Review Report

October 10, 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) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	January 23, 2019
Dosage Form/Strength	Injection: Each vial (20.0 mL) contains 1200 mg of Atezolizumab (Genetical Recombination).
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product in combination with a platinum agent and pemetrexed sodium hydrate and the product in combination with carboplatin and paclitaxel (albumin-bound) have efficacy in the treatment of chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer, and that the combinations have acceptable safety in view of their 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
Extensive-stage small cell lung cancer

(No change made in the present partial change application. Double underline denotes additions made as of August 22, 2019 after submission of the present partial change application.)

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)~~ other anti-neoplastic drugs

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, and strikethrough denotes deletions. Double underline denotes additions made as of August 22, 2019 after submission of the present partial change application.)

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

August 30, 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	January 23, 2019
Dosage Form/Strength	Injection: Each vial (20.0 mL) contains 1200 mg of Atezolizumab (Genetical Recombination).
Proposed Indication	Unresectable advanced or recurrent non-small cell lung cancer (No change)

Proposed 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)~~ <u>other anti-neoplastic drugs</u>

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.

(Strikethrough denotes deletions, and 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 (ATZ) 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) ATZ as monotherapy was approved in January 2018 and (b) ATZ in combination with carboplatin (CBDCA), paclitaxel (PTX), and bevacizumab (genetical recombination) (BV) in December 2018, for the indication of "unresectable advanced or recurrent non-small cell lung cancer." ATZ in combination with CBDCA and etoposide (ETP) was approved for the indication of "extensive-stage small cell lung cancer" in August 2019.

1.2 Development history etc.

In the clinical development of ATZ/a platinum agent/pemetrexed sodium hydrate (PEM) and ATZ/CBDCA/paclitaxel (albumin-bound) (nab-PTX) for chemotherapy-naïve patients with unresectable advanced or recurrent non-small cell lung cancer (NSCLC), Roche (Switzerland) and Genentech (the US) initiated a global phase III study (IMpower132 study) and a foreign phase III study (IMpower130 study) in this patient population in April 2016 and April 2015, respectively.

As of July 2019, ATZ in combination with a platinum agent and PEM has not been approved in any country or region, and ATZ in combination with CBDCA and nab-PTX has been approved in 6 counties.

In Japan, the IMpower132 study initiated patient enrollment in July 2016.

The applicant has filed a partial change application for additional regimens of ATZ/platinum/PEM and ATZ/CBDCA/nab-PTX for the treatment of NSCLC, based mainly on the results from the IMpower132 study and the IMpower130 study.

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

Since the present application is intended for 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 dosage, the non-clinical pharmacology data were previously evaluated for the initial approval of ATZ, 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 dosage, the non-clinical pharmacokinetic data were previously evaluated for the initial approval of ATZ, 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 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 dosage, the data on biopharmaceutic studies and associated analytical methods were previously evaluated for the initial approval of ATZ, and no new study data have been submitted.

The applicant submitted the results from the IMpower132 study as clinical pharmacology data and explained that the study results etc. showed no pharmacokinetic interactions between ATZ and cisplatin (CDDP)/PEM, 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 a total of 2 studies presented in Table 1: 1 global phase III study and 1 foreign phase III study.

Table 1. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study Identity	Phase	Study population	No. of subjects enrolled	Dosing regimen*	Main endpoints
Evaluation	Global	IMpower132	III	Chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC	578 (a) 292 (b) 286	(a) 4 or 6 cycles of ATZ in combination with platinum/PEM intravenously, followed by ATZ/PEM intravenously (b) 4 or 6 cycles of platinum/PEM intravenously, followed by PEM intravenously	Efficacy Safety
	Foreign	IMpower130	III	Chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC	724 (a) 484 (b) 240	(a) 4 or 6 cycles of ATZ/CBDCA/nab-PTX intravenously, followed by ATZ intravenously (b) 4 or 6 cycles of CBDCA/nab-PTX intravenously, followed by PEM intravenously	Efficacy Safety

*: ATZ 1200 mg, CBDCA AUC 6 mg·min/mL, CDDP 75 mg/m^2, and PEM 500 mg/m^2 were administered intravenously on Day 1 and nab-PTX 100 mg/m^2 was administered intravenously on Days 1, 8, and 15 of each 3-week cycle.

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

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1-1, IMpower132 study [ongoing since April 2016 (data cutoff date of May 22, 2018)])

An open-label, randomized study was conducted at 164 sites in 26 countries or regions including Japan to evaluate the efficacy and safety of ATZ/platinum/PEM compared with platinum/PEM in

chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous (NSQ)-NSCLC (target sample size, 568 subjects[1)]).

Subjects were to receive 3-week cycles of the following treatment until disease progression or a criterion for discontinuation was met.

- ATZ/platinum/PEM group
  Subjects were to receive 4 or 6 cycles of ATZ 1200 mg in combination with platinum and PEM Q3W intravenously, followed by ATZ 1200 mg and PEM 500 mg/m^2 Q3W intravenously.
- Platinum/PEM group
  Subjects were to receive 4 or 6 cycles of platinum and PEM 500 mg/m^2 Q3W intravenously, followed by PEM 500 mg/m^2 Q3W intravenously.

All of 578 subjects who were enrolled in the study and randomized (292 in the ATZ/platinum/PEM group, 286 in the platinum/PEM group) were included in the intention-to-treat (ITT) population, which was used as the efficacy analysis population (including 48 Japanese patients in the ATZ/platinum/PEM group and 53 Japanese patients in the platinum/PEM group). Among the ITT population, 565 subjects (291 in the ATZ/platinum/PEM group, 274 in the platinum/PEM group) after excluding 13 subjects who did not receive study drug (1 in the ATZ/platinum/PEM group, 12 in the platinum/PEM group) were included in the safety population (including 48 Japanese patients in the ATZ/platinum/PEM group and 52 Japanese patients in the platinum/PEM group).

At the time of initiating the study, the primary endpoint for the study was investigator-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1, and the primary analysis of PFS was to be conducted in the ITT population and the PD-L1-positive[2)] subpopulation. However, since (a) the results from the OAK study[3)] etc. suggested the efficacy of ATZ, regardless of PD-L1 expression status, and (b) the results from the POPLAR study[4)] etc. indicated that overall survival (OS) may be a more appropriate efficacy endpoint for ATZ, the protocol was amended as follows (Protocol Version [redacted] [as of [redacted], 20[redacted]]).

- The PD-L1-positive subpopulation was omitted from the analysis.
- OS was promoted from a secondary endpoint to a co-primary endpoint.
- The primary analysis of PFS and the first interim analysis of OS were to be conducted when approximately 396 PFS events had been observed.
- The second interim analysis of OS was to be conducted when approximately 332 OS events had occurred.
- The final analysis of OS was to be performed when approximately 414 OS events had occurred.

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1) The study was initially planned to enroll 680 subjects. A protocol amendment (Protocol Version [redacted] [as of [redacted], 20[redacted]]) reduced the sample size to 568 because OS was added as a co-primary endpoint, and the statistical analysis plan was amended accordingly.
2) The PD-L1-positive subpopulation was defined as patients whose PD-L1 status was TC2/3 or IC2/3.
3) A global phase III study to evaluate the efficacy and safety of ATZ compared with DTX in patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy
4) A foreign phase II study to evaluate the efficacy and safety of ATZ compared with DTX in patients with advanced or recurrent NSCLC previously treated with platinum-containing chemotherapy

Then, the results from the OAK study[3)] indicated that long-term follow-up is needed to evaluate the efficacy of ATZ, etc. Thus, only one interim analysis of OS was planned; the primary analysis of PFS and the interim OS analysis were to be performed when approximately 458 PFS events had been observed and all of the patients who were enrolled in the study and randomized had been followed-up for 10 months; and the final analysis of OS was to be conducted when approximately 398 OS events had occurred (Protocol Version [redacted] [as of [redacted], 20[redacted]]).

In order to adjust for multiplicity of the two co-primary endpoints, the Bonferroni method was used, and a one-sided alpha of 0.2% and a one-sided alpha of 2.3% were allocated to PFS and OS, respectively (Protocol Version [redacted] [as of [redacted], 20[redacted]]). However, the multiplicity strategy was changed to the group sequential Holm variable 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 above alpha level, OS (PFS) was to be tested at a one-sided alpha level of 2.5% (Protocol Version [redacted] [as of [redacted], 20[redacted]]). The interim analysis of OS was to use the Lan-DeMets alpha spending function to approximate the Pocock boundary to control for the type I error rate.

The results of the primary analysis of the co-primary efficacy endpoint of PFS (data cutoff date of May 22, 2018) and the Kaplan-Meier curves for PFS are shown in Table 2 and Figure 1, respectively, and the superiority of ATZ/platinum/PEM over platinum/PEM was demonstrated.

Table 2. Results of primary analysis of PFS
(Investigator assessment, ITT population, data cutoff date of May 22, 2018)

	ATZ/platinum/PEM	Platinum/PEM
N	292	286
No. of events (%)	209 (71.6)	249 (87.1)
Median [95% CI] (months)	7.6 [6.6, 8.5]	5.2 [4.3, 5.6]
Hazard ratio [95% CI]*1	0.596 [0.494, 0.719]	
P-value (two-sided)*2	<0.0001	

*1: Cox regression stratified by sex (male, female), ECOG PS (0, 1), and type of platinum agent (CBDCA, CDDP)
*2: Log-rank test stratified by sex (male, female), ECOG PS (0, 1), and type of platinum agent (CBDCA, CDDP), a significance level (two-sided) of 0.004

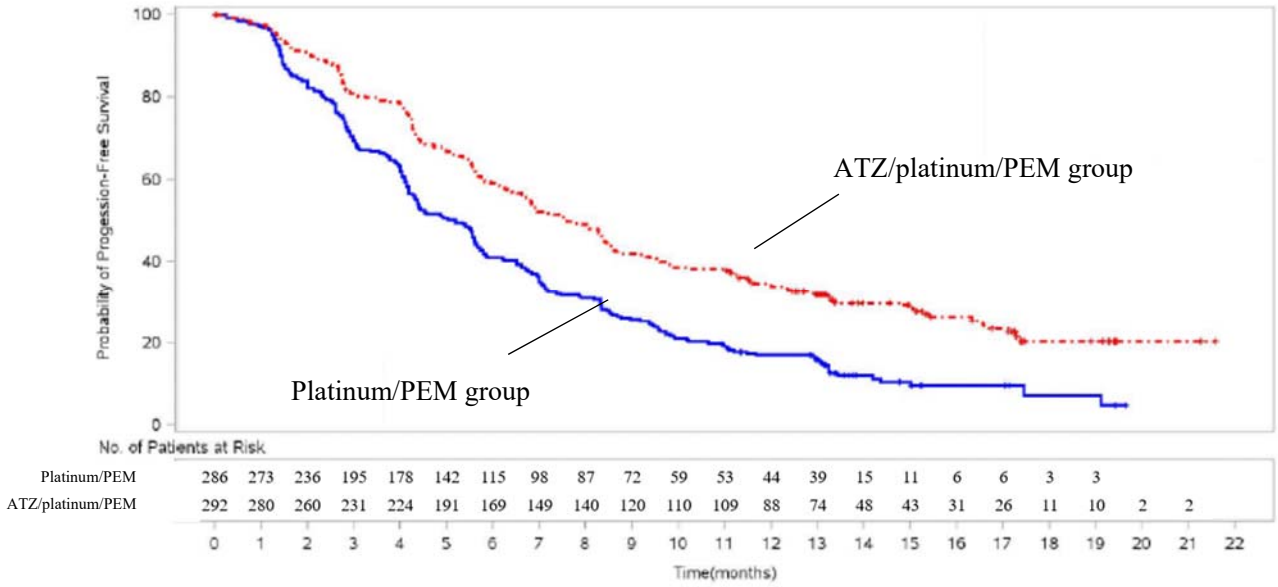

Figure 1. Kaplan-Meier curves for PFS at the time of primary analysis (Investigator assessment, ITT population, data cutoff date of May 22, 2018)

The results of the interim analysis of the co-primary endpoint of OS (data cutoff date of May 22, 2018) and the Kaplan-Meier curves for OS are shown in Table 3 and Figure 2, respectively, and the interim analysis failed to demonstrate the superiority of ATZ/platinum/PEM over platinum/PEM.

