2018 after submission of the present partial change application.)

Condition of Approval

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

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Attachment

Review Report (1)

June 14, 2019

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	December 7, 2018
Dosage Form/Strength	Injection: Each vial (20.0 mL) contains 1200 mg of Atezolizumab (Genetical Recombination).
Proposed Indications	Unresectable advanced or recurrent non-small cell lung cancer Unresectable small cell lung cancer

(Underline denotes additions.)

Proposed Dosage and Administration

Unresectable advanced or recurrent non-small cell lung cancer

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.

Unresectable small cell lung cancer

Atezolizumab in combination with carboplatin and etoposide

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.

(Underline denotes additions.)

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

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.

In Japan, (a) atezolizumab as monotherapy was approved in January 2018 and (b) atezolizumab in combination with carboplatin (CBDCA)/paclitaxel (PTX)/bevacizumab (genetical recombination) (BV) in December 2018 for the treatment of "unresectable advanced or recurrent non-small cell lung cancer."

1.2 Development history etc.

In the clinical development of atezolizumab for patients with extensive-stage small cell lung cancer (SCLC), Roche (Switzerland) and Genentech (the US) initiated a global phase I/III study in chemotherapy-naïve patients with extensive-stage SCLC (IMpower133 study) in June 2016.

US and EU applications for extensive-stage SCLC were filed based mainly on the results from the IMpower133 study in September and October 2018, respectively. In the US, atezolizumab was approved for the following indication in March 2019: "TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)." The EU application is currently under review.

As of May 2019, atezolizumab has been approved for the indication of extensive-stage SCLC in 4 countries.

In Japan, the IMpower133 study initiated patient enrollment in August 2016.

The applicant has filed a partial change application for an additional indication of extensive-stage SCLC, based mainly on the results from the IMpower133 study.

Atezolizumab received an orphan drug designation (Orphan Drug Designation No. 421 of 2018 [*30 yaku*]) with the intended indication of "small cell lung cancer" in December 2018.

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

Since the present application is intended for a new indication and a new dosage, no data relating to quality have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacology data were previously evaluated for the initial approval of atezolizumab, and no new study data have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacokinetic data were previously evaluated for the initial approval of atezolizumab, and no new study data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no toxicity data have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the data on biopharmaceutic studies and associated analytical methods were previously evaluated for the initial approval of atezolizumab, and no new study data have been submitted.

The applicant submitted the results from the IMpower133 study as clinical pharmacology data and explained that the study results etc. showed no pharmacokinetic interactions between atezolizumab and etoposide (ETP), etc.

Based on the submitted data, PMDA accepted the above explanation by the applicant.

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 1 global phase I/III study presented in Table 1.

Table 1. Efficacy and safety clinical study

Data category	Geographical location	Study Identity	Phase	Study population	No. of subjects enrolled	Dosing regimen*	Main endpoints
Evaluation	Global	IMpower133	I/III	Chemotherapy-naïve patients with extensive-stage SCLC	403 (a) 201 (b) 202	(a) 4 cycles of atezolizumab/CBDCA/ETP intravenously, followed by atezolizumab intravenously (b) 4 cycles of placebo/CBDCA/ETP intravenously, followed by placebo intravenously	Efficacy Safety

*: Atezolizumab 1200 mg and CBDCA AUC 5 mg·min/mL on Day 1 and ETP 100 mg/m^2 intravenously on Days 1, 2, and 3 of each 3-week cycle.

The clinical study is summarized below. The main adverse events other than deaths observed in the clinical study are described in Section "7.2 Adverse events etc. observed in clinical studies."

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase I/III[1] study (CTD 5.3.5.1-1, IMpower133 study [ongoing since June 2016 (data cutoff date of April 24, 2018)])

A double-blind, randomized, placebo-controlled study was conducted at 106 sites in 21 countries or regions, including Japan, to evaluate the efficacy and safety of CBDCA plus ETP with or without atezolizumab in chemotherapy-naïve patients with extensive-stage SCLC[2] (target sample size, 400 subjects).

Subjects were to receive CBDCA and ETP with either atezolizumab 1200 mg or placebo intravenously for 4 3-week cycles, followed by either atezolizumab 1200 mg or placebo intravenously until disease progression or a criterion for discontinuation was met.

All of 403 subjects who were enrolled in the study and randomized (201 in the atezolizumab group, 202 in the placebo group) were included in the intention-to-treat (ITT) population, which was included in efficacy analyses (including 20 Japanese patients in the atezolizumab group and 22 Japanese patients in the placebo group). Among the ITT population, 394 subjects (198 in the atezolizumab group, 196 in the placebo group) after excluding 9 subjects who did not receive study drug (3 in the atezolizumab group, 6 in the placebo group) were included in safety analyses (including 20 Japanese patients in the atezolizumab group and 22 Japanese patients in the placebo group).

The primary endpoints for the study were investigator-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1 and overall survival (OS). Interim analyses for efficacy evaluation were planned. The primary analysis of PFS and the first interim OS analysis were to be conducted when 233 PFS events had occurred. The second interim OS analysis was to take place when 258 OS events had been observed. The final analysis of OS was to be performed when 298 OS events had been observed. However, since the results of the OAK study[3] suggested that the treatment effect of atezolizumab may be delayed than initially expected at the time of planning the study, etc., the second interim OS analysis was removed, the primary analysis of PFS and the interim analysis of OS were planned when 220 OS events had occurred, and the final OS analysis was planned when 280 OS events had been observed (Protocol Version 4 [as of [redacted], 20[redacted]]). Moreover, the results of the IMpower150 study[4] suggested that the treatment effect of atezolizumab may be further delayed than expected based on the results of the OAK study. Thus, the primary analysis of PFS and the interim analysis of OS were planned when 240 OS events had occurred, and the final

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1) The phase of this study was changed from Phase III at the time of initiation of the study to Phase I/III because the protocol stated that unblinded safety data will be reviewed by the IDMC after a minimum of 12 patients have been enrolled into each treatment arm and have received treatment for 2 cycles (Protocol Version 2 [as of [redacted], 20[redacted]]).

2) The Veterans Administration Lung Study Group (VALG) staging system for SCLC was used to define extensive-stage SCLC. Patients who received prior CRT for limited-stage SCLC with curative intent and were diagnosed as having extensive-stage SCLC ≥6 months after the last chemotherapy, radiotherapy, or CRT cycle were also enrolled in the study.

3) A global phase III study to evaluate the efficacy and safety of atezolizumab compared with DOC in patients with unresectable advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy

4) A global phase III study to evaluate the efficacy and safety of atezolizumab/CBDCA/PTX or atezolizumab/CBDCA/PTX/BV compared with CBDCA/PTX/BV in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC

OS analysis was planned when 306 OS events had been observed (Statistical Analysis Plan Version 2 [as of [redacted], 20[redacted]]).

To adjust for multiplicity due to having two co-primary endpoints, the Bonferroni method was used: the hypothesis test for PFS was to be conducted at a two-sided alpha of 0.005 and OS was to be tested at a two-sided alpha of 0.045. However, the multiplicity strategy was changed to a group sequential Holm procedure (*Stat Med*. 2013;32:1112-24) in order to maximize power while controlling for the overall type I error rate: If PFS (OS) was statistically significant at the two-sided alpha level of 0.005 (0.045), OS (PFS) was to be tested at a two-sided alpha level of 0.05 (Protocol Version 4 [as of [redacted], 20[redacted]]). The interim analysis of OS was to use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary to control for the type I error rate.

The results of the interim analysis of OS, the co-primary efficacy endpoint, (data cutoff date of April 24, 2018), and the Kaplan-Meier curves for OS are shown in Table 2 and Figure 1, respectively, and the superiority of the atezolizumab group over the placebo group was demonstrated.

Table 2. Results of interim analysis of OS (ITT population, data cutoff date of April 24, 2018)

	Atezolizumab	Placebo
N	201	202
No. of events (%)	104 (51.7)	134 (66.3)
Median [95% CI] (months)	12.3 [10.8, 15.9]	10.3 [9.3, 11.3]
Hazard ratio [95% CI]*1	0.701 [0.541, 0.909]	
P-value (two-sided)*2	0.0069	

*1: Cox regression stratified by sex (male, female) and ECOG PS (0, 1), *2: Log-rank test stratified by sex (male, female) and ECOG PS (0, 1), A significance level (two-sided) of 0.0193

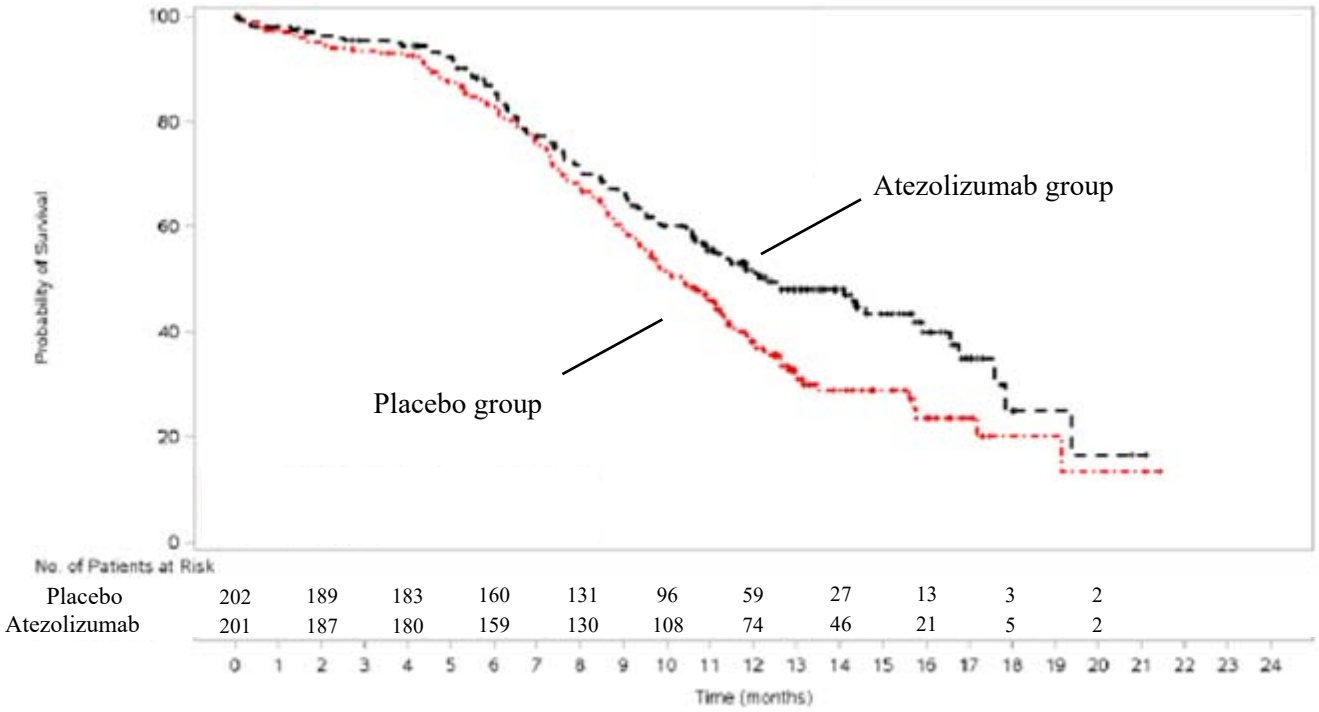

Figure 1. Kaplan-Meier curves for OS at the time of interim analysis (ITT population, data cutoff date of April 24, 2018)

The results of primary analysis of PFS, the co-primary endpoint, (data cutoff date of April 24, 2018), are shown in Table 3.

Table 3. Results of primary analysis of PFS (investigator assessment, ITT population, data cutoff date of April 24, 2018)

	Atezolizumab	Placebo
N	201	202
No. of events (%)	171 (85.1)	189 (93.6)
Median [95% CI] (months)	5.2 [4.4, 5.6]	4.3 [4.2, 4.5]
Hazard ratio [95% CI]*1	0.772 [0.624, 0.955]	
P-value (two-sided)*2	0.0170	

*1: Cox regression stratified by sex (male, female) and ECOG PS (0, 1), *2: Log-rank test stratified by sex (male, female) and ECOG PS (0, 1), A significance level (two-sided) of 0.05

Regarding safety, 31 of 198 subjects (15.7%) in the atezolizumab group and 40 of 196 subjects (20.4%) in the placebo group died during the study treatment period or the follow-up period[5)] (including 2 of 20 Japanese patients in the atezolizumab group and 4 of 22 Japanese patients in the placebo group). The causes of deaths other than disease progression (27 in the atezolizumab group, 29 in the placebo group) were pneumonia; respiratory failure; neutropenia; and death (1 subject each) in the atezolizumab group and pneumonia (2 subjects); and septic shock; sepsis; pulmonary sepsis; acute respiratory failure; haemoptysis; cardiopulmonary failure; pericardial effusion; general physical condition decreased; and death (1 subject each) in the placebo group. A causal relationship to study drug could not be ruled out for pneumonia; neutropenia; and death (1 subject each) in the atezolizumab group and pneumonia; septic shock; and cardiopulmonary failure (1 subject each) in the placebo group (the cause of death in a Japanese patient with an adverse event leading to death [0 in the atezolizumab group, 1 in the placebo group] was pneumonia, and its causal relationship to study drug was denied).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA decided to focus its review on the overall population of the IMpower133 study submitted, and evaluated the efficacy of atezolizumab in Japanese patients in terms of the consistency of the results between the overall population and the Japanese subgroup, 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), "Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018), etc.

Based on the following considerations, PMDA concluded that the efficacy of atezolizumab in chemotherapy-naïve patients with extensive-stage SCLC was demonstrated.

5) Up to 90 days after the last dose of study treatment or initiation of new anti-cancer therapy after the last dose of study treatment, whichever occurred first.

7.R.1.1 Choice of control group

The applicant's explanation about choice of a control group in the IMpower133 study:

Given that the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Small Cell Lung Cancer (NCCN guidelines) (v.1.2016) at the time of planning the IMpower133 study recommended a platinum agent/ETP or a platinum agent/irinotecan hydrochloride hydrate (CPT-11) for patients with extensive-stage SCLC, and taking also account of the following points, patients treated with CBDCA/ETP were chosen as a control group.

- The ESMO guidelines (Small-cell lung cancer [SCLC]: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up) etc. strongly recommended cisplatin (CDDP)/ETP, compared with CDDP/CPT-11, because CDDP/CPT-11 did not significantly increase OS compared with CDDP/ETP, and the incidence of gastrointestinal toxicity was higher with CDDP/CPT-11 in multiple foreign clinical trials in patients with extensive-stage SCLC (*J Clin Oncol*. 2006;24:2038-43 etc.).
- Since no clear differences in efficacy between CDDP-based chemotherapy and CBDCA-based chemotherapy in the treatment of SCLC have been reported (*J Clin Oncol*. 2012;30:1692-8), there should be no clear differences in efficacy between CDDP/ETP and CBDCA/ETP.
- Adverse events such as gastrointestinal toxicity and renal toxicity are milder with CBDCA-based chemotherapy compared with CDDP-based chemotherapy (*J Clin Oncol.* 2012;30:1692-8).

PMDA asked the applicant to explain the appropriateness of 100 mg/m^2 selected as the dose of ETP when administered with CBDCA in the IMpower133 study, instead of 80 mg/m^2 of ETP for use with CBDCA for patients with extensive-stage SCLC in the Japanese clinical practice guidelines (Version 2015) (EBM-based clinical practice guidelines for lung cancer 2015, The Japan Lung Cancer Society ed.).

The applicant's response:

Taking account of the following points, 100 mg/m^2 was selected as the dose of ETP when administered with CBDCA. Thus, this selected dose is appropriate.

- The NCCN guidelines (v.1.2016) recommended 100 mg/m^2 as the dose of ETP when administered with CBDCA for patients with extensive-stage SCLC.
- Although the dose of ETP when administered with CBDCA for patients with extensive-stage SCLC was 80 mg/m^2 in the Japanese clinical practice guidelines (Version 2015), this dose was recommended for (i) patients with performance status (PS) 0 to 2 who are not able to tolerate full-dose CDDP, (ii) patients aged ≥75 years, and (iii) patients with PS 3. Given that the patient population for the IMpower133 study was PS 0 or 1 patients with extensive-stage SCLC aged ≥18 years, administration of ETP 100 mg/m^2 to Japanese patients with extensive-stage SCLC is justified.
- Adverse events occurring after the administration of CBDCA and ETP 100 mg/m^2 were manageable in a Japanese clinical study in patients with SCLC aged ≥70 years (*J Clin Oncol*. 1999;17:3540-5).

PMDA accepted the applicant's explanation.

7.R.1.2 Efficacy endpoint and results of evaluation

The IMpower133 study demonstrated the superiority of the atezolizumab group over the placebo group in the co-primary endpoint of OS [see Section 7.1.1.1].

In the IMpower133 study, the results of analysis of OS and the Kaplan-Meier curves for OS in Japanese patients are shown in Table 4 and Figure 2, respectively.

Table 4. Results of interim analysis of OS in Japanese patients (ITT population, data cutoff date of April 24, 2018)

	Atezolizumab	Placebo
N	20	22
No. of events (%)	12 (60.0)	14 (63.6)
Median [95% CI] (months)	14.6 [11.8, 17.8]	11.9 [8.4, 15.8]
Hazard ratio [95% CI]*1	0.717 [0.307, 1.671]	
P-value (two-sided)*2	0.4386	

*1: Cox regression stratified by sex (male, female) and ECOG PS (0, 1), *2: Log-rank test stratified by sex (male, female) and ECOG PS (0, 1)

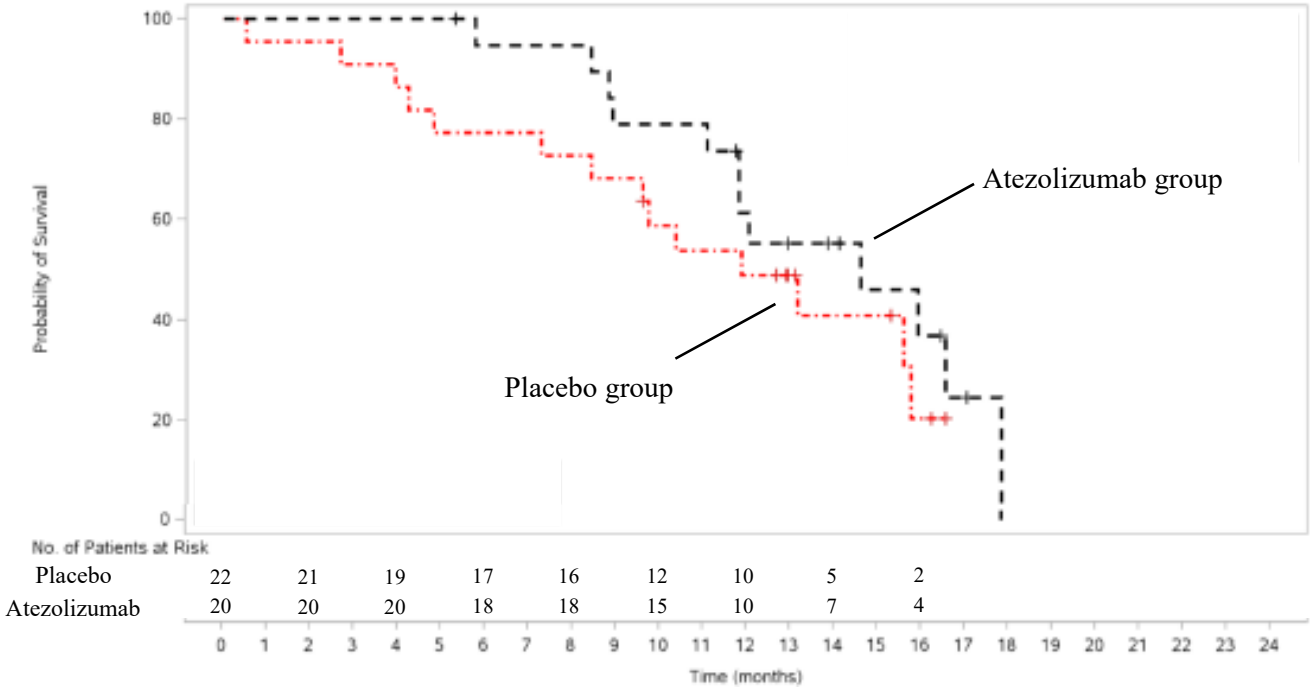

Figure 2. Kaplan-Meier curves for OS at the time of interim analysis in Japanese patients (ITT population, data cutoff date of April 24, 2018)

PMDA's discussion:

For the following reasons etc., PMDA concluded that the efficacy of atezolizumab was demonstrated in the study population for the IMpower133 study.