Table 3. Results of interim OS analysis (ITT population, data cutoff date of May 22, 2018)

	ATZ/platinum/PEM	Platinum/PEM
N	292	286
No. of events (%)	137 (46.9)	154 (53.8)
Median [95% CI] (months)	18.1 [13.0, —]	13.6 [11.4, 15.5]
Hazard ratio [95% CI][*1]	0.813 [0.644, 1.025]	
P-value (two-sided)[*2]	0.0797	

*1: Cox regression stratified by sex (male, female), ECOG PS (0, 1), and type of platinum agent (CBDCA, CDDP)
*2: Log-rank test stratified by sex (male, female), ECOG PS (0, 1), and type of platinum agent (CBDCA, CDDP), a significance level (two-sided) of 0.0406

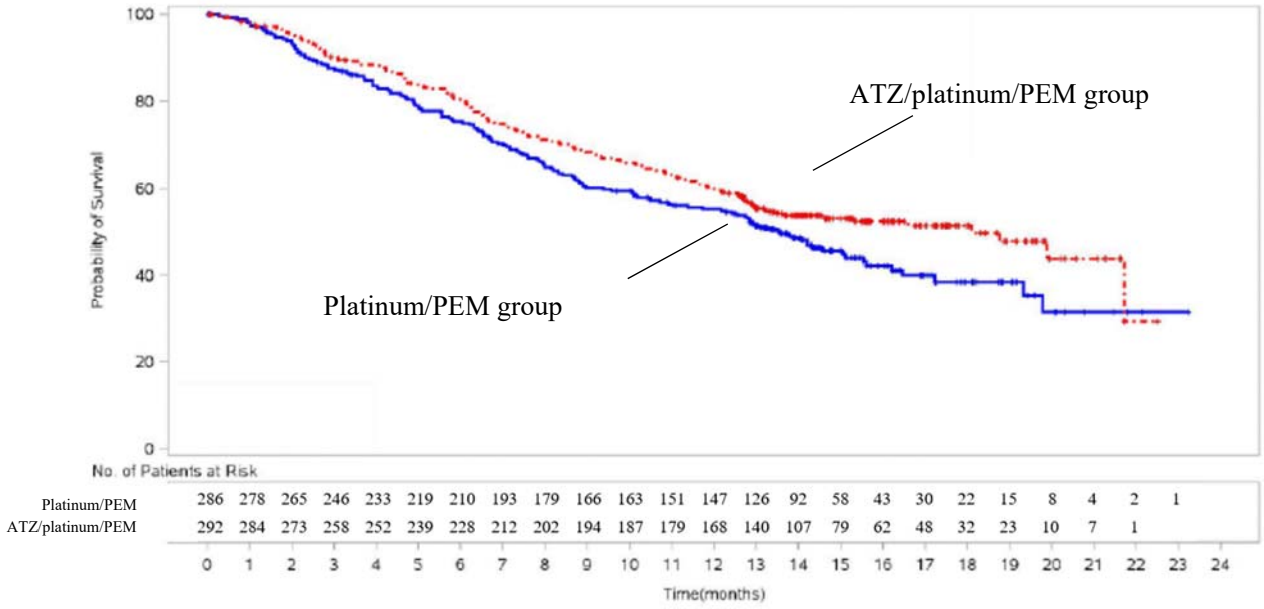

Figure 2. Kaplan-Meier curves for OS at the time of interim analysis (ITT population, data cutoff date of May 22, 2018)

Regarding safety, 63 of 291 subjects (21.6%) in the ATZ/platinum/PEM group and 56 of 274 subjects (20.4%) in the platinum/PEM group died during the study treatment period or the follow-up period[5)] (including 1 of 48 Japanese patients in the ATZ/platinum/PEM group and 1 of 52 Japanese patients in the platinum/PEM group). The causes of deaths other than disease progression (41 in the ATZ/platinum/PEM group, 40 in the platinum/PEM group) were death (4 subjects); pneumonia; and pulmonary embolism (2 subjects each); and pneumonitis; cerebrovascular accident; tumour embolism; hepatotoxicity; interstitial lung disease (ILD); neutropenic sepsis; small intestinal perforation; decreased appetite; ulcerative proctitis; seizure; influenza; acute kidney injury; subdural haematoma; and completed suicide (1 subject each) in the ATZ/platinum/PEM group and death (4 subjects); pneumonia (3 subjects); and pneumonitis; cerebrovascular accident; tumour embolism; acute cardiac failure; pancytopenia; acute myocardial infarction; renal failure; sepsis; and pulmonary haemorrhage (1 subject each) in the platinum/PEM group. A causal relationship to study drug could not be ruled out for death; pneumonia; pneumonitis; hepatotoxicity; ILD; neutropenic sepsis; small intestinal perforation; decreased appetite; ulcerative proctitis; and seizure (1 subject each) in the ATZ/platinum/PEM group and pneumonia (2 subjects); and pneumonitis; cerebrovascular accident; acute cardiac failure; and pancytopenia (1 subject each) in the platinum/PEM group (the cause of death in a Japanese patient with an adverse event leading to death [1 in the ATZ/platinum/PEM group, 0 in the platinum/PEM group] was pneumonitis, and its causal relationship to study drug could not be ruled out).

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.

7.1.2 Foreign study

7.1.2.1 Foreign phase III study (CTD 5.3.5.1-3, IMpower130 study [ongoing since April 2015 (data cutoff date of March 15, 2018)])

An open-label, randomized study was conducted at 131 sites outside Japan to evaluate the efficacy and safety of ATZ/CBDCA/nab-PTX compared with CBDCA/nab-PTX in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC (target sample size, 715 subjects).

Subjects were to receive 3-week cycles of the following treatment until disease progression or a criterion for discontinuation was met.

- ATZ/CBDCA/nab-PTX group
  Subjects were to receive 4 or 6 cycles of ATZ 1200 mg in combination with CBDCA and nab-PTX intravenously, followed by ATZ 1200 mg Q3W intravenously.
- CBDCA/nab-PTX group
  Subjects were to receive 4 or 6 cycles of CBDCA and nab-PTX intravenously, followed by PEM Q3W intravenously.[6)]

Among 724 subjects who were enrolled in the study and randomized, 723 subjects (483 in the ATZ/CBDCA/nab-PTX group, 240 in the CBDCA/nab-PTX group) after excluding 1 subject who died prior to randomization, but was randomized (simply not knowing the subject's death) (1 in the ATZ/CBDCA/nab-PTX group, 0 in the CBDCA/nab-PTX group) were included in the ITT population, which was used as the efficacy analysis population. Among the ITT population, 705 subjects (473 in the ATZ/CBDCA/nab-PTX group, 232 in the CBDCA/nab-PTX group) after excluding 18 subjects who did not receive study drug (10 in the ATZ/CBDCA/nab-PTX group, 8 in the CBDCA/nab-PTX group) were included in the safety population.

At the time of initiating the study, the primary endpoint for the study was investigator-assessed PFS per RECIST ver.1.1, and the primary analysis of PFS was to be conducted in the ITT population and the PD-L1-positive subpopulation.[7)] However, since the results from the POPLAR study[4)] indicated that OS may be a more appropriate efficacy endpoint for ATZ, OS was added as a co-primary endpoint (Protocol Version [redacted] [as of [redacted], 20[redacted]]). Then, the protocol was amended as follows.

- Based on the following published articles etc., the primary analysis of PFS was to be conducted in the T-effector high wild type (Teff-high-WT) population and the ITT-WT population, and OS was to be analyzed in the ITT-WT population (Protocol Version 6 [as of March 1, 2017]).

6) At the time of initiating the study, subjects were to receive 4 or 6 cycles of CBDCA and nab-PTX intravenously, followed by erlotinib QD orally or PEM Q3W intravenously. However, since a foreign phase III study to evaluate the efficacy and safety of erlotinib compared with placebo in patients with advanced or recurrent NSCLC who had not progressed following platinum-based chemotherapy (Study BO25460) failed to demonstrate the superiority of erlotinib over placebo in the primary endpoint of OS, new patients enrolled in the CBDCA/nab-PTX group were not allowed to receive erlotinib orally (Protocol Version [redacted] [as of [redacted], 20[redacted]]).

7) The PD-L1-positive subpopulation was defined as patients whose PD-L1 status was TC1/2/3 or IC1/2/3.

- The results from the POPLAR study[4)] and the OAK study[3)] demonstrated that compared with PD-L1 expression in tumors, T-effector gene signature[8)] is more associated with the efficacy of ATZ (*Lancet.* 2016;387:1837-46).
- In the OAK study, the OS hazard ratio did not favor ATZ over docetaxel hydrate (DTX) in patients with epidermal growth factor receptor (*EGFR*) mutation-positive status (*Lancet.* 2017;389:255-65).

• Since the results from the IMpower150 study [9)] demonstrated the efficacy of ATZ/CBDCA/PTX/BV in the ITT-WT population, the primary analysis of PFS was to be conducted in the ITT-WT population (Statistical Analysis Plan Version 3 [as of [redacted], 20[redacted]]).

In accordance with the above changes, the primary analysis of PFS and the interim OS analysis were to be conducted when approximately 352 OS events had occurred in the ITT-WT population, and the final analysis of OS was to be performed when approximately 457 OS events had occurred in the ITT-WT population. The interim analysis of OS was to use the Lan-DeMets alpha spending function to approximate the Pocock boundary to control for the type I error rate.

In order to adjust for multiplicity of the two co-primary endpoints, the Bonferroni method was used, and a one-sided alpha of 0.3% and a one-sided alpha of 2.2% were allocated to PFS and OS, respectively. If PFS was statistically significant at the above alpha level, OS was to be tested at a one-sided alpha level of 2.5%.

The results of the primary analysis of the co-primary efficacy endpoint of PFS (data cutoff date of March 15, 2018) and the Kaplan-Meier curves for PFS are shown in Table 4 and Figure 3, respectively, and the superiority of ATZ/CBDCA/nab-PTX over CBDCA/nab-PTX was demonstrated.

Table 4. Results of primary analysis of PFS
(Investigator assessment, ITT-WT population, data cutoff date of March 15, 2018)

	ATZ/CBDCA/nab-PTX	CBDCA/nab-PTX
N	451	228
No. of events (%)	347 (76.9)	198 (86.8)
Median [95% CI] (months)	7.0 [6.2, 7.3]	5.5 [4.4, 5.9]
Hazard ratio [95% CI][*1]	0.643 [0.539, 0.768]	
P-value (two-sided)[*2]	<0.0001	

*1: Cox regression stratified by sex (male, female) and PD-L1 expression (TC3 or [TC0/1/2 and IC2/3] vs. TC0/1/2 and IC0/1)
*2: Log-rank test stratified by sex (male, female) and PD-L1 expression (TC3 or [TC0/1/2 and IC2/3] vs. TC0/1/2 and IC0/1), a significance level (two-sided) of 0.006

8) The Teff gene signature is defined by mRNA expression of 3 genes (PD-L1, CXCL9, and IFN-γ, which are considered to be involved in immune responses) in tumor tissue, and patients are classified by Teff signature score.
9) A global phase III study to evaluate the efficacy and safety of ATZ/CBDCA/PTX or ATZ/CBDCA/PTX/BV compared with CBDCA/PTX/BV in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC

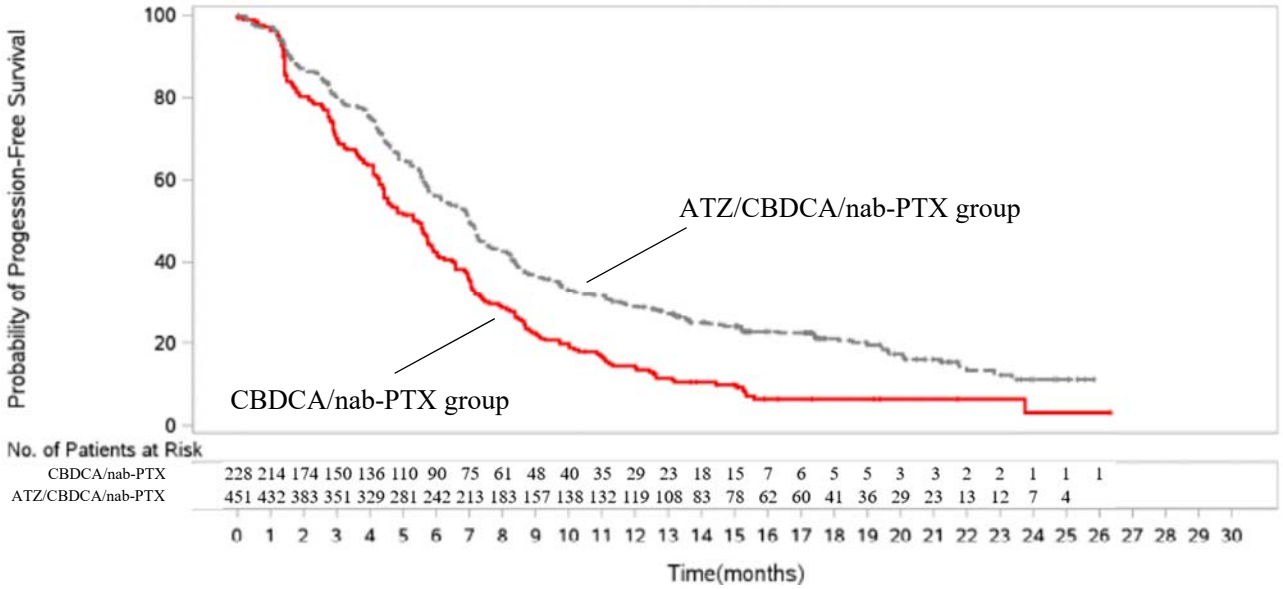

Figure 3. Kaplan-Meier curves for PFS at the time of primary analysis (Investigator assessment, ITT-WT population, data cutoff date of March 15, 2018)

The results of the interim analysis of the co-primary endpoint of OS (data cutoff date of March 15, 2018) and the Kaplan-Meier curves for OS are shown in Table 5 and Figure 4, respectively, and the superiority of ATZ/CBDCA/nab-PTX over CBDCA/nab-PTX was demonstrated.

Table 5. Results of interim OS analysis (ITT-WT population, data cutoff date of March 15, 2018)

	ATZ/CBDCA/nab-PTX	CBDCA/nab-PTX
N	451	228
No. of events (%)	226 (50.1)	131 (57.5)
Median [95% CI] (months)	18.6 [16.0, 21.2]	13.9 [12.0, 18.7]
Hazard ratio [95% CI]*1	0.791 [0.637, 0.982]	
P-value (two-sided)*2	0.0331	

*1: Cox regression stratified by sex (male, female) and PD-L1 expression (TC3 or [TC0/1/2 and IC2/3] vs. TC0/1/2 and IC0/1)
*2: Log-rank test stratified by sex (male, female) and PD-L1 expression (TC3 or [TC0/1/2 and IC2/3] vs. TC0/1/2 and IC0/1), a significance level (two-sided) of 0.0425

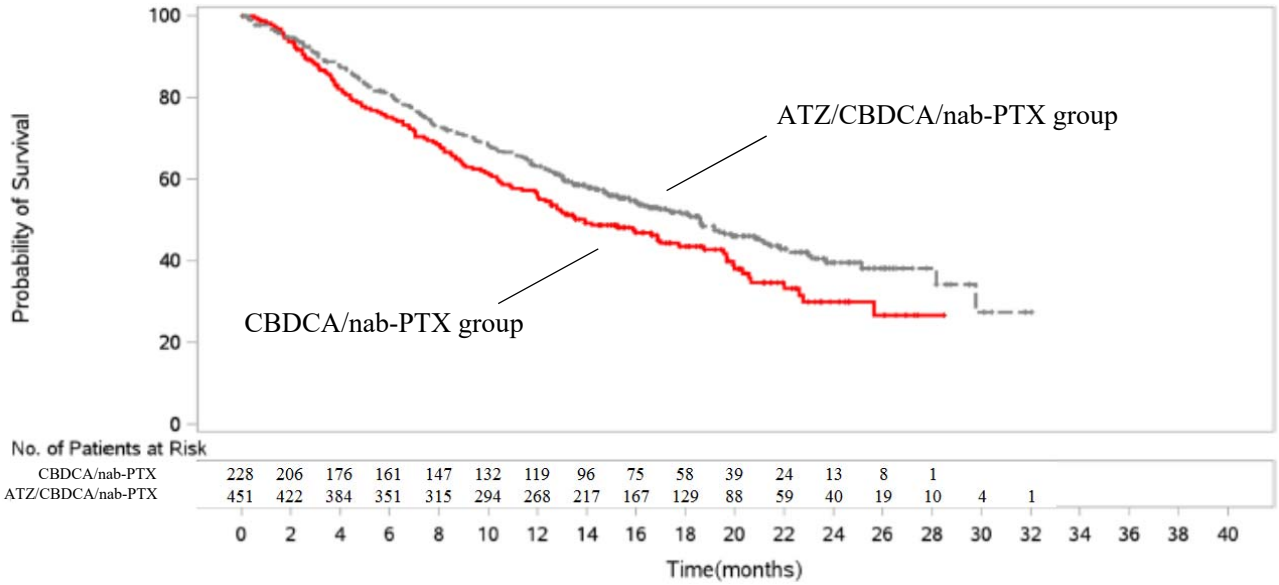

Figure 4. Kaplan-Meier curves for OS at the time of interim analysis

(ITT-WT population, data cutoff date of March 15, 2018)

Regarding safety, 88 of 473 subjects (18.6%) in the ATZ/CBDCA/nab-PTX group and 56 of 232 subjects (24.1%) in the CBDCA/nab-PTX group died during the study treatment period or the follow-up period.[10)] The causes of deaths other than disease progression (65 in the ATZ/CBDCA/nab-PTX group, 43 in the CBDCA/nab-PTX group) were pneumonia; and pulmonary embolism (4 subjects each); myocardial infarction (3 subjects); pneumonitis; and cardiac arrest (2 subjects each); and sepsis; septic shock; hepatic cirrhosis; ventricular tachycardia; staphylococcal sepsis; respiratory distress; aspiration; and cardio-respiratory arrest (1 subject each) in the ATZ/CBDCA/nab-PTX group and death (4 subjects); sepsis (2 subjects); and pneumonia; pulmonary embolism; septic shock; sudden death; chronic obstructive pulmonary disease; pleural effusion; and acute myocardial infarction (1 subject each) in the CBDCA/nab-PTX group. A causal relationship to study drug could not be ruled out for pneumonitis (2 subjects); and septic shock; myocardial infarction; cardiac arrest; hepatic cirrhosis; and ventricular tachycardia (1 subject each) in the ATZ/CBDCA/nab-PTX group and sepsis; and acute myocardial infarction (1 subject each) in the CBDCA/nab-PTX group.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA review strategy:

The pivotal clinical studies to evaluate the efficacy and safety of ATZ in combination with platinum-containing chemotherapy are the following 2 studies (a) (b). PMDA decided to focus its review on these studies, and evaluated its efficacy in Japanese patients in terms of the consistency of the results between the overall population and the Japanese subgroup in the IMpower132 study, based on "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Basic

[10)] 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.

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.

(a) A global phase III study to evaluate the efficacy and safety of ATZ/platinum/PEM compared with platinum/PEM in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC (IMpower132 study)
(b) A foreign phase III study to evaluate the efficacy and safety of ATZ/CBDCA/nab-PTX compared with CBDCA/nab-PTX in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC (IMpower130 study)

7.R.2 Efficacy

Based on the following considerations, PMDA concluded that the efficacy of ATZ in combination with platinum-containing chemotherapy in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC was demonstrated.

7.R.2.1 Choice of control group

The applicant's explanation about choice of a control group in (a) the IMpower132 study and (b) the IMpower130 study:

(a) At the time of planning the IMpower132 study, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer (NCCN guidelines) (v.7.2015) etc. recommended platinum/PEM for the patient population of the IMpower132 study, based on reports that platinum/PEM provided high efficacy in this patient population (*J Clin Oncol.* 2008;26:3543-51, *J Clin Oncol.* 2013;31:2895-902) etc. Thus, platinum/PEM was chosen as a comparator.
(b) At the time of planning the IMpower130 study, the NCCN guidelines (v.2.2013) etc. recommended CBDCA/nab-PTX for the patient population of the IMpower130 study, based on a report that CBDCA/nab-PTX provided high efficacy in this patient population (*J Clin Oncol.* 2012;30:2055-62), etc. Thus, CBDCA/nab-PTX was chosen as a comparator.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoint and results of evaluation

The applicant's explanation about the appropriateness of the co-primary endpoints for the IMpower132 study and the IMpower130 study:

Prolongation of PFS in patients with unresectable advanced or recurrent NSQ-NSCLC is clinically meaningful because it is expected that the time to disease progression will become longer and that the worsening of clinical symptoms associated with disease progression will be delayed. Patients with unresectable advanced or recurrent NSQ-NSCLC are treated with an expectation of survival benefit. Thus, selecting PFS and OS as the co-primary endpoints for the IMpower132 study and the IMpower130 study was appropriate.

The applicant's explanation about the results of efficacy evaluation in (a) the IMpower132 study and (b) the IMpower130 study:

(a) IMpower132 study

The study demonstrated the superiority of ATZ/platinum/PEM over platinum/PEM in the co-primary endpoint of investigator-assessed PFS per RECIST ver.1.1 [see Section 7.1.1.1]. The results of independent review facility (IRF)-assessed PFS and the Kaplan-Meier curves are shown in Table 6 and Figure 5, respectively.

Table 6. Results of primary analysis of PFS (IRF assessment, ITT population, data cutoff date of May 22, 2018)

	ATZ/platinum/PEM	Platinum/PEM
N	292	286
No. of events (%)	198 (67.8)	211 (73.8)
Median [95% CI] (months)	7.2 [6.7, 8.4]	6.6 [5.7, 7.5]
Hazard ratio [95% CI]*1	0.758 [0.623, 0.923]	
P-value (two-sided)*2	0.0055	

*1: Cox regression stratified by sex (male, female), ECOG PS (0, 1), and type of platinum agent (CBDCA, CDDP)
*2: Log-rank test stratified by sex (male, female), ECOG PS (0, 1), and type of platinum agent (CBDCA, CDDP)

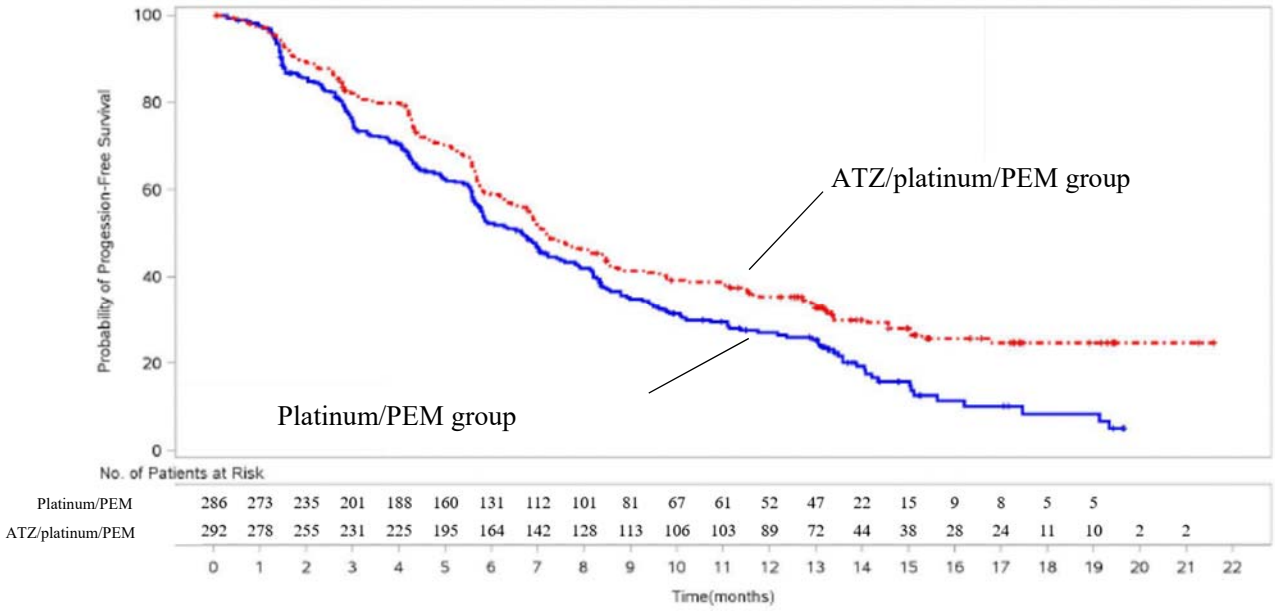

Figure 5. Kaplan-Meier curves for PFS at the time of primary analysis (IRF assessment, ITT population, data cutoff date of May 22, 2018)

Although ATZ/platinum/PEM did not demonstrate a statistically significant improvement in the co-primary endpoint of OS compared with platinum/PEM, there was no trend towards shorter OS in the ATZ/platinum/PEM group than in the platinum/PEM group [see Section 7.1.1.1].