- The IMpower133 study demonstrated the superiority of the atezolizumab group over the placebo group in the co-primary endpoint of OS.
- While the number of Japanese patients and the number of events in Japanese patients in the IMpower133 study were limited, and there are limitations to evaluating the efficacy of atezolizumab in Japanese patients based on the results from the Japanese subgroup, there was no trend towards clear differences in the efficacy results between the Japanese subgroup and the overall population.

7.R.2 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 attention following administration of atezolizumab/CBDCA/ETP in chemotherapy naïve patients with extensive-stage SCLC are myocarditis in addition to the events that were considered to require attention at the time of the initial approval of atezolizumab (use in the previously approved indication).[6)] As with use in the previously approved indication, 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 dose interruption/reduction, discontinuation, etc. of atezolizumab and the concomitant anti-neoplastic drugs.

7.R.2.1 Safety profile of atezolizumab

The applicant's explanation about the safety profile of atezolizumab based on atezolizumab safety information from the IMpower133 study:

Safety data from the IMpower133 study are summarized in Table 5.

Table 5. Summary of safety data (IMpower133 study)

	n (%)	
	Atezolizumab N = 198	Placebo N = 196
All adverse events	198 (100)	189 (96.4)
Grade ≥3 adverse events	137 (69.2)	136 (69.4)
Adverse events leading to death	4 (2.0)	11 (5.6)
Serious adverse events	74 (37.4)	68 (34.7)
Adverse events leading to treatment discontinuation		
Atezolizumab or Placebo	21 (10.6)	5 (2.6)
CBDCA	5 (2.5)	1 (0.5)
ETP	8 (4.0)	2 (1.0)
Adverse events leading to dose interruption		
Atezolizumab or Placebo	117 (59.1)	102 (52.0)
CBDCA	97 (49.0)	81 (41.3)
ETP	101 (51.0)	83 (42.3)
Adverse events leading to dose reduction		
CBDCA	27 (13.6)	28 (14.3)
ETP	20 (10.1)	23 (11.7)

In the IMpower133 study, adverse events of any grade reported at a ≥5% higher incidence in the atezolizumab group than in the placebo group were anaemia (86 subjects [43.4%] in the atezolizumab group, 69 subjects [35.2%] in the placebo group), nausea (75 subjects [37.9%], 64 subjects [32.7%]), decreased

6) 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, myasthenia gravis, and febrile neutropenia (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of October 23, 2017" etc.)

appetite (54 subjects [27.3%], 36 subjects [18.4%]), and hypothyroidism (20 subjects [10.1%], 1 subject [0.5%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in the atezolizumab group than in the placebo group were anaemia (31 subjects [15.7%], 26 subjects [13.3%]) and fatigue (5 subjects [2.5%], 1 subject [0.5%]). Adverse events leading to study drug discontinuation reported at a ≥2% higher incidence in the atezolizumab group than in the placebo group were infusion related reaction (5 subjects [2.5%], 0 subjects). Adverse events leading to study drug interruption reported at a ≥2% higher incidence in the atezolizumab group than in the placebo group were neutropenia (47 subjects [23.7%], 31 subjects [15.8%]), anaemia (17 subjects [8.6%], 8 subjects [4.1%]), leukopenia (13 subjects [6.6%], 3 subjects [1.5%]), thrombocytopenia (11 subjects [5.6%], 7 subjects [3.6%]), fatigue (9 subjects [4.5%], 0 subjects), infusion related reaction (7 subjects [3.5%], 1 subject [0.5%]), and pyrexia (4 subjects [2.0%], 0 subjects). There were no adverse events leading to death or serious adverse events reported at a ≥2% higher incidence in the atezolizumab group than in the placebo group.

The applicant's explanation about differences in the safety profile between chemotherapy-naïve extensive-stage SCLC (IMpower133 study) and chemotherapy-naïve unresectable advanced or recurrent non-squamous (NSQ)-NSCLC (IMpower150 study) (the previously approved indication for which atezolizumab was used in combination with other anti-neoplastic drugs, as in the IMpower133 study):
Table 6 shows the results of comparison of the incidence of adverse events between the atezolizumab group of the IMpower133 study and the atezolizumab/CBDCA/PTX/BV group of the IMpower150 study.

Table 6. Summary of safety data (IMpower133 study and IMpower150 study)

	n (%)	
	IMpower133	IMpower150
	Atezolizumab N = 198	Atezolizumab/CBDCA/PTX/BV N = 393
All adverse events	198 (100)	386 (98.2)
Grade ≥3 adverse events	137 (69.2)	274 (69.7)
Adverse events leading to death	4 (2.0)	24 (6.1)
Serious adverse events	74 (37.4)	174 (44.3)
Adverse events leading to study drug discontinuation	22 (11.1)	133 (33.8)
Adverse events leading to study drug interruption	126 (63.6)	226 (57.5)
Adverse events leading to dose reduction of study drug	31 (15.7)	97 (24.7)

Adverse events of any grade reported at a ≥10% higher incidence in the atezolizumab group of the IMpower133 study than in the atezolizumab/CBDCA/PTX/BV group of the IMpower150 study were anaemia (chemotherapy-naïve extensive-stage SCLC, 86 subjects [43.4%]; chemotherapy-naïve unresectable advanced or recurrent NSQ-NSCLC, 115 subjects [29.3%]) and neutropenia (74 subjects [37.4%], 73 subjects [18.6%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the atezolizumab group of the IMpower133 study than in the atezolizumab/CBDCA/PTX/BV group of the IMpower150 study were neutropenia (46 subjects [23.2%], 55 subjects [14.0%]), neutrophil count decreased (31 subjects [15.7%], 34 subjects [8.7%]), anaemia (31 subjects [15.7%], 28 subjects [7.1%]), and thrombocytopenia (20 subjects [10.1%], 17 subjects [4.3%]). Adverse events leading to study drug interruption reported at a ≥5% higher incidence in the atezolizumab group of the IMpower133 study than in the atezolizumab/CBDCA/PTX/BV group of

the IMpower150 study were neutropenia (47 subjects [23.7%], 27 subjects [6.9%]), neutrophil count decreased (22 subjects [11.1%], 14 subjects [3.6%]), anaemia (17 subjects [8.6%], 8 subjects [2.0%]), and leukopenia (13 subjects [6.6%], 4 subjects [1.0%]). There were no adverse events leading to death, serious adverse events, or adverse events leading to study drug discontinuation reported at a ≥5% higher incidence in the atezolizumab group of the IMpower133 study than in the atezolizumab/CBDCA/PTX/BV group of the IMpower150 study.

PMDA's discussion:
In the IMpower133 study, some adverse events were reported at a higher incidence in the atezolizumab group than in the placebo group, and the incidences of some adverse events were higher than those during use in the previously approved indication. However, given that all of these events were known adverse events associated with atezolizumab or the concomitant chemotherapy, atezolizumab/CBDCA/ETP in chemotherapy-naïve patients with extensive-stage SCLC is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy continue to 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.

7.R.2.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in safety between Japanese and non-Japanese populations:
Safety data from Japanese and non-Japanese patients in the atezolizumab group of the IMpower133 study are summarized in Table 7.

Table 7. Summary of safety data from Japanese and non-Japanese patients (IMpower133 study)

	n (%)	
	Japanese patients Atezolizumab group N = 20	Non-Japanese patients Atezolizumab group N = 178
All adverse events	20 (100)	178 (100)
Grade ≥3 adverse events	19 (95.0)	118 (66.3)
Adverse events leading to death	0	4 (2.2)
Serious adverse events	5 (25.0)	69 (38.8)
Adverse events leading to treatment discontinuation		
Atezolizumab	0	21 (11.8)
CBDCA	0	5 (2.8)
ETP	0	8 (4.5)
Adverse events leading to dose interruption		
Atezolizumab	18 (90.0)	99 (55.6)
CBDCA	16 (80.0)	81 (45.5)
ETP	16 (80.0)	85 (47.8)
Adverse events leading to dose reduction		
CBDCA	6 (30.0)	21 (11.8)
ETP	5 (25.0)	15 (8.4)

In the atezolizumab group, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (15 subjects [75.0%] in the Japanese subgroup, 22 subjects [12.4%] in the non-Japanese subgroup), alopecia (14 subjects [70.0%], 59

subjects [33.1%]), constipation (13 subjects [65.0%], 38 subjects [21.3%]), platelet count decreased (11 subjects [55.0%], 14 subjects [7.9%]), decreased appetite (10 subjects [50.0%], 44 subjects [24.7%]), white blood cell count decreased (8 subjects [40.0%], 10 subjects [5.6%]), leukopenia (6 subjects [30.0%], 19 subjects [10.7%]), rash (4 subjects [20.0%], 10 subjects [5.6%]), malaise (4 subjects [20.0%], 2 subjects [1.1%]), stomatitis (3 subjects [15.0%], 8 subjects [4.5%]), peripheral sensory neuropathy (3 subjects [15.0%], 5 subjects [2.8%]), taste abnormality (3 subjects [15.0%], 5 subjects [2.8%]), and dry skin (3 subjects [15.0%], 4 subjects [2.2%]). Grade ≥3 adverse events reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (14 subjects [70.0%], 17 subjects [9.6%]), platelet count decreased (4 subjects [20.0%], 3 subjects [1.7%]), leukopenia (3 subjects [15.0%], 7 subjects [3.9%]), white blood cell count decreased (3 subjects [15.0%], 4 subjects [2.2%]), and constipation (2 subjects [10.0%], 0 subjects). Adverse events leading to interruption of atezolizumab reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (10 subjects [50.0%], 11 subjects [6.2%]) and leukopenia (4 subjects [20.0%], 9 subjects [5.1%]). There were no adverse events leading to death, serious adverse events, or adverse events leading to atezolizumab discontinuation reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

Among Grade ≥3 adverse events with a higher incidence in the Japanese subgroup than in the non-Japanese subgroup, leukopenia (3 subjects [15.0%] in the atezolizumab group, 1 subject [4.5%] in the placebo group) and constipation (2 subjects [10.0%], 0 subjects) were reported at a ≥10% higher incidence in the atezolizumab group than in the placebo group in the Japanese subgroup. However, given that no serious cases were reported and that none of these events led to study drug discontinuation, etc., these events will not become a particular problem in Japanese patients.