The results of investigator-assessed PFS and the Kaplan-Meier curves in the Japanese subgroup of the IMpower132 study are shown in Table 7 and Figure 6, respectively.

Table 7. Results of primary analysis of PFS in Japanese subgroup (Investigator assessment, ITT population, data cutoff date of May 22, 2018)

	ATZ/platinum/PEM	Platinum/PEM
N	48	53
No. of events (%)	30 (62.5)	48 (90.6)
Median [95% CI] (months)	12.8 [8.6, 16.6]	4.5 [4.1, 6.7]
Hazard ratio [95% CI]*	0.347 [0.208, 0.579]	

*: Cox regression stratified by sex (male, female), ECOG PS (0, 1), and type of platinum agent (CBDCA, CDDP)

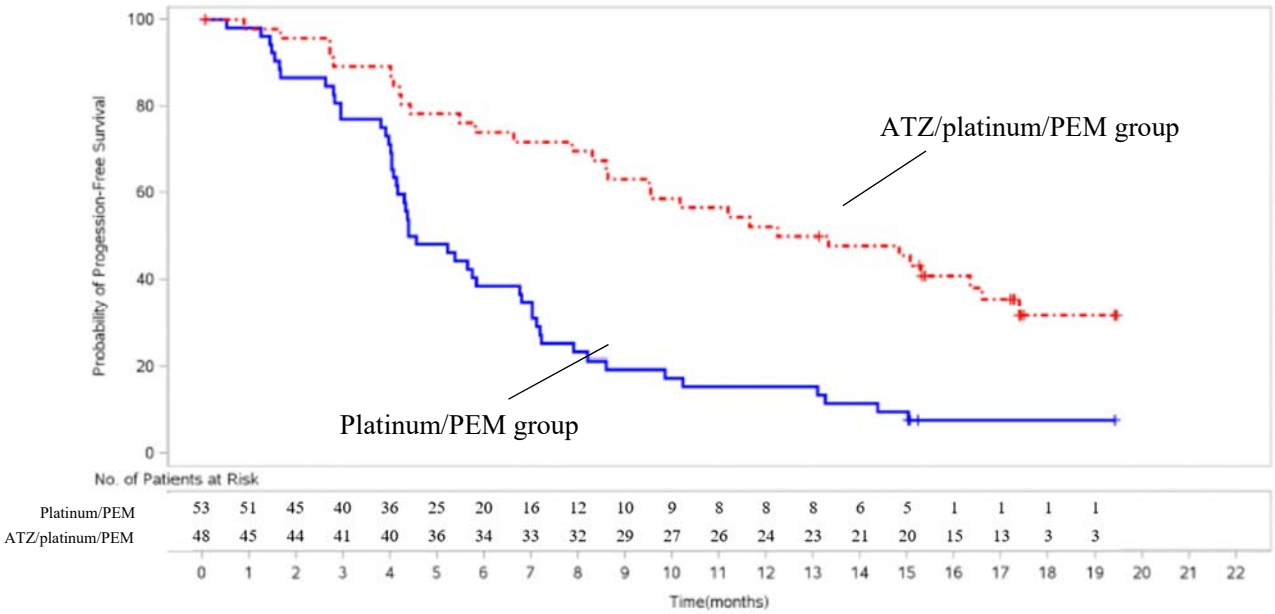

Figure 6. Kaplan-Meier curves for PFS at the time of primary analysis in Japanese subgroup (Investigator assessment, ITT population, data cutoff date of May 22, 2018)

(b) IMpower130 study

The study demonstrated the superiority of ATZ/CBDCA/nab-PTX over CBDCA/nab-PTX in the co-primary endpoint of investigator-assessed PFS per RECIST ver.1.1 [see Section 7.1.2.1]. The results of IRF-assessed PFS and the Kaplan-Meier curves are shown in Table 8 and Figure 7, respectively.

Table 8. Results of primary analysis of PFS (IRF assessment, ITT-WT population, data cutoff date of March 15, 2018)

	ATZ/CBDCA/nab-PTX	CBDCA/nab-PTX
N	451	228
No. of events (%)	329 (72.9)	177 (77.6)
Median [95% CI] (months)	7.2 [6.7, 8.3]	6.4 [5.6, 7.4]
Hazard ratio [95% CI]*1	0.754 [0.627, 0.907]	
P-value (two-sided)*2	0.0026	

*1: Cox regression stratified by sex (male, female) and PD-L1 expression (TC3 or [TC0/1/2 and IC2/3] vs. TC0/1/2 and IC0/1)
*2: Log-rank test stratified by sex (male, female) and PD-L1 expression (TC3 or [TC0/1/2 and IC2/3] vs. TC0/1/2 and IC0/1)

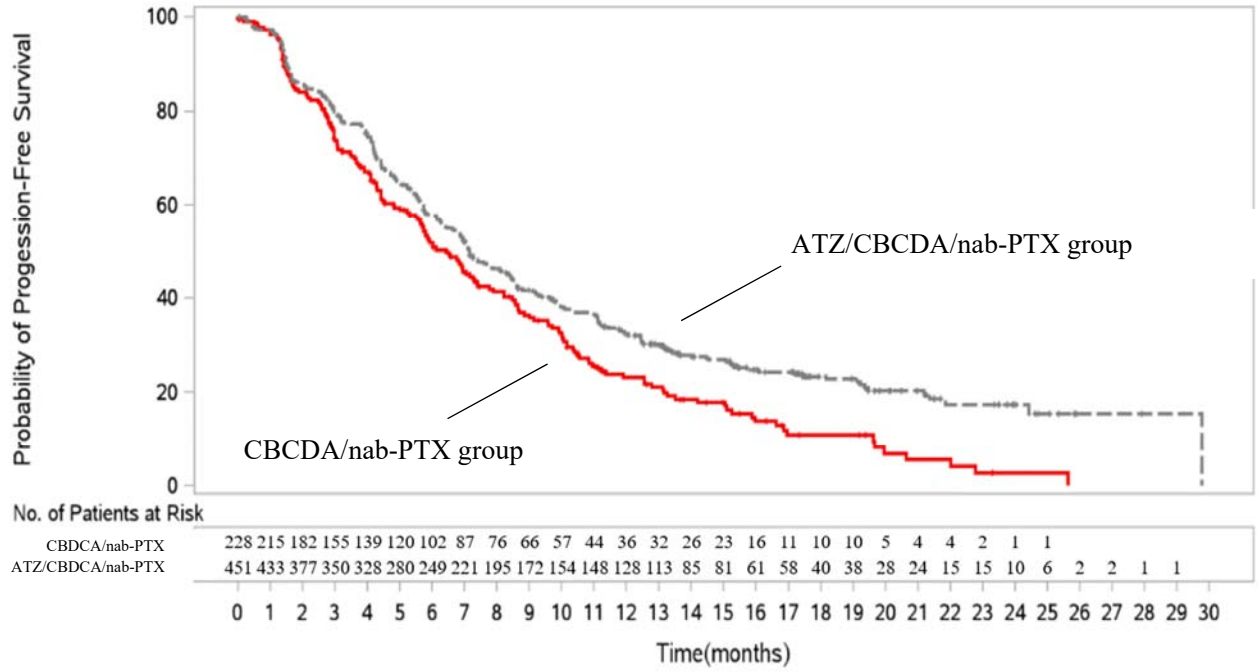

Figure 7. Kaplan-Meier curves for PFS at the time of primary analysis (IRF assessment, ITT-WT population, data cutoff date of March 15, 2018)

The study demonstrated the superiority of ATZ/CBDCA/nab-PTX over CBDCA/nab-PTX in the co-primary endpoint of OS in the ITT-WT population [see Section 7.1.2.1].

PMDA's discussion:

For the following reasons etc., PMDA concluded that the efficacy of ATZ in combination with platinum-containing chemotherapy was demonstrated in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC.

- The following findings were obtained from the IMpower132 study.
  - The superiority of ATZ/platinum/PEM over platinum/PEM in the co-primary endpoint of PFS was demonstrated, and the magnitude of the observed effects was clinically relevant.
  - There was no trend towards shorter OS (the co-primary endpoint) in the ATZ/platinum/PEM group than in the platinum/PEM group.
  - While the number of Japanese patients and the number of events in Japanese patients were limited, and there are limitations to evaluating the efficacy of ATZ in Japanese patients based on the results from the Japanese subgroup, there was no trend towards clear differences in the results between the Japanese subgroup and the overall population.
- The IMpower130 study demonstrated the superiority of ATZ/CBDCA/nab-PTX over CBDCA/nab-PTX in the co-primary endpoint of OS.

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

PMDA's conclusion:

Based on the following considerations, adverse events that require attention following administration of ATZ in combination with platinum-containing chemotherapy in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC are the events that were considered to require attention at the time of the previous approval of ATZ (use in the previously approved indications of unresectable advanced or recurrent non-small cell lung cancer and extensive-stage small cell lung cancer) etc.[11)] As with use in the previously approved indications, attention should be paid to the possible occurrence of these adverse events during treatment with ATZ.

Although attention should be paid to the possible occurrence of the above-mentioned adverse events during treatment with ATZ, ATZ is tolerable, also when administered in combination with platinum-containing chemotherapy in patients with NSQ-NSCLC, 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 and discontinuation of ATZ and the concomitant anti-neoplastic drugs.

7.R.3.1 Safety profile of ATZ

The applicant's explanation about the safety profile of ATZ based on safety information from the IMpower132 study and the IMpower130 study:

Safety data from the IMpower132 study and the IMpower130 study are summarized in Table 9.

11) 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, febrile neutropenia, and myocarditis (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of October 23, 2017," "Review Report on Tecentriq Intravenous Infusion 1200 mg as of November 12, 2018," and "Review Report on Tecentriq Intravenous Infusion 1200 mg as of June 14, 2019")

Table 9. Summary of safety data (IMpower132 study and IMpower130 study)

	n (%)			
	IMpower132		IMpower130	
	ATZ/Platinum/PEM N = 291	Platinum/PEM N = 274	ATZ/CBDCA/nab-PTX N = 473	CBDCA/nab-PTX N = 232
All adverse events	286 (98.3)	266 (97.1)	471 (99.6)	230 (99.1)
Grade ≥3 adverse events	202 (69.4)	161 (58.8)	406 (85.8)	177 (76.3)
Adverse events leading to death	21 (7.2)	14 (5.1)	25 (5.3)	13 (5.6)
Serious adverse events	134 (46.0)	84 (30.7)	240 (50.7)	88 (37.9)
Adverse events leading to treatment discontinuation				
ATZ	44 (15.1)	—	59 (12.5)	—
Platinum	24 (8.2)	33 (12.0)	85 (18.0)	36 (15.5)
PEM	55 (18.9)	29 (10.6)	—	—
nab-PTX	—	—	97 (20.5)	44 (19.0)
Adverse events leading to dose interruption				
ATZ	148 (50.9)	—	295 (62.4)	—
Platinum	108 (37.1)	83 (30.3)	269 (56.9)	127 (54.7)
PEM	150 (51.5)	115 (42.0)	—	—
nab-PTX	—	—	351 (74.2)	160 (69.0)
Adverse events leading to dose reduction				
Platinum	27 (9.3)	25 (9.1)	146 (30.9)	75 (32.3)
PEM	29 (10.0)	30 (10.9)	—	—
nab-PTX	—	—	120 (25.4)	67 (28.9)

—: Not applicable

In the IMpower132 study, adverse events of any grade reported at a ≥5% higher incidence in the ATZ/platinum/PEM group than in the platinum/PEM group were asthenia (81 subjects [27.8%] in the ATZ/platinum/PEM group, 54 subjects [19.7%] in the platinum/PEM group), pyrexia (62 subjects [21.3%], 37 subjects [13.5%]), ALT increased (56 subjects [19.2%], 24 subjects [8.8%]), AST increased (53 subjects [18.2%], 28 subjects [10.2%]), thrombocytopenia (46 subjects [15.8%]), 24 subjects [8.8%]), rash (37 subjects [12.7%]), 21 subjects [7.7%]), and hypokalaemia (20 subjects [6.9%], 4 subjects [1.5%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in the ATZ/platinum/PEM group than in the platinum/PEM group were neutropenia (29 subjects [10.0%], 16 subjects [5.8%]), asthenia (18 subjects [6.2%], 8 subjects [2.9%]), vomiting (10 subjects [3.4%], 2 subjects [0.7%]), nausea (8 subjects [2.7%], 2 subjects [0.7%]), ALT increased (8 subjects [2.7%], 2 subjects [0.7%]), and lymphocyte count decreased (7 subjects [2.4%], 1 subject [0.4%]). Serious adverse events reported at a ≥2% higher incidence in the ATZ/platinum/PEM group than in the platinum/PEM group were pyrexia (12 subjects [4.1%], 1 subject [0.4%]), thrombocytopenia (11 subjects [3.8%], 4 subjects [1.5%]), and vomiting (6 subjects [2.1%], 0 subjects). Adverse events leading to study drug interruption reported at a ≥2% higher incidence in the ATZ/platinum/PEM group than in the platinum/PEM group were neutropenia (29 subjects [10.0%], 21 subjects [7.7%]), anaemia (27 subjects [9.3%], 17 subjects [6.2%]), thrombocytopenia (19 subjects [6.5%], 10 subjects [3.6%]), blood creatinine increased (15 subjects [5.2%], 2 subjects [0.7%]), ALT increased (11 subjects [3.8%], 3 subjects [1.1%]), diarrhoea (8 subjects [2.7%], 2 subjects [0.7%]), pneumonitis (6 subjects [2.1%], 0 subjects), weight decreased (6 subjects [2.1%], 0 subjects), and vomiting (6 subjects [2.1%], 0 subjects). There were no adverse events leading to death or study drug discontinuation reported at a ≥2% higher incidence in the ATZ/platinum/PEM group than in the platinum/PEM group.

In the IMpower130 study, adverse events of any grade reported at a ≥5% higher incidence in the ATZ/CBDCA/nab-PTX group than in the CBDCA/nab-PTX group were diarrhoea (201 subjects [42.5%] in the ATZ/CBDCA/nab-PTX group, 73 subjects [31.5%] in the CBDCA/nab-PTX group), constipation (171 subjects [36.2%], 72 subjects [31.0%]), dyspnoea (133 subjects [28.1%], 47 subjects [20.3%]), vomiting (128 subjects [27.1%], 45 subjects [19.4%]), cough (126 subjects [26.6%], 39 subjects [16.8%]), platelet count decreased (108 subjects [22.8%], 39 subjects [16.8%]), neutrophil count decreased (95 subjects [20.1%], 35 subjects [15.1%]), pyrexia (82 subjects [17.3%], 23 subjects [9.9%]), back pain (82 subjects [17.3%]), 16 subjects [6.9%]), headache (77 subjects [16.3%], 23 subjects [9.9%]), dizziness (76 subjects [16.1%], 25 subjects [10.8%]), rash (66 subjects [14.0%], 16 subjects [6.9%]), taste abnormality (57 subjects [12.1%], 14 subjects [6.0%]), pruritus (53 subjects [11.2%], 12 subjects [5.2%]), hypothyroidism (53 subjects [11.2%], 1 subject [0.4%]), pain in extremity (52 subjects [11.0%], 14 subjects [6.0%]), and musculoskeletal pain (45 subjects [9.5%], 10 subjects [4.3%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in the ATZ/CBDCA/nab-PTX group than in the CBDCA/nab-PTX group were neutropenia (153 subjects [32.3%], 66 subjects [28.4%]), anaemia (151 subjects [31.9%], 56 subjects [24.1%]), neutrophil count decreased (59 subjects [12.5%], 20 subjects [8.6%]), thrombocytopenia (47 subjects [9.9%], 16 subjects [6.9%]), white blood cell count decreased (32 subjects [6.8%], 7 subjects [3.0%]), hypokalaemia (22 subjects [4.7%], 6 subjects [2.6%]), dyspnoea (22 subjects [4.7%], 2 subjects [0.9%]), syncope (13 subjects [2.7%], 0 subjects), and lung infection (12 subjects [2.5%], 1 subject [0.4%]). Serious adverse events reported at a ≥2% higher incidence in the ATZ/CBDCA/nab-PTX group than in the CBDCA/nab-PTX group were neutropenia (14 subjects [3.0%], 2 subjects [0.9%]), diarrhoea (14 subjects [3.0%], 2 subjects [0.9%]), and lung infection (14 subjects [3.0%], 1 subject [0.4%]). Adverse events leading to study drug interruption reported at a ≥2% higher incidence in the ATZ/CBDCA/nab-PTX group than in the CBDCA/nab-PTX group were neutropenia (166 subjects [35.1%], 68 subjects [29.3%]), platelet count decreased (61 subjects [12.9%], 19 subjects [8.2%]), diarrhoea (37 subjects [7.8%], 7 subjects [3.0%]), fatigue (29 subjects [6.1%], 9 subjects [3.9%]), pyrexia (23 subjects [4.9%], 3 subjects [1.3%]), nausea (16 subjects [3.4%], 3 subjects [1.3%]), and pneumonitis (13 subjects [2.7%], 1 subject [0.4%]). There were no adverse events leading to death or study drug discontinuation reported at a ≥2% higher incidence in the ATZ/CBDCA/nab-PTX group than in the CBDCA/nab-PTX group.

The applicant's explanation about differences in the safety profile between the IMpower132/IMpower130 study and the IMpower150 study in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC (a previously approved regimen in which ATZ was used in combination with other anti-neoplastic drugs, as in the IMpower132/IMpower130 study):
Table 10 shows the results of comparison of the incidence of adverse events among the ATZ/platinum/PEM group of the IMpower132 study, the ATZ/CBDCA/nab-PTX group of the IMpower130 study, and the ATZ/CBDCA/PTX/BV group of the IMpower150 study.[9)]

Table 10. Summary of safety data (IMpower132 study, IMpower130 study, IMpower150 study)

	n (%)		
	IMpower132	IMpower130	IMpower150
	ATZ/platinum/PEM N = 291	ATZ/CBDCA/nab-PTX N = 473	ATZ/CBDCA/PTX/BV N = 393
All adverse events	286 (98.3)	471 (99.6)	386 (98.2)
Grade ≥3 adverse events	202 (69.4)	406 (85.8)	274 (69.7)
Adverse events leading to death	21 (7.2)	25 (5.3)	24 (6.1)
Serious adverse events	134 (46.0)	240 (50.7)	174 (44.3)
Adverse events leading to study drug discontinuation	69 (23.7)	125 (26.4)	133 (33.8)
Adverse events leading to study drug interruption	162 (55.7)	389 (82.2)	226 (57.5)
Adverse events leading to dose reduction of study drug	39 (13.4)	160 (33.8)	97 (24.7)

Adverse events of any grade reported at a ≥10% higher incidence in the IMpower132 or IMpower130 study than in the IMpower150 study were anaemia (131 subjects [45.0%] in the IMpower132 study, 265 subjects [56.0%] in the IMpower130 study, 115 subjects [29.3%] in the IMpower150 study), nausea (108 subjects [37.1%], 234 subjects [49.5%], 154 subjects [39.2%]), fatigue (69 subjects [23.7%], 223 subjects [47.1%], 130 subjects [33.1%]), diarrhoea (59 subjects [20.3%], 201 subjects [42.5%], 126 subjects [32.1%]), ALT increased (56 subjects [19.2%], 25 subjects [5.3%], 30 subjects [7.6%]), AST increased (53 subjects [18.2%], 17 subjects [3.6%], 30 subjects [7.6%]), neutropenia (49 subjects [16.8%], 220 subjects [46.5%], 73 subjects [18.6%]), thrombocytopenia (46 subjects [15.8%], 133 subjects [28.1%], 53 subjects [13.5%]), and dyspnoea (40 subjects [13.7%], 133 subjects [28.1%], 53 subjects [13.5%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the IMpower132 or IMpower130 study than in the IMpower150 study were anaemia (46 subjects [15.8%], 151 subjects [31.9%], 28 subjects [7.1%]), neutropenia (29 subjects [10.0%], 153 subjects [32.3%], 55 subjects [14.0%]), and thrombocytopenia (19 subjects [6.5%], 47 subjects [9.9%], 17 subjects [4.3%]). Adverse events leading to study drug interruption reported at a ≥5% higher incidence in the IMpower132 or IMpower130 study than in the IMpower150 study were neutropenia (29 subjects [10.0%], 166 subjects [35.1%], 27 subjects [6.9%]), anaemia (27 subjects [9.3%], 64 subjects [13.5%], 8 subjects [2.0%]), neutrophil count decreased (21 subjects [7.2%], 64 subjects [13.5%], 14 subjects [3.6%]), thrombocytopenia (19 subjects [6.5%], 82 subjects [17.3%], 18 subjects [4.6%]), and platelet count decreased (13 subjects [4.5%], 61 subjects [12.9%], 23 subjects [5.9%]). 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 IMpower132 or IMpower130 study than in the IMpower150 study.

PMDA's discussion:

In the IMpower132 study and the IMpower130 study, some adverse events were reported at a higher incidence in the ATZ/platinum/PEM group or the ATZ/CBDCA/nab-PTX group than in the control group, and the incidences of some adverse events were higher than those with the previously approved regimen. However, given that all of those events were known adverse events associated with ATZ or concomitant platinum-containing chemotherapy, ATZ/platinum/PEM and ATZ/CBDCA/nab-PTX in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC are tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take

appropriate measures, e.g. monitoring for adverse events; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and interruption of ATZ.

7.R.3.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in the safety of ATZ in combination with platinum-containing chemotherapy between Japanese and non-Japanese populations:

Safety data from Japanese and non-Japanese patients in the ATZ/platinum/PEM group of the IMpower132 study are summarized in Table 11.

Table 11. Summary of safety data (IMpower132 study)

	n (%)	
	Japanese patients N = 48	Non-Japanese patients N = 243
All adverse events	48 (100)	238 (97.9)
Grade ≥3 adverse events	37 (77.1)	165 (67.9)
Adverse events leading to death	2 (4.2)	19 (7.8)
Serious adverse events	22 (45.8)	112 (46.1)
Adverse events leading to treatment discontinuation		
ATZ	13 (27.1)	31 (12.8)
Platinum	4 (8.3)	20 (8.2)
PEM	14 (29.2)	41 (16.9)
Adverse events leading to dose interruption		
ATZ	32 (66.7)	116 (47.7)
Platinum	27 (56.3)	81 (33.3)
PEM	35 (72.9)	115 (47.3)
Adverse events leading to dose reduction		
Platinum	6 (12.5)	21 (8.6)
PEM	3 (6.3)	26 (10.7)

In the ATZ/platinum/PEM group, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were nausea (30 subjects [62.5%] in the Japanese subgroup, 78 subjects [32.1%] in the non-Japanese subgroup), decreased appetite (27 subjects [56.3%], 51 subjects [21.0%]), pyrexia (23 subjects [47.9%], 39 subjects [16.0%]), constipation (22 subjects [45.8%], 65 subjects [26.7%]), ALT increased (22 subjects [45.8%], 34 subjects [14.0%]), AST increased (21 subjects [43.8%], 32 subjects [13.2%]), neutrophil count decreased (19 subjects [39.6%], 24 subjects [9.9%]), platelet count decreased (17 subjects [35.4%], 22 subjects [9.1%]), stomatitis (16 subjects [33.3%], 18 subjects [7.4%]), white blood cell count decreased (15 subjects [31.3%], 5 subjects [2.1%]), rash (12 subjects [25.0%], 25 subjects [10.3%]), hiccups (12 subjects [25.0%], 4 subjects [1.6%]), malaise (11 subjects [22.9%], 3 subjects [1.2%]), lymphocyte count decreased (9 subjects [18.8%], 3 subjects [1.2%]), rash maculo-papular (7 subjects [14.6%], 4 subjects [1.6%]), lung infection (6 subjects [12.5%], 5 subjects [2.1%]), and oedema (6 subjects [12.5%], 4 subjects [1.6%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (11 subjects [22.9%], 17 subjects [7.0%]), neutropenia (7 subjects [14.6%], 22 subjects [9.1%]), white blood cell count decreased (7 subjects [14.6%], 2 subjects [0.8%]), lymphocyte count decreased (7 subjects [14.6%], 0 subjects), hypertension (3 subjects [6.3%], 3 subjects [1.2%]), decreased appetite (3 subjects [6.3%], 3 subjects [1.2%]), hyponatraemia (3 subjects