PMDA's discussion:
Although the number of Japanese patients included in the IMpower133 study was limited, and there are limitations to rigorous comparison of safety between the Japanese and non-Japanese subgroups, given the following points etc., atezolizumab/CBDCA/ETP is tolerable also in Japanese patients as long as physicians take appropriate measures e.g. dose interruption/reduction and discontinuation of atezolizumab and the concomitant drugs.

- There was no trend towards clearly higher incidences of adverse events leading to death and serious adverse events in the Japanese subgroup than in the non-Japanese subgroup.
- Although the incidence of hematologic toxicity tended to be higher in the Japanese subgroup than in the non-Japanese subgroup, there were no clear differences in the incidence of hematologic toxicity etc. between the atezolizumab and placebo groups in the Japanese subgroup.

Though the number of Japanese patients treated was limited, the incidence of hematologic toxicity with atezolizumab/CBDCA/ETP was higher in the Japanese subgroup than in the non-Japanese subgroup. Thus, it

is necessary to watch for the occurrence of hematologic toxicity etc. after the market launch and appropriately provide any new information to healthcare professionals in clinical practice.

In the following section, PMDA focused its safety review on myositis, which was listed as a precaution in the Company Core Data Sheet (CCDS) after submission of the present partial change application (December 7, 2018).

7.R.2.3 Myositis (including myocarditis)

The applicant's explanation about the incidences of (a) myositis (excluding myocarditis) and (b) myocarditis associated with atezolizumab:

(a) Myositis (excluding myocarditis)

As adverse events of myositis (excluding myocarditis), events in the MedDRA HLTs "muscle infections and inflammations" and "muscular autoimmune disorders" excluding events in the MedDRA HLT "myasthenia gravis and related conditions" were counted.

In atezolizumab clinical studies and marketing experience in and outside Japan, myositis (excluding myocarditis) was reported in 46 patients. Myositis (excluding myocarditis) leading to death occurred in 3 patients (myositis [2 patients], polymyositis [1 patient]), and a causal relationship to atezolizumab could not be ruled out for all those events. Serious myositis (excluding myocarditis) occurred in 17 patients (myositis [12 patients]; polymyositis [3 patients]; dermatomyositis [2 patients]; and orbital myositis [1 patient] [some patients had more than 1 event]), and a causal relationship to atezolizumab could not be ruled out for all those events.

In atezolizumab clinical studies and marketing experience in and outside Japan, the median time to the onset of myositis (excluding myocarditis) (range) was 73 days (13-510 days).

The details of patients with myositis (excluding myocarditis) leading to death associated with atezolizumab in atezolizumab clinical studies and marketing experience in and outside Japan are shown in Table 8.

Table 8. Listing of patients with myositis (excluding myocarditis) leading to death

Age	Sex	Race	Primary disease	Atezolizumab dosage	Concomitant drug	PT (MedDRA ver.21.1)	Grade	Time to onset (days)	Duration (days)	Causality to atezolizumab
Study CO39385 *1										
75	M	Non-Japanese	Prostate cancer	1200 mg/body Q3W	Enzalutamide	Myositis	5	55	15	Yes
Study BO30013 *2										
86	M	Non-Japanese	Prostate cancer	840 mg/body Q3W	Radium-223	Myositis	5	71	20	Yes
Study MO39196 *3										
4[redacted]	F	Japanese	Breast cancer	Unknown	PTX	Polymyositis	5	204	45	Yes

*1: A global phase III study in patients with metastatic CRPC previously treated with an androgen synthesis inhibitor or a taxane regimen,
*2: A foreign phase Ib study in patients with CRPC previously treated with an androgen pathway inhibitor,
*3: A foreign phase III study in chemotherapy-naïve patients with inoperable or recurrent HR-negative and HER2-negative breast cancer

(b) Myocarditis

As adverse events of myocarditis, MedDRA PTs "hypersensitivity myocarditis," "autoimmune myocarditis," "eosinophilic myocarditis," and "myocarditis" were counted.

In atezolizumab clinical studies and marketing experience in and outside Japan, myocarditis was reported in 45 patients. Myocarditis leading to death (all PT myocarditis) occurred in 7 patients, and a causal relationship to atezolizumab could not be ruled out for all those events. Serious myocarditis occurred in 43 patients (myocarditis [41 patients], autoimmune myocarditis [2 patients]).

In atezolizumab clinical studies and marketing experience in and outside Japan, the median time to the onset of myocarditis (range) was 37 days (1-281 days).

The details of patients with myocarditis leading to death associated with atezolizumab in atezolizumab clinical studies and marketing experience in and outside Japan are shown in Table 9.

Table 9. Listing of patients with myocarditis leading to death

Age	Sex	Race	Primary disease	Atezolizumab dosage	Concomitant drug	PT (MedDRA ver.21.1)	Grade	Time to onset (days)	Duration (days)	Causality to atezolizumab
Study MO29996 *1										
69	F	Non-Japanese	Ovarian cancer	Unknown	BV/CBDCA/ PLD	Myocarditis	4	57	57	Yes
MAP-AU-12880*2										
Un-known	F	Non-Japanese	NSCLC	1200 mg/body Q3W	None	Myocarditis	Unknown	Unknown	Unknown	Yes
Study GO29527 *3										
81	M	Non-Japanese	NSCLC	1200 mg/body Q3W	None	Myocarditis	5	45	14	Yes
JTAIL study*4										
7[redacted]	M	Japanese	NSCLC	1200 mg/body	None	Myocarditis	Unknown	54	4	Yes
Marketing experience										
42	M	Non-Japanese	Lung cancer	1200 mg/body	None	Myocarditis	Unknown	Unknown	Unknown	Yes
42	M	Non-Japanese	NSCLC	1200 mg/body Q3W	None	Myocarditis	Unknown	Unknown	Unknown	Yes
69	F	Non-Japanese	NSCLC	Unknown	None	Myocarditis	Unknown	Unknown	Unknown	Yes

*1: A foreign phase III study in patients with platinum-sensitive relapse of ovarian cancer,
*2: Atezolizumab patient support program,
*3: A global phase III study in patients with NSCLC following adjuvant platinum-based chemotherapy,
*4: An observational study in patients with unresectable advanced or recurrent NSCLC

PMDA's discussion:

Since cases of myositis (including myocarditis) leading to death for which a causal relationship to atezolizumab could not be ruled out were reported in atezolizumab clinical studies and marketing experience, attention should be paid to the possible occurrence of myositis (including myocarditis) following initiation of treatment with atezolizumab, and it is necessary to appropriately advise healthcare professionals in clinical practice about myositis (including myocarditis), using the package insert etc.

7.R.3 Clinical positioning and indication

The proposed indication for atezolizumab was "unresectable small cell lung cancer." The following statements were included in the PRECAUTIONS CONCERNING INDICATION section of the proposed package insert.

- 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 concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of atezolizumab.

Based on Sections "7.R.1 Efficacy" and "7.R.2 Safety," and the considerations in the following sections, PMDA concluded as follows: the CLINICAL STUDIES section of the package insert should state that extensive-stage disease was defined per the VALG staging system for SCLC in the IMpower133 study, etc.; the following statement should be included in the PRECAUTIONS CONCERNING INDICATION section; and then the appropriate indication should be "extensive-stage small cell lung cancer."

- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the definition of extensive-stage disease for patients enrolled in the clinical study, etc., and of the efficacy and safety of atezolizumab.

7.R.3.1 Clinical positioning of atezolizumab and target population

Atezolizumab for chemotherapy-naïve patients with extensive-stage SCLC is described as follows in the major foreign clinical practice guidelines and textbook of clinical oncology. At present, there is no mention of atezolizumab for chemotherapy-naïve patients with extensive-stage SCLC in the Japanese clinical practice guidelines (Version 2018) (Clinical practice guidelines for lung cancer 2018, The Japan Lung Cancer Society ed.) or New Clinical Oncology, the 5th edition (Nankodo, 2018).

- NCCN guidelines (v.1.2019)

Atezolizumab/CBDCA/ETP is strongly recommended for the treatment of chemotherapy-naïve extensive-stage SCLC.

The applicant's explanation about the clinical positioning of atezolizumab and the proposed indication:
Since the IMpower133 study in chemotherapy-naïve patients with extensive-stage SCLC demonstrated the clinical usefulness of atezolizumab/CBDCA/ETP compared with the existing treatment regimen, CBDCA/ETP, atezolizumab/CBDCA/ETP is recommended for chemotherapy-naïve patients with extensive-stage SCLC.

On the other hand, as there are currently no data demonstrating the clinical usefulness of atezolizumab in patients with limited-stage SCLC, i.e. the patient population that was not enrolled in the IMpower133 study, the use of atezolizumab is not recommended for these patients. However, given the following points, the CLINICAL STUDIES section of the package insert should state that patients with extensive-stage SCLC were enrolled in the study, but there is no need to exclude patients with limited-stage SCLC from treatment with atezolizumab.

- There are differences in the definitions of extensive-stage SCLC and limited-stage SCLC between Japan and outside Japan.
- Patients who received prior chemoradiotherapy (CRT) for limited-stage SCLC with curative intent and were diagnosed as having extensive-stage SCLC ≥6 months after the last chemotherapy, radiotherapy, or CRT cycle were also enrolled in the IMpower133 study.

Based on the above, the following statements were included in the PRECAUTIONS CONCERNING INDICATION section, and then the indication of "unresectable small cell lung cancer" was proposed. However, since there are no clinical study data demonstrating the clinical usefulness of atezolizumab in patients with SCLC in a post-operative adjuvant setting, and the use of atezolizumab is not recommended for these patients, the relevant statement is included in the PRECAUTIONS CONCERNING INDICATION section. In addition, since the IMpower133 study population should be made known appropriately, as with the previously approved package insert, the PRECAUTIONS CONCERNING INDICATION section states that 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.

- 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 concerning prior therapies etc. of patients enrolled in the clinical study, and of the efficacy and safety of atezolizumab.

The applicant's explanation about when to use atezolizumab/CBDCA/ETP and when to use the previously approved anti-neoplastic drugs [(a) CDDP/ETP, (b) CDDP/CPT-11], in patients with SCLC:

(a) Since the results of a meta-analysis comparing the efficacy etc. of CDDP-based chemotherapy versus CBDCA-based chemotherapy in patients with SCLC showed no clear differences in efficacy (*J Clin Oncol*. 2012;30:1692-8), there should be no clear differences in efficacy between CDDP/ETP and CBDCA/ETP, and atezolizumab/CBDCA/ETP is positioned as the preferred treatment option over CDDP/ETP.
(b) As there are no clinical study data comparing the efficacy and safety of atezolizumab/CBDCA/ETP versus CDDP/CPT-11, the preferred treatment is unknown at present.

PMDA's discussion:

The Japanese and foreign clinical practice guidelines make a clear distinction between the treatment paradigm for extensive-stage SCLC and that for limited-stage SCLC. While chemotherapy is used for the first-line treatment of extensive-stage SCLC, CRT is used for the first-line treatment of unresectable limited-stage SCLC. Given that these treatment paradigms are widely accepted in clinical practice, the INDICATION section should clarify that the target population is patients with extensive-stage SCLC.

Then, as the definition of extensive-stage SCLC for patients enrolled in the IMpower133 study, etc., are important information for selecting eligible patients, the relevant information should be included in the

CLINICAL STUDIES section of the package insert, and the relevant statement should be included also in the PRECAUTIONS CONCERNING INDICATION section. Since surgery is not the standard of care for extensive-stage SCLC recommended in the Japanese and foreign clinical practice guidelines etc., there is little need to specify that atezolizumab is indicated for "unresectable" disease, and to state that the efficacy and safety of atezolizumab in a post-operative adjuvant setting have not been established (the PRECAUTIONS CONCERNING INDICATION section of the proposed package insert).

Based on the above, the following information regarding the IMpower133 study should be included in the CLINICAL STUDIES section of the package insert, and the PRECAUTIONS CONCERNING INDICATION section should state that eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the definition of extensive-stage disease for patients enrolled in the clinical study, etc., and of the efficacy and safety of atezolizumab. Then, the appropriate indication for atezolizumab should be "extensive-stage small cell lung cancer."

- Extensive-stage disease was defined per the VALG staging system for SCLC.
- Patients who received prior CRT for limited-stage SCLC with curative intent and were diagnosed as having extensive-stage SCLC ≥6 months after the last chemotherapy, radiotherapy, or CRT cycle were also enrolled in the study.

Since there are no clinical study data comparing the efficacy and safety of atezolizumab/CBDCA/ETP versus anti-neoplastic drugs [(a) CDDP/ETP, (b) CDDP/CPT-11], the preferred treatment is unknown at present, and treatment will be chosen according to individual patients' conditions.

7.R.3.2 Efficacy and safety of atezolizumab by PD-L1 expression status and target population

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

The applicant's response:

Since the submission of a tumor tissue sample was not mandatory in the IMpower133 study for the following reasons, based on the data from some patients with PD-L1 status available, an exploratory analysis was performed by PD-L1 expression status. Ventana Medical Systems' diagnostic, "Ventana PD-L1 (SP142) assay," has been approved as an aid in identifying patients with NSCLC who may be eligible for treatment with atezolizumab. However, (1) the submission of a formalin-fixed paraffin-embedded (FFPE) section was permitted in the IMpower133 study, and (2) in FFPE sections, the epitope of SP142 on PD-L1 is stable for 3 months, while the epitope of SP263 on PD-L1 is stable for a longer period of time, i.e. 12 months. Thus, its "Ventana PD-L1 (SP263) assay" was used to measure PD-L1 expression in tumor specimens.

- While fine-needle aspiration biopsy etc. are commonly used for diagnosing of SCLC, adequate tumor tissues for PD-L1 testing cannot be obtained by these techniques.
- Patients with SCLC may experience fast clinical deterioration. Therefore, there is a need for rapid treatment initiation for these patients.

The results of (a) efficacy and (b) safety of atezolizumab by PD-L1 expression status are shown below.

(a) Efficacy

The results of the final analysis of OS (data cutoff date of January 24, 2019) and the Kaplan Meier curves for OS by PD-L1 expression status in the ITT population of the IMpower133 study are shown in Table 10 and Figures 3 to 6, respectively. Given that patients evaluable for PD-L1 expression are only a portion of the ITT population, 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 10. Results of final analysis of OS by PD-L1 expression status in tumor specimens (data cutoff date of January 24, 2019)

PD-L1 expression	Treatment group	N	OS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
TC <1% and IC <1%	Atezolizumab	28	10.2 [7.9, 15.7]	0.54 [0.32, 0.91]	0.2437
	Placebo	37	8.3 [6.9, 9.1]		
TC ≥1% or IC ≥1%	Atezolizumab	36	9.7 [7.6, 17.4]	0.84 [0.49, 1.44]	
	Placebo	36	10.6 [8.3, 14.7]		
TC <5% and IC <5%	Atezolizumab	49	9.2 [7.6, 12.2]	0.78 [0.51, 1.18]	0.4336
	Placebo	59	8.9 [8.0, 10.0]		
TC ≥5% or IC ≥5%	Atezolizumab	15	21.6 [9.4, NE]	0.53 [0.22, 1.28]	
	Placebo	14	9.2 [6.1, 15.7]		

*: Unstratified Cox regression, NE: Not estimable

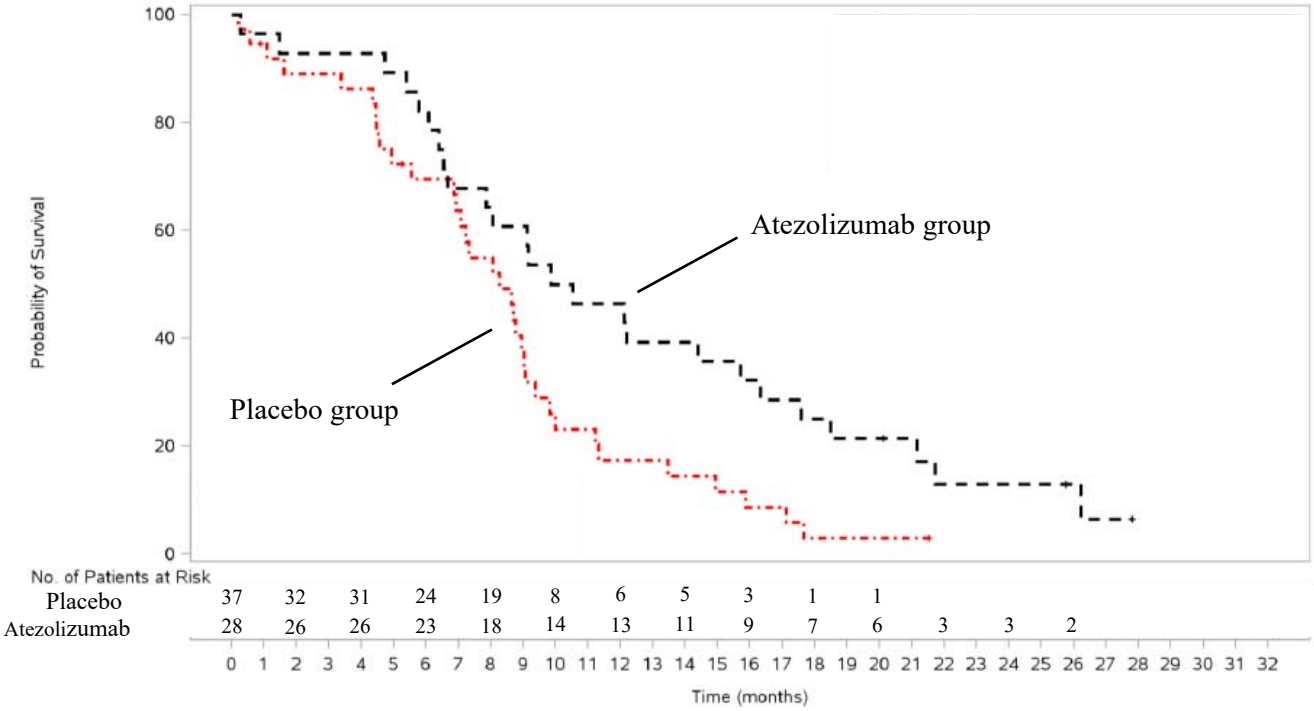

Figure 3. Kaplan-Meier curves for OS at the time of final analysis by PD-L1 expression status (TC <1% and IC <1% subgroup, data cutoff date of January 24, 2019)