[6.3%], 3 subjects [1.2%]), and leukopenia (3 subjects [6.3%], 1 subject [0.4%]). Adverse events leading to study drug discontinuation reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were pneumonitis (4 subjects [8.3%], 3 subjects [1.2%]) and renal impairment (3 subjects [6.3%], 1 subject [0.4%]). Adverse events leading to study drug interruption reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (8 subjects [16.7%], 13 subjects [5.3%]), neutropenia (7 subjects [14.6%], 22 subjects [9.1%]), platelet count decreased (5 subjects [10.4%], 8 subjects [3.3%]), ALT increased (4 subjects [8.3%], 7 subjects [2.9%]), pyrexia (4 subjects [8.3%], 6 subjects [2.5%]), AST increased (3 subjects [6.3%], 3 subjects [1.2%]), and lung infection (3 subjects [6.3%], 3 subjects [1.2%]). There were no adverse events leading to death or serious adverse events reported at a ≥5% 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, neutropenia (7 subjects [14.6%] in the ATZ/platinum/PEM group, 0 subjects in the platinum/PEM group), white blood cell count decreased (7 subjects [14.6%], 5 subjects [9.6%]), lymphocyte count decreased (7 subjects [14.6%], 1 subject [1.9%]), hyponatraemia (3 subjects [6.3%], 0 subjects), and leukopenia (3 subjects [6.3%], 0 subjects) were reported at a ≥5% higher incidence in the ATZ/platinum/PEM group than in the platinum/PEM group in the Japanese subgroup. However, given that there was no trend towards clearly higher incidences of those adverse events that were serious in the Japanese subgroup than in the non-Japanese subgroup and that none of those events led to study drug discontinuation, etc., no adverse events that require particular attention in Japanese patients were observed.

Although the IMpower130 study was conducted outside Japan, in the ATZ/CBDCA/nab-PTX group of the IMpower131 study, (a) adverse events reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup were all known adverse events associated with ATZ or the concomitant anti-neoplastic drugs, and (b) there were no clear differences in the safety of the previously approved regimen of ATZ between Japanese and non-Japanese populations. Given these findings, ATZ/CBDCA/nab-PTX is tolerable also in Japanese patients.

PMDA's discussion:
Although the number of Japanese patients included in the IMpower132 study was limited, and there are limitations to rigorous comparison of safety between the Japanese and non-Japanese subgroups, the incidences of Grade ≥3 neutropenia, leukopenia, etc. were higher in the Japanese subgroup than in the non-Japanese subgroup. However, given the following points etc., ATZ in combination with platinum-containing chemotherapy is tolerable also in Japanese patients as long as physicians take appropriate measures, e.g. dose interruption/reduction and discontinuation of ATZ and the concomitant anti-neoplastic drugs.

- Adverse events reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup were all known adverse events.
- There was no trend towards clearly higher incidences of adverse events leading to death or serious adverse events in the Japanese subgroup than in the non-Japanese subgroup.

7.R.4 Clinical positioning and indication

The proposed indication for ATZ in the present partial change application is the same as the previously approved indication of "unresectable advanced or recurrent non-small cell lung cancer." The PRECAUTIONS CONCERNING INDICATION section of the current package insert for unresectable advanced or recurrent non-small cell lung cancer was also unchanged, and the following statements were included in this section of the proposed package insert.

- The efficacy and safety of ATZ in chemotherapy-naïve patients with squamous disease have not been established.
- The efficacy and safety of ATZ 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 ATZ.

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the considerations in the following sections, PMDA concluded that the INDICATION and PRECAUTIONS CONCERNING INDICATION sections as proposed by the applicant are acceptable.

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

ATZ (information in the present partial change application) is described as follows in the major Japanese/foreign clinical practice guidelines and textbook of clinical oncology.

[Clinical practice guidelines]

- Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (ESMO guidelines) (*Ann Oncol*. 2018;29(Supplement 4):iv192-iv237)
  First-line treatment with ATZ/platinum/PEM is an option in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC.

The applicant's explanation about the clinical positioning of ATZ:
Based on the results from the IMpower132 study and the IMpower130 study, ATZ/platinum/PEM and ATZ/CBDCA/nab-PTX are positioned as treatment options for chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC.

Pembrolizumab/platinum/PEM demonstrated improvement of OS in a clinical study conducted in the same patient population as the IMpower132 study and the IMpower130 study (see "Review Report on Keytruda Injection 20 mg and 100 mg as of November 19, 2018"). When to use pembrolizumab/platinum/PEM and when to use ATZ/platinum/PEM are unknown at present because there are no clinical study data comparing the efficacy and safety of pembrolizumab/platinum/PEM versus ATZ/platinum/PEM. Treatment will be chosen with an understanding of the efficacy and safety of the individual agents, according to individual patients' conditions.

PMDA accepted the applicant's explanation.

7.R.4.2 Efficacy and safety of ATZ by PD-L1 expression status and target population

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

The applicant's response:

In the IMpower132 study and the IMpower130 study, Ventana Medical Systems' "Ventana PD-L1 (SP142) assay" was used to measure PD-L1 expression in tumor specimens. The efficacy and safety of ATZ in (a) the IMpower132 study and (b) the IMpower130 study were analyzed by PD-L1 expression status as shown below. Based on the analysis results, ATZ is recommended for chemotherapy-naïve patients with advanced or recurrent NSQ-NSCLC, regardless of PD-L1 expression status.

(a) IMpower132 study

The results of the primary analysis of investigator-assessed PFS (data cutoff date of May 22, 2018) and the Kaplan-Meier curves by PD-L1 expression status in the ITT population are shown in Table 12 and Figures 8 to 13, respectively.

As the PD-L1-evaluable subjects are a fraction of the ITT population,[12)] care should be taken when interpreting the results. However, since all subgroup analyses showed an improvement in PFS with ATZ/platinum/PEM versus platinum/PEM, the efficacy of ATZ is expected, regardless of PD-L1 expression status.

Table 12. Results of primary analysis of PFS by PD-L1 expression status in tumor specimens (Investigator assessment, data cutoff date of May 22, 2018)

PD-L1 expression	Treatment group	N	Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
TC0 and IC0	ATZ/platinum/PEM	88	8.5 [6.1, 11.2]	0.448 [0.313, 0.642]	0.1236
	Platinum/PEM	75	4.9 [4.2, 5.8]		
TC1/2/3 or IC1/2/3	ATZ/platinum/PEM	88	7.9 [5.6, 8.6]	0.686 [0.494, 0.953]	
	Platinum/PEM	93	5.7 [4.5, 7.9]		
TC0/1 and IC0/1	ATZ/platinum/PEM	131	8.1 [6.1, 9.5]	0.524 [0.397, 0.690]	0.8627
	Platinum/PEM	123	5.4 [4.3, 5.9]		
TC2/3 or IC2/3	ATZ/platinum/PEM	45	8.4 [5.7, 13.3]	0.592 [0.361, 0.970]	
	Platinum/PEM	42	5.6 [2.7, 9.6]		
TC0/1/2 and IC0/1/2	ATZ/platinum/PEM	151	7.9 [5.8, 8.6]	0.562 [0.435, 0.726]	0.4902
	Platinum/PEM	145	5.2 [4.3, 5.8]		
TC3 or IC3	ATZ/platinum/PEM	25	10.8 [7.9, NE]	0.464 [0.224, 0.960]	
	Platinum/PEM	20	6.5 [2.4, 10.6]		

*: Unstratified Cox regression

[12)] In the IMpower132 study, PD-L1 testing was not required under Protocol Version [redacted] (as of [redacted], 20[redacted]) or later. An exploratory analysis was performed by PD-L1 expression status based on the data from patients with PD-L1 status available.

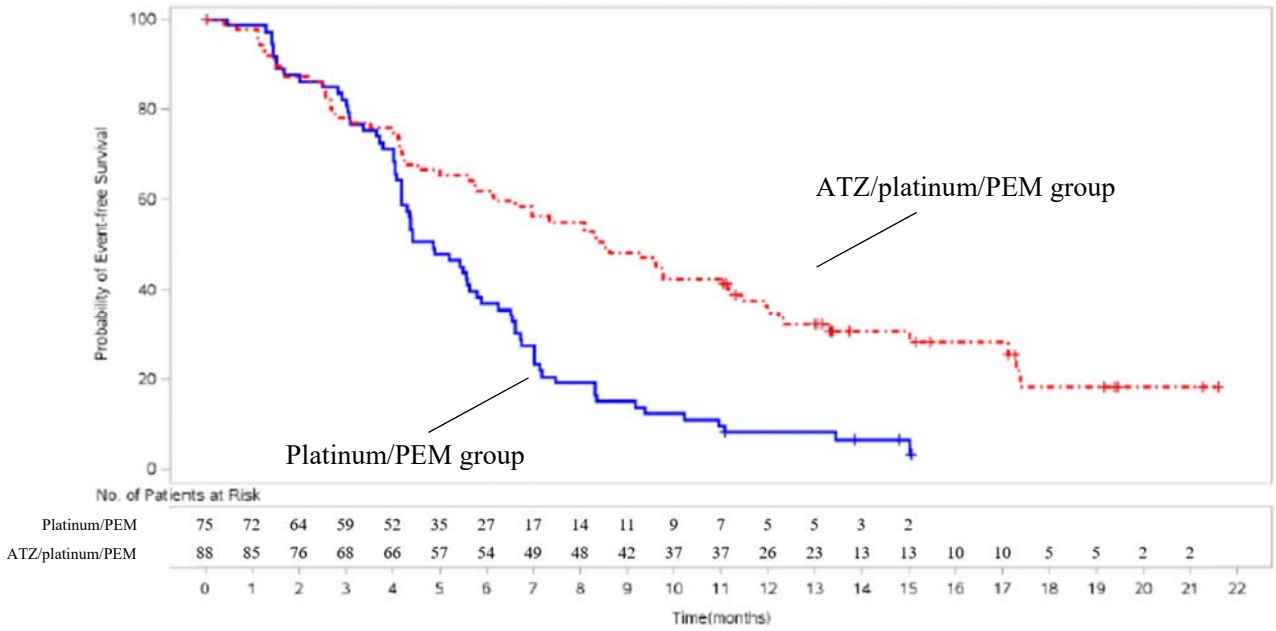

Figure 8. Kaplan-Meier curves for PFS at the time of primary analysis by PD-L1 expression status (Investigator assessment, TC0 and IC0 subgroup, data cutoff date of May 22, 2018)

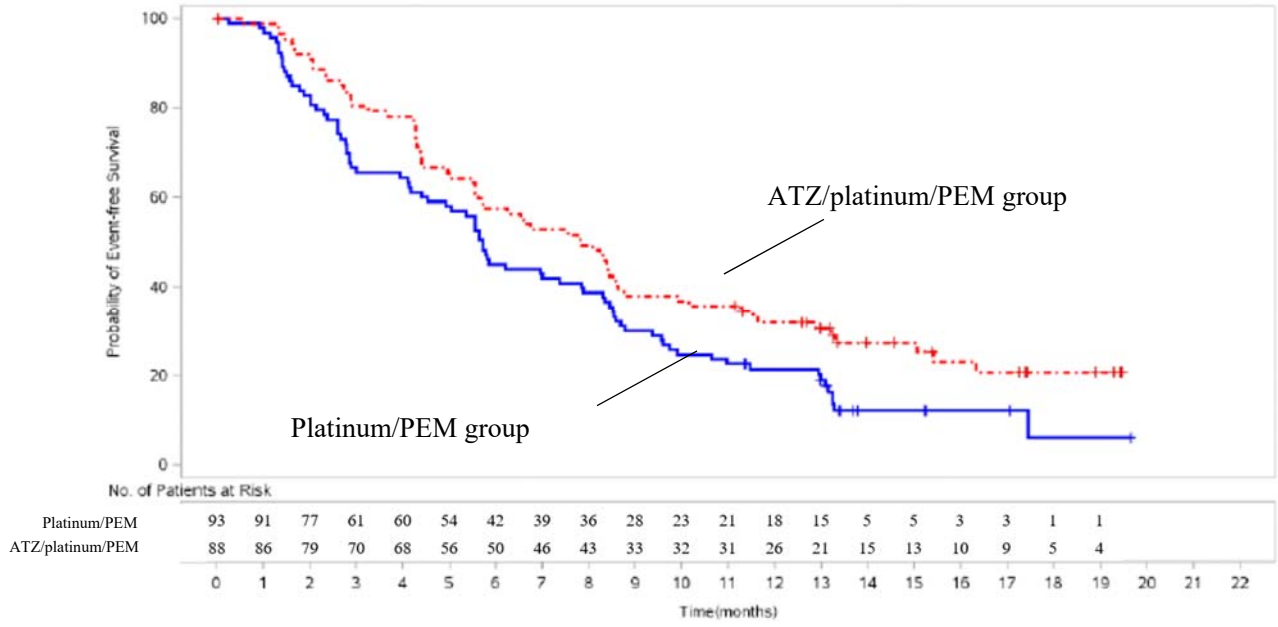

Figure 9. Kaplan-Meier curves for PFS at the time of primary analysis by PD-L1 expression status (Investigator assessment, TC1/2/3 or IC1/2/3 subgroup, data cutoff date of May 22, 2018)