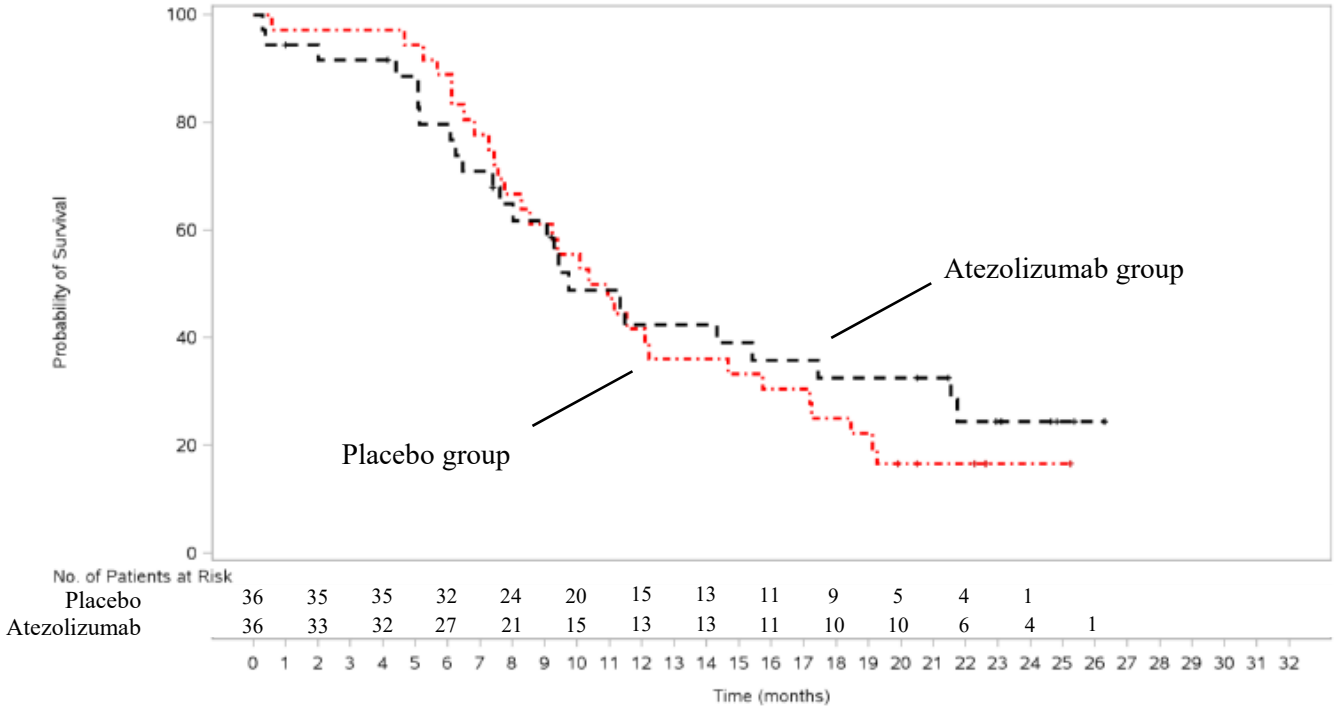

Figure 4. Kaplan-Meier curves for OS at the time of final analysis by PD-L1 expression status (TC ≥1% or IC ≥1% subgroup, data cutoff date of January 24, 2019)

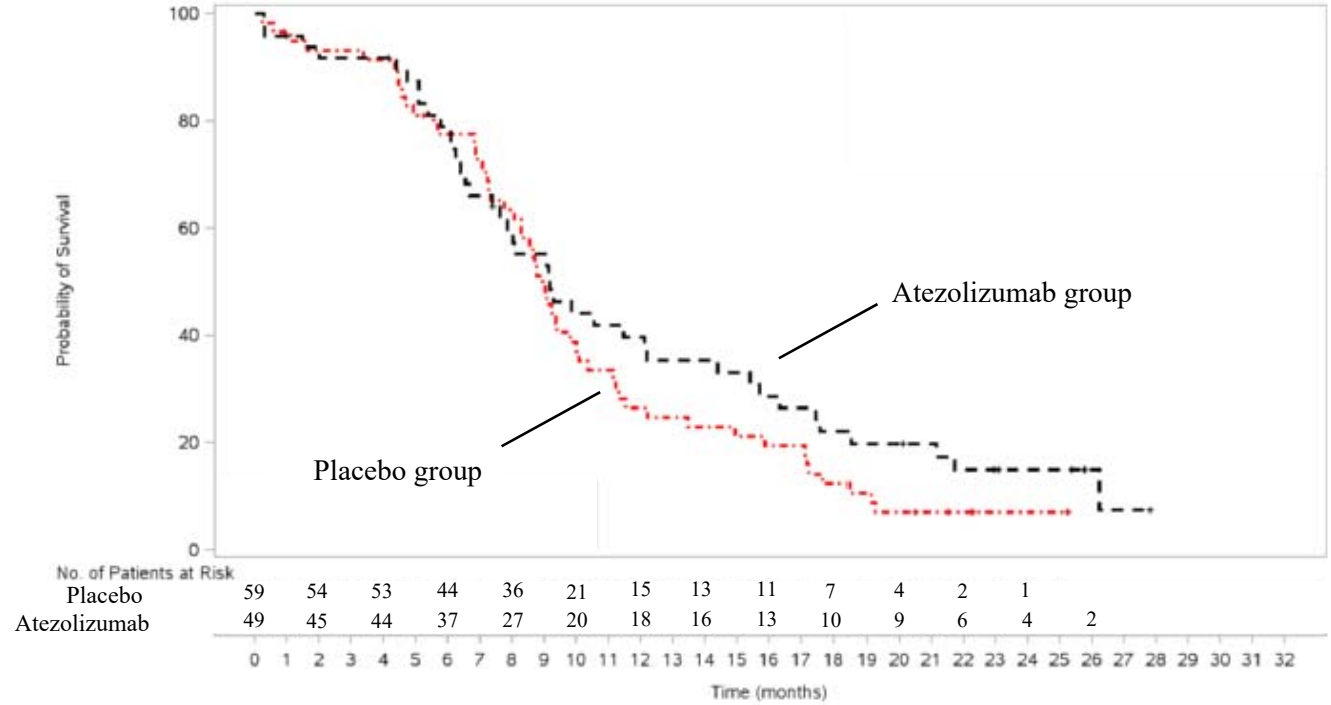

Figure 5. Kaplan-Meier curves for OS at the time of final analysis by PD-L1 expression status (TC <5% and IC <5% subgroup, data cutoff date of January 24, 2019)

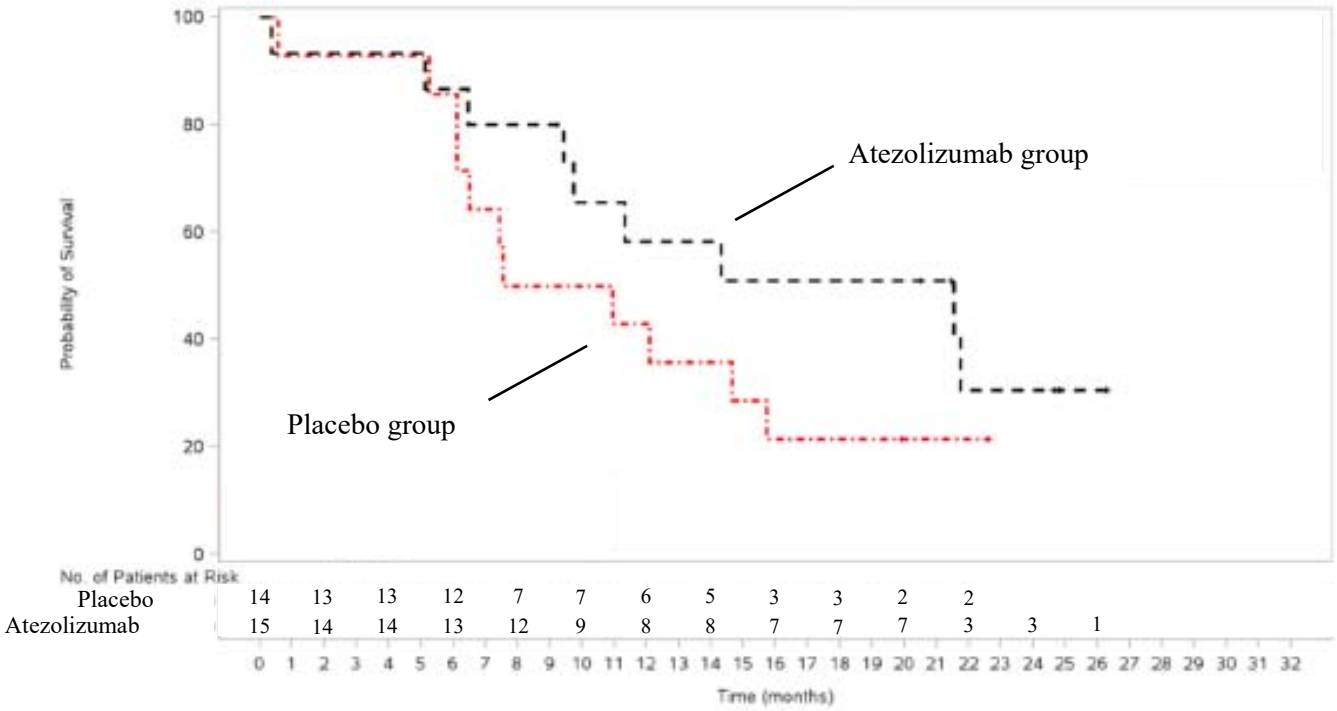

Figure 6. Kaplan-Meier curves for OS at the time of final analysis by PD-L1 expression status (TC ≥5% or IC ≥5% subgroup, data cutoff date of January 24, 2019)

(b) Safety

In the atezolizumab group of the IMpower133 study, the incidences of adverse events of any grade in the TC <1% and IC <1% subgroup and the TC ≥1% or IC ≥1% subgroup were both 100%, the incidences of Grade ≥3 adverse events were 57.1% and 70.3%, respectively, and the incidences of serious adverse events were 32.1% and 40.5%, respectively. The incidences of adverse events of any grade in the TC <5% and IC <5% subgroup and the TC ≥5% or IC ≥5% subgroup were both 100%, the incidences of Grade ≥3 adverse events were 66.0% and 60.0%, respectively, and the incidences of serious adverse events were 42.0% and 20.0%, respectively. There was no clear difference in the safety of atezolizumab on the basis of PD-L1 expression status in tumor specimens.

PMDA's discussion:

PMDA largely accepted the above explanation by the applicant. However, it is necessary to 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.4 Dosage and administration

The proposed dosage and administration statement was "*Atezolizumab in combination with carboplatin and etoposide*; 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 following statements were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert.

- Infusion solution preparation procedure
- Recommended dosage modifications for adverse reactions

Based on Sections "7.R.1 Efficacy" and "7.R.2 Safety," and the considerations in the following sections, PMDA concluded that the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement is appropriate.

- Atezolizumab should be used in combination with carboplatin and etoposide in the treatment of extensive-stage small cell lung cancer, with a full understanding of the information presented in the CLINICAL STUDIES section, especially, the dosing regimens of the concomitant anti-neoplastic drugs.
- Infusion solution preparation procedure
- Recommended dosage modifications for adverse reactions

7.R.4.1 Dosage and administration for atezolizumab

The applicant's explanation about the dosing rationale for atezolizumab:

The dosing regimen for the IMpower133 study was selected based on the following study results etc., and the IMpower133 study demonstrated the clinical usefulness of atezolizumab in combination with CBDCA/ETP in chemotherapy-naïve patients with extensive-stage SCLC. Thus, the proposed dosing regimen was selected based on the IMpower133 study.

- The efficacy and safety of atezolizumab 1200 mg/body Q3W in patients with unresectable advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy was demonstrated (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of October 23, 2017").

PMDA's discussion:

PMDA largely accepted the above explanation by the applicant. However, given that the dose of ETP used in the IMpower133 study is different from the dose of ETP in the Japanese clinical practice guidelines (Version 2018), the dose of ETP used in the IMpower133 study should be specified in the CLINICAL STUDIES section of the package insert to provide information on the dose of ETP in the atezolizumab/CBDCA/ETP regimen.

Based on the above, 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 ("*Atezolizumab in combination with carboplatin and etoposide*; 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.") is appropriate.

- Atezolizumab should be used in combination with carboplatin and etoposide in the treatment of extensive-stage small cell lung cancer, with a full understanding of the information presented in the CLINICAL STUDIES section, especially, the dosing regimens of the concomitant anti-neoplastic drugs.

7.R.4.2 Recommended dosage modifications

The applicant's explanation about the recommended dosage modifications for atezolizumab:

The IMpower133 study was conducted according to the specific dosage modification guidelines for atezolizumab for adverse events, and demonstrated the tolerability and safety of atezolizumab. Thus, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section will include a revised version of these guidelines as shown below.

After the submission of the present partial change application (as of March 2019), taking account of the incidence of immune-related myositis in clinical studies of atezolizumab, etc., the atezolizumab dosage modification guidelines for myositis have been added to the CCDS for atezolizumab, etc. Thus, these guidelines will also be added to the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

PMDA's discussion:

PMDA accepted the applicant's explanation, and concluded that the following recommended dosage modifications for adverse reactions should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section as proposed by the applicant (Underline denotes additions to the approved labeling).

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

Recommended dosage modifications for adverse reactions

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.

Adverse reaction	Severity of adverse reaction	Dosage modifications
	• Grade 2 or 3 hypophysitis • Grade 2 or 3 hypopituitarism	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	• Grade 4 or recurrent hypophysitis • Grade 4 or recurrent hypopituitarism	Permanently discontinue
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
Nephritis	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
Myositis	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 3 recurrent or Grade 4	Permanently discontinue
Myocarditis	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
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 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

7.R.5 Post-marketing investigations

The applicant is planning to conduct a post-marketing database survey to compare the incidence of neutropenia with atezolizumab/CBDCA/ETP and that with chemotherapy without atezolizumab in patients with extensive-stage SCLC because the incidences of Grade ≥3 neutrophil count decreased and neutrophil count decreased leading to dose interruption were higher in Japanese patients with extensive-stage SCLC treated with atezolizumab/CBDCA/ETP than in non-Japanese patients in the IMpower133 study, etc.

PMDA's discussion:

Given the considerations in Section "7.R.2 Safety," the limited safety information from Japanese patients with extensive-stage SCLC treated with atezolizumab/CBDCA/ETP, and a concern about the possible occurrence of febrile neutropenia associated with serious neutrophil count decreased, febrile neutropenia, in addition to neutropenia, should be included in the safety specification of atezolizumab, and PMDA concluded that it is necessary to investigate the occurrence of neutropenia and febrile neutropenia after the market launch.

Although the applicant may collect information via post-marketing database survey as planned, the details of the method of collecting information, etc., via post-marketing database survey, should continue to be discussed.

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 Global phase I/III study (IMpower133 study)

Adverse events occurred in 198 of 198 subjects (100%) in the atezolizumab group and 189 of 196 subjects (96.4%) in the placebo group, and those for which a causal relationship to study drug could not be ruled out occurred in 188 of 198 subjects (94.9%) in the atezolizumab group and 181 of 196 subjects (92.3%) in the placebo group. Adverse events reported by ≥10% of subjects are shown in Table 11.

Table 11. Adverse events reported by ≥10% of subjects in either group

SOC PT (MedDRA ver.21.0)	n (%)			
	Atezolizumab N = 198		Placebo N = 196	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	198 (100)	137 (69.2)	189 (96.4)	136 (69.4)
Blood and lymphatic system disorders				
Anaemia	86 (43.4)	31 (15.7)	69 (35.2)	26 (13.3)
Neutropenia	74 (37.4)	46 (23.2)	69 (35.2)	49 (25.0)
Thrombocytopenia	33 (16.7)	20 (10.1)	31 (15.8)	17 (8.7)
Leukopenia	25 (12.6)	10 (5.1)	19 (9.7)	8 (4.1)
Gastrointestinal disorders				
Nausea	75 (37.9)	1 (0.5)	64 (32.7)	1 (0.5)
Constipation	51 (25.8)	2 (1.0)	58 (29.6)	1 (0.5)
Vomiting	39 (19.7)	3 (1.5)	33 (16.8)	5 (2.6)
Diarrhoea	35 (17.7)	4 (2.0)	31 (15.8)	2 (1.0)
General disorders and administration site conditions				
Fatigue	54 (27.3)	5 (2.5)	49 (25.0)	1 (0.5)
Asthenia	25 (12.6)	5 (2.5)	20 (10.2)	4 (2.0)
Pyrexia	20 (10.1)	0	16 (8.2)	0
Skin and subcutaneous tissue disorders				
Alopecia	73 (36.9)	0	68 (34.7)	0
Investigations				
Neutrophil count decreased	37 (18.7)	31 (15.7)	46 (23.5)	33 (16.8)
Platelet count decreased	25 (12.6)	7 (3.5)	29 (14.8)	8 (4.1)
White blood cell count decreased	18 (9.1)	7 (3.5)	25 (12.8)	9 (4.6)
Weight decreased	20 (10.1)	0	10 (5.1)	1 (0.5)
Respiratory, thoracic and mediastinal disorders				
Cough	18 (9.1)	1 (0.5)	25 (12.8)	2 (1.0)
Dyspnoea	20 (10.1)	3 (1.5)	18 (9.2)	2 (1.0)
Metabolism and nutrition disorders				
Decreased appetite	54 (27.3)	2 (1.0)	36 (18.4)	0
Nervous system disorders				
Headache	24 (12.1)	0	23 (11.7)	0
Endocrine disorders				
Hypothyroidism	20 (10.1)	0	1 (0.5)	0

Serious adverse events occurred in 74 of 198 subjects (37.4%) in the atezolizumab group and 68 of 196 subjects (34.7%) in the placebo group. Those reported by ≥3 subjects in each group were pneumonia (9 subjects [4.5%]); neutropenia (7 subjects [3.5%]); febrile neutropenia; and thrombocytopenia (5 subjects each [2.5%]); and vomiting; anaemia; diarrhoea; fatigue; and syncope (3 subjects each [1.5%]) in the atezolizumab group and febrile neutropenia (9 subjects [4.6%]); neutropenia (8 subjects [4.1%]); pneumonia (7 subjects [3.6%]); thrombocytopenia; hyponatraemia; and pancytopenia (4 subjects each [2.0%]); and vomiting; and lung infection (3 subjects each [1.5%]) in the placebo group. A causal relationship to study drug could not be ruled out for neutropenia (7 subjects); thrombocytopenia (5 subjects); febrile neutropenia; and pneumonia (4 subjects each); anaemia; and diarrhoea (3 subjects each); vomiting (2 subjects); and fatigue (1 subject) in the atezolizumab group and febrile neutropenia (9 subjects); neutropenia (8 subjects); thrombocytopenia; and pancytopenia (4 subjects each); vomiting; and lung infection (2 subjects each); and pneumonia (1 subject) in the placebo group.

Adverse events leading to study drug discontinuation occurred in 22 of 198 subjects (11.1%) in the atezolizumab group and 6 of 196 subjects (3.1%) in the placebo group. Those reported by ≥3 subjects in either group were infusion related reactions (5 subjects [2.5%]) in the atezolizumab group, and their causal relationship to study drug could not be ruled out.

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 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.

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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 extensive-stage SCLC, and that atezolizumab has acceptable safety in view of its benefits. Atezolizumab/CBDCA/ETP is clinically meaningful because it offers a treatment option for patients with

extensive-stage SCLC. PMDA considers that the indication 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)

July 24, 2019

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	December 7, 2018

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.1 Efficacy" in the Review Report (1), since a global phase I/III study in chemotherapy-naïve patients with extensive-stage SCLC (IMpower133 study) demonstrated the superiority of the atezolizumab group over the placebo group in the co-primary endpoint of OS, PMDA concluded that the efficacy of atezolizumab was demonstrated in this patient population.