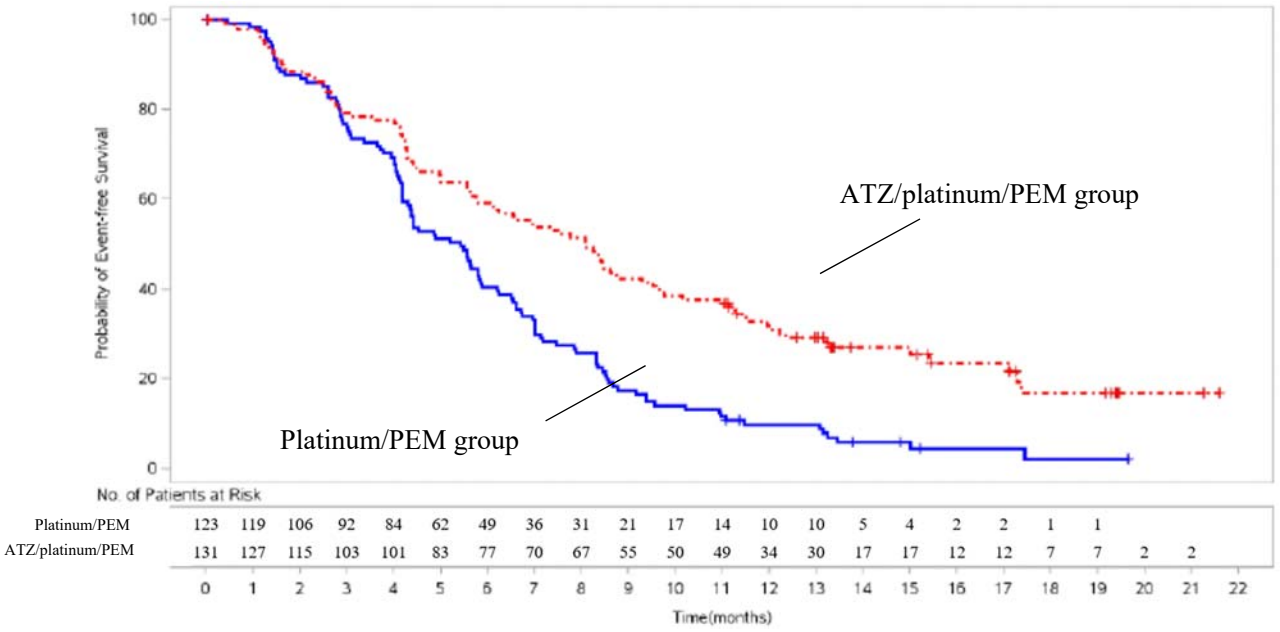

Figure 10. Kaplan-Meier curves for PFS at the time of primary analysis by PD-L1 expression status (Investigator assessment, TC0/1 and IC0/1 subgroup, data cutoff date of May 22, 2018)

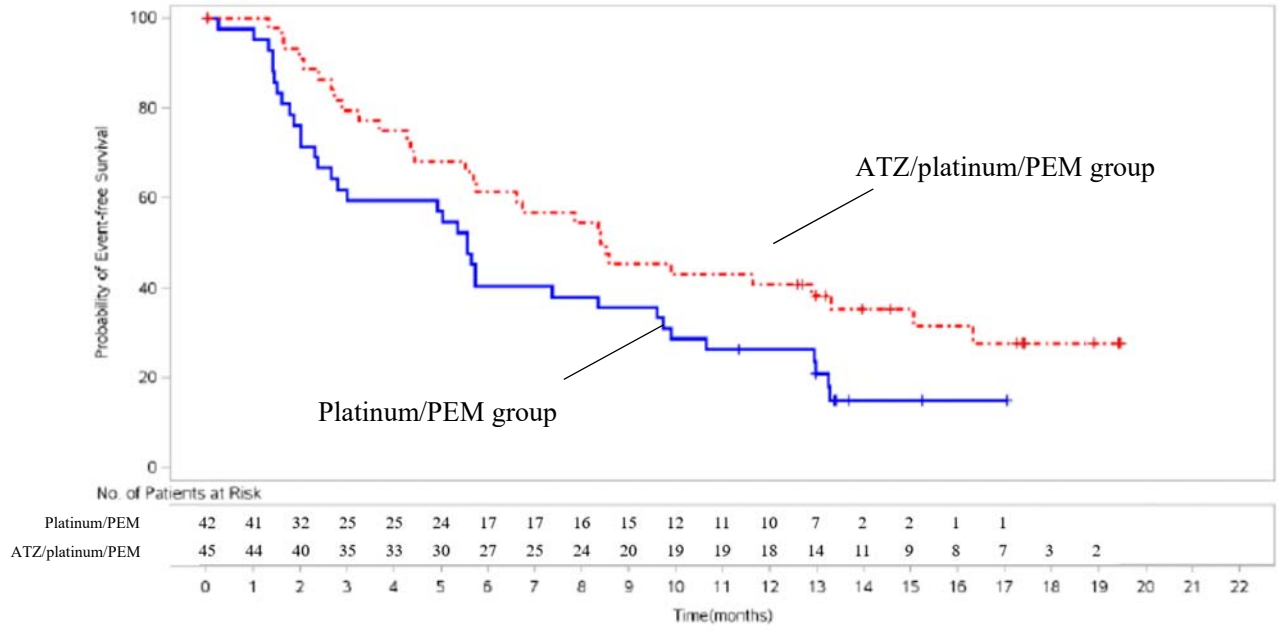

Figure 11. Kaplan-Meier curves for PFS at the time of primary analysis by PD-L1 expression status (Investigator assessment, TC2/3 or IC2/3 subgroup, data cutoff date of May 22, 2018)

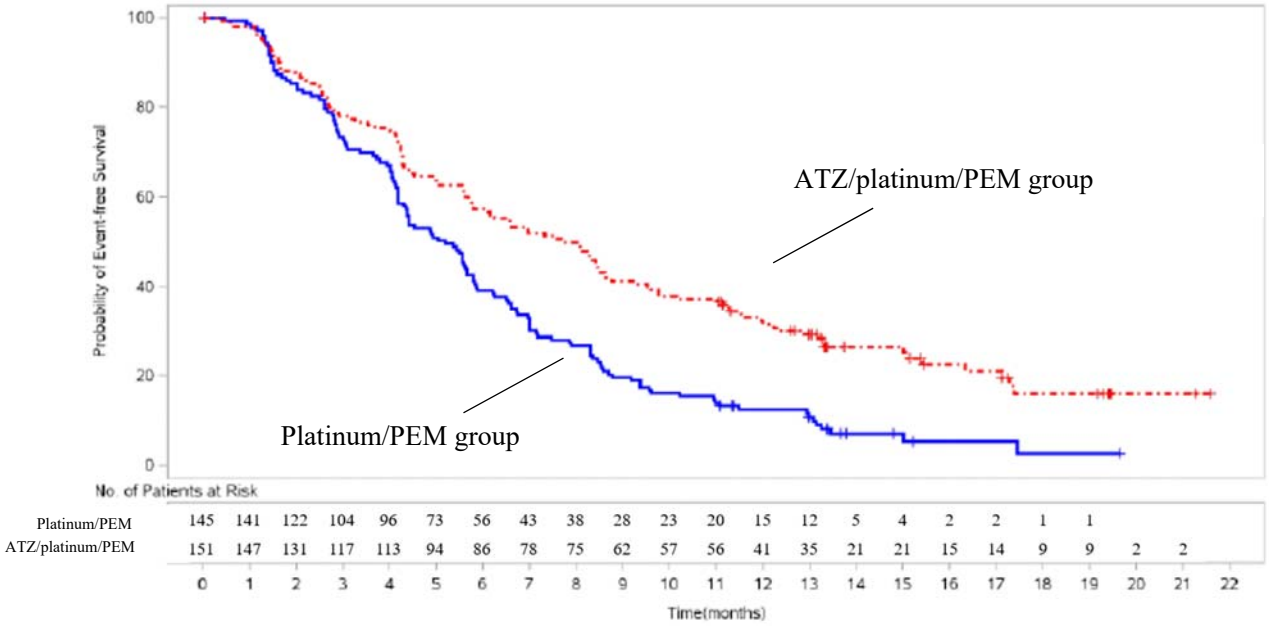

Figure 12. Kaplan-Meier curves for PFS at the time of primary analysis by PD-L1 expression status (Investigator assessment, TC0/1/2 and IC0/1/2 subgroup, data cutoff date of May 22, 2018)

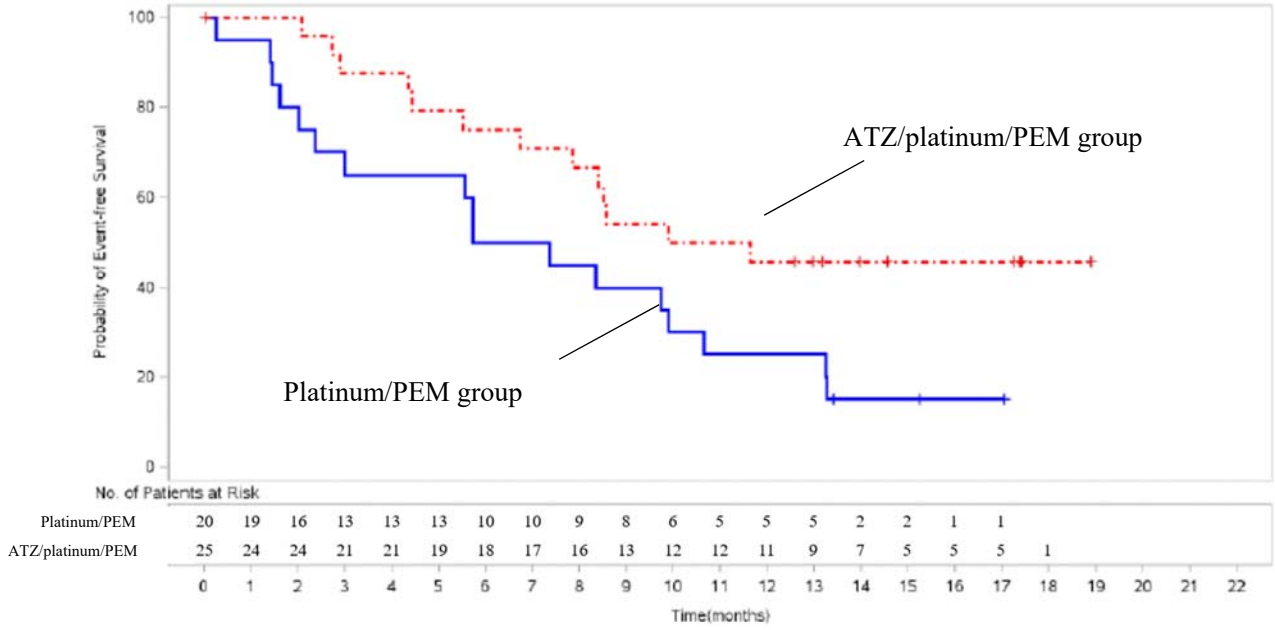

Figure 13. Kaplan-Meier curves for PFS at the time of primary analysis by PD-L1 expression status (Investigator assessment, TC3 or IC3 subgroup, data cutoff date of May 22, 2018)

In the ATZ/platinum/PEM group, the incidences of adverse events of any grade in the TC0 and IC0 subgroup and the TC1/2/3 or IC1/2/3 subgroup were 97.7% and 98.9%, respectively, the incidences of Grade ≥3 adverse events were 68.2% and 66.7%, respectively, and the incidences of serious adverse events were 39.8% and 41.4%, respectively. The incidences of adverse events of any grade in the TC0/1 and IC0/1 subgroup and the TC2/3 or IC2/3 subgroup were 98.5% and 97.7%, respectively, the incidences of Grade ≥3 adverse events were 69.5% and 61.4%, respectively, and the incidences of serious adverse events were 42.0% and 36.4%, respectively. The incidences of adverse events of

any grade in the TC0/1/2 and IC0/1/2 subgroup and the TC3 or IC3 subgroup were 98.7% and 95.8%, respectively, the incidences of Grade ≥3 adverse events were 68.9% and 58.3%, respectively, and the incidences of serious adverse events were 41.7% and 33.3%, respectively. There was no clear difference in the safety of ATZ on the basis of PD-L1 expression status in tumor specimens.