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

1.2 Safety

PMDA's conclusion:

Based on the considerations in Section "7.R.2 Safety" in the Review Report (1), adverse events that require attention following administration of atezolizumab/CBDCA/ETP in chemotherapy-naïve patients with extensive-stage SCLC are myocarditis in addition to the events that were considered to require attention at the time of the initial approval of atezolizumab (use in the previously approved indication).[7)] Attention should be paid to the possible occurrence of these adverse events during treatment with atezolizumab.

7) 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, myasthenia gravis, and febrile neutropenia (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of October 23, 2017" etc.)

Although attention should be paid to the possible occurrence of the above adverse events during treatment with atezolizumab, atezolizumab is tolerable also in chemotherapy-naïve patients with extensive-stage SCLC 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 dose interruption/reduction, discontinuation, etc. of atezolizumab and the concomitant anti-neoplastic drugs.

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.3 Clinical positioning and indication" in the Review Report (1), the following information regarding the IMpower133 study should be included in the CLINICAL STUDIES section of the package insert: (1) Extensive-stage disease was defined per the VALG staging system for SCLC. and (2) Patients who received prior CRT for limited-stage SCLC with curative intent and were diagnosed as having extensive-stage SCLC ≥6 months after the last chemotherapy, radiotherapy, or CRT cycle were also enrolled in the study. The following statement should be included in the PRECAUTIONS CONCERNING INDICATION section. Then, the appropriate indication should be "extensive-stage small cell lung cancer."

- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the definition of extensive-stage disease for patients enrolled in the clinical study, etc., 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 amend the INDICATION and PRECAUTIONS CONCERNING INDICATION sections accordingly. The applicant agreed.

1.4 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.4 Dosage and administration" in the Review Report (1), PMDA concluded that the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement ("*Atezolizumab in combination with carboplatin and etoposide*; 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.") is appropriate.

Precautions Concerning Dosage and Administration

- Atezolizumab should be used in combination with carboplatin and etoposide in the treatment of extensive-stage small cell lung cancer, with a full understanding of the information presented in the CLINICAL STUDIES section, especially, the dosing regimens of the concomitant anti-neoplastic drugs.
- Infusion solution preparation procedure
- Recommended dosage modifications for adverse reactions

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.

1.5 Risk management plan (draft)

The applicant is planning to conduct a post-marketing database survey to compare the incidence of neutropenia with atezolizumab/CBDCA/ETP and that with chemotherapy without atezolizumab in patients with extensive-stage SCLC because the incidences of Grade ≥3 neutrophil count decreased and neutrophil count decreased leading to dose interruption were higher in Japanese patients with extensive-stage SCLC treated with atezolizumab/CBDCA/ETP than in non-Japanese patients in the IMpower133 study, etc.

PMDA's conclusion:
Based on the considerations in Section "7.R.5 Post-marketing investigations" in the Review Report (1), febrile neutropenia, in addition to neutropenia, should be included in the safety specification of atezolizumab, and PMDA concluded that it is necessary to investigate the occurrence of neutropenia and febrile neutropenia with atezolizumab/CBDCA/ETP and that with chemotherapy without atezolizumab in patients with extensive-stage SCLC after the market launch.

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

Based on the above, PMDA instructed the applicant to reconsider the post-marketing surveillance plan etc.

The applicant's response:
- A post-marketing database survey will be conducted to investigate the occurrence of neutropenia and febrile neutropenia in patients with SCLC treated with atezolizumab/CBDCA/ETP.
- Neutropenia and febrile neutropenia will be included in the safety specification, and the incidences of these events, etc., with atezolizumab/CBDCA/ETP, will be compared with those with chemotherapy without atezolizumab in patients with SCLC.

PMDA accepted the applicant's response.

In view of the discussion above and the considerations in Section "7.R.2 Safety" in the Review Report (1), PMDA has concluded that the risk management plan (draft) for atezolizumab should include the safety specification presented in Table 12, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 13.

Table 12. 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 • Myocarditis • IRR	• Hemolytic anemia • Immune thrombocytopenic purpura • Embryo-fetal toxicity • Use in organ transplant recipients (including hematopoietic stem cell transplant recipients) • Hematologic toxicity when combined with chemotherapy (neutropenia, febrile neutropenia)	None
Efficacy specification		
None		

Underline denotes additions.

Table 13. Summary of additional pharmacovigilance activities, surveillance/studies for efficacy, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillance/studies for efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy • Use-results survey in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy (all-case surveillance) • Post-marketing database survey in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC [hematologic toxicity when combined with chemotherapy (febrile neutropenia)] • Post-marketing database survey in patients with extensive-stage SCLC (hematologic toxicity when combined with chemotherapy [neutropenia and febrile neutropenia]) • Post-marketing clinical studies (extension studies of OAK, BIRCH, and IMpower133) • Post-marketing clinical study (Study BO39633-01)	None	• 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.

Underline denotes planned activities for the additional dosage regimen claimed

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition, 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 has been designated as an orphan drug, the re-examination period is 10 years.

Indications (Underline denotes additions.)
Unresectable advanced or recurrent non-small cell lung cancer
Extensive-stage small cell lung cancer

Dosage and Administration (Single underline denotes new additions. Double underline denotes additions made as of December 21, 2018 after submission of the present partial change application.)
For chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer
Atezolizumab in combination with carboplatin, paclitaxel, and bevacizumab (genetical recombination)
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.

For patients with unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy
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.

For patients with extensive-stage small cell lung cancer
Atezolizumab in combination with carboplatin and etoposide
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 Condition
The applicant is required to develop and appropriately implement a risk management plan.

Warnings (No change)
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 (No change)
Patients with a history of hypersensitivity to any of the components of atezolizumab.

Precautions Concerning Indications (Single underline denotes new additions. Double underline denotes additions made as of December 21, 2018 after submission of the present partial change application.)
Unresectable advanced or recurrent non-small cell lung cancer

1. The efficacy and safety of atezolizumab in chemotherapy-naïve patients with squamous disease have not been established.
2. The efficacy and safety of atezolizumab in a post-operative adjuvant 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.

Extensive-stage small cell lung cancer
Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the definition of extensive-stage disease for patients enrolled in the clinical study, etc., and of the efficacy and safety of atezolizumab.

Precautions Concerning Dosage and Administration (Single underline denotes new additions. Double underline denotes additions made as of December 21, 2018 after submission of the present partial change application.)

1. In patients with unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy, the efficacy and safety of atezolizumab in combination with other anti-neoplastic drugs have not been established.
2. Atezolizumab should be used in combination with carboplatin and etoposide in the treatment of extensive-stage small cell lung cancer, with a full understanding of the information presented in the CLINICAL STUDIES section, especially, the dosing regimens of the concomitant anti-neoplastic drugs.

32. 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.
43. 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.
	• Grade 2 or 3 hypophysitis • Grade 2 or 3 hypopituitarism	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	• Grade 4 or recurrent hypophysitis • Grade 4 or recurrent hypopituitarism	Permanently discontinue
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
Nephritis	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
Myositis	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 3 recurrent or Grade 4	Permanently discontinue
Myocarditis	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
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

Appendix

List of Abbreviations

ALT	alanine aminotransferase
a partial change application	an application for partial change of marketing approval
a platinum agent	CBDCA or CDDP
a platinum agent/CPT-11	the combination of a platinum agent and CPT-11
a platinum agent/ETP	the combination of a platinum agent and ETP
AST	aspartate aminotransferase
atezolizumab	Atezolizumab (Genetical Recombination)
atezolizumab/CBDCA/ETP	the combination of atezolizumab, CBDCA, and ETP
atezolizumab/CBDCA/PTX	the combination of atezolizumab, CBDCA, and PTX
atezolizumab/CBDCA/PTX/BV	the combination of atezolizumab, CBDCA, PTX, and BV
AUC	area under the blood concentration-time curve
BV	bevacizumab (genetical recombination)
CBDCA	carboplatin
CBDCA/ETP	the combination of CBDCA and ETP
CBDCA/PTX/BV	the combination of CBDCA, PTX, and BV
CCDS	company core data sheet
CDDP	cisplatin
CDDP/CPT-11	the combination of CDDP and CPT-11
CDDP/ETP	the combination of CDDP and ETP
CI	confidence interval
CPT-11	irinotecan hydrochloride hydrate
CRPC	castration-resistance prostate cancer
CRT	chemoradiotherapy
DOC	docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
ESMO guidelines	Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
ETP	etoposide
FFPE	formalin fixed paraffin embedded
HER	human epidermal growth factor receptor
HLT	high level terms
HR	hormone receptor (estrogen receptor or progesterone receptor)
IC	the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IDMC	independent data monitoring committee
Ig	immunoglobulin
ILD	interstitial lung disease
IMpower133 study	Study GO30081
IMpower150 study	Study GO29436
IRR	infusion related reaction
ITT	intention-to-treat
Japanese clinical practice guidelines (Version 2015)	EBM-based clinical practice guidelines for lung cancer 2015, The Japan Lung Cancer Society ed.
Japanese clinical practice guidelines (Version 2018)	Clinical practice guidelines for lung cancer 2018, The Japan Lung Cancer Society ed.
MedDRA	Medical Dictionary for Regulatory Activities
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Small Cell Lung Cancer
NSCLC	non-small cell lung cancer
NSQ-NSCLC	non-squamous non-small cell lung cancer

OAK study	Study GO28915
OS	overall survival
PD-L	programmed cell death-ligand
PD-1	programmed cell death-1
PFS	progression-free survival
placebo/CBDCA/ETP	the combination of placebo, CBDCA, and ETP
PLD	pegylated liposomal doxorubicin hydrochloride
PMDA	Pharmaceuticals and Medical Devices Agency
PS	performance status
PT	preferred term
PTX	paclitaxel
Q3W	quaque 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	small cell lung cancer
SOC	system organ class
TC	the proportion of tumor area occupied by PD-L1-expressing tumor cells