(b) IMpower130 study

The results of the interim OS analysis (data cutoff date of March 15, 2018) and the Kaplan Meier curves for OS by PD-L1 expression status in the ITT-WT population are shown in Table 13 and Figures 14 to 19, respectively.

Since all subgroup analyses showed an improvement in OS with ATZ/CBDCA/nab-PTX versus CBDCA/nab-PTX, the efficacy of ATZ is expected, regardless of PD-L1 expression status.

Table 13. Results of interim OS analysis by PD-L1 expression status in tumor specimens (ITT-WT population, data cutoff date of March 15, 2018)

PD-L1 expression	Treatment group	N	Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
TC0 and IC0	ATZ/CBDCA/nab-PTX	235	15.2 [12.9, 19.2]	0.813 [0.611, 1.081]	0.7607
	CBDCA/nab-PTX	121	12.0 [9.0, 17.7]		
TC1/2/3 or IC1/2/3	ATZ/CBDCA/nab-PTX	216	21.2 [18.1, 28.2]	0.746 [0.536, 1.038]	
	CBDCA/nab-PTX	107	16.9 [12.5, 22.0]		
TC0/1 and IC0/1	ATZ/CBDCA/nab-PTX	293	18.6 [14.0, 21.2]	0.777 [0.598, 1.011]	0.8918
	CBDCA/nab-PTX	147	13.1 [10.3, 17.7]		
TC2/3 or IC2/3	ATZ/CBDCA/nab-PTX	158	18.6 [16.1, NE]	0.807 [0.553, 1.179]	
	CBDCA/nab-PTX	81	16.9 [12.0, NE]		
TC0/1/2 and IC0/1/2	ATZ/CBDCA/nab-PTX	363	18.6 [14.9, 21.4]	0.779 [0.614, 0.989]	0.8844
	CBDCA/nab-PTX	186	13.4 [10.5, 17.7]		
TC3 or IC3	ATZ/CBDCA/nab-PTX	88	17.3 [14.8, NE]	0.839 [0.505, 1.393]	
	CBDCA/nab-PTX	42	16.9 [10.9, NE]		

*: Unstratified Cox regression

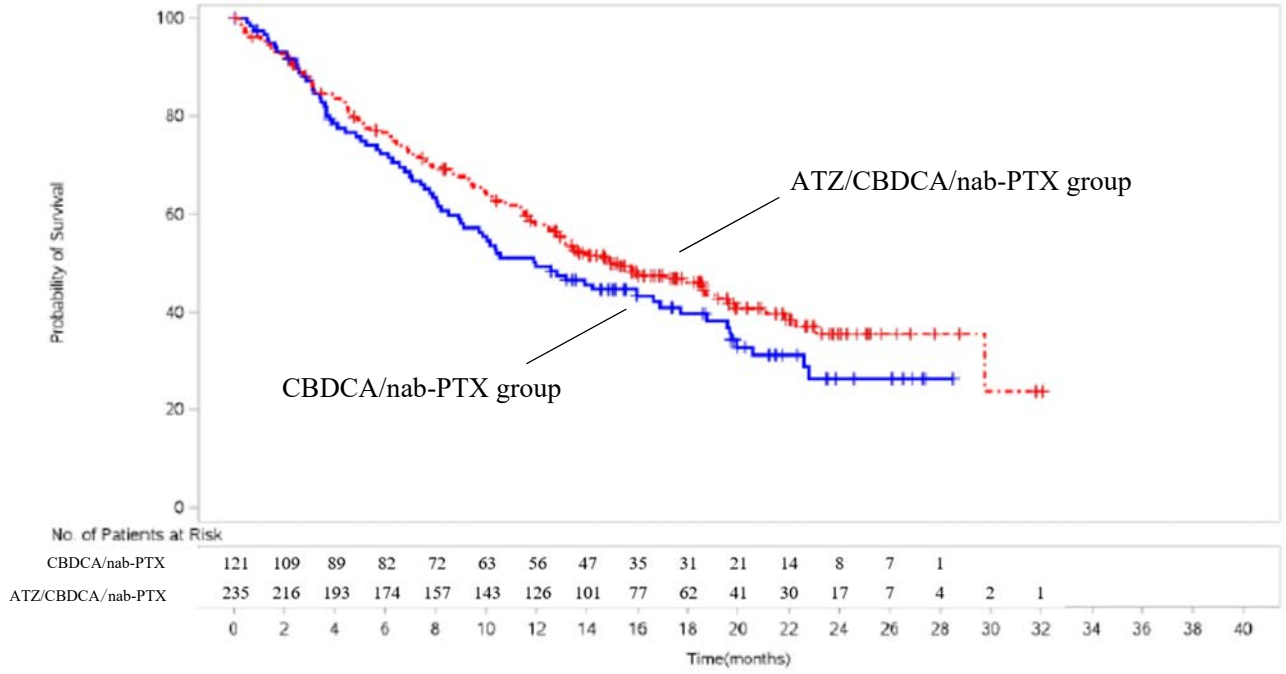

Figure 14. Kaplan-Meier curves for OS at the time of interim analysis by PD-L1 expression status (TC0 and IC0 subgroup, data cutoff date of March 15, 2018)

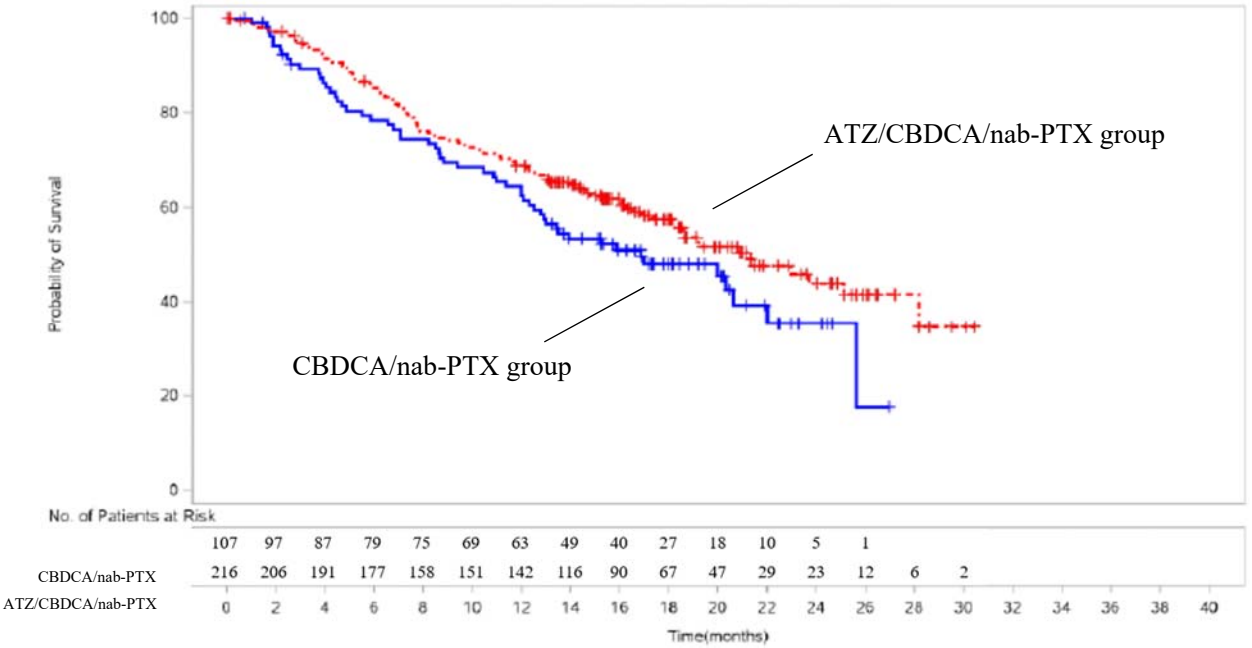

Figure 15. Kaplan-Meier curves for OS at the time of interim analysis by PD-L1 expression status (TC1/2/3 or IC1/2/3 subgroup, data cutoff date of March 15, 2018)

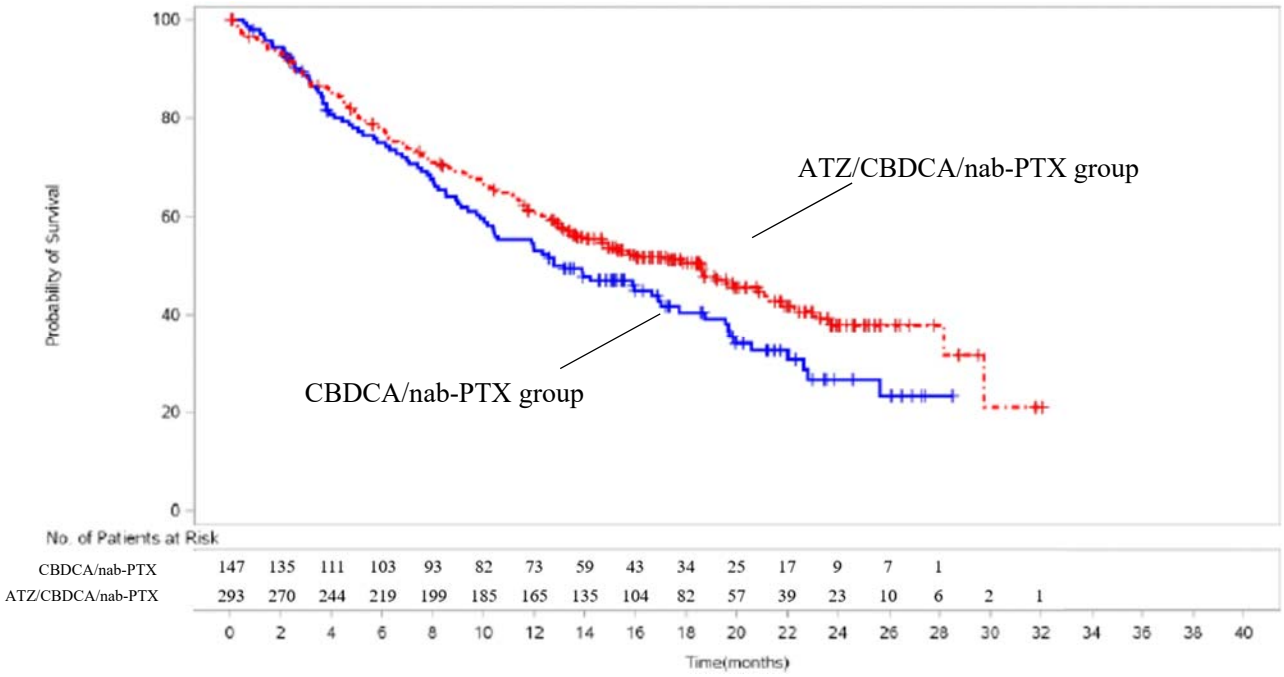

Figure 16. Kaplan-Meier curves for OS at the time of interim analysis by PD-L1 expression status (TC0/1 and IC0/1 subgroup, data cutoff date of March 15, 2018)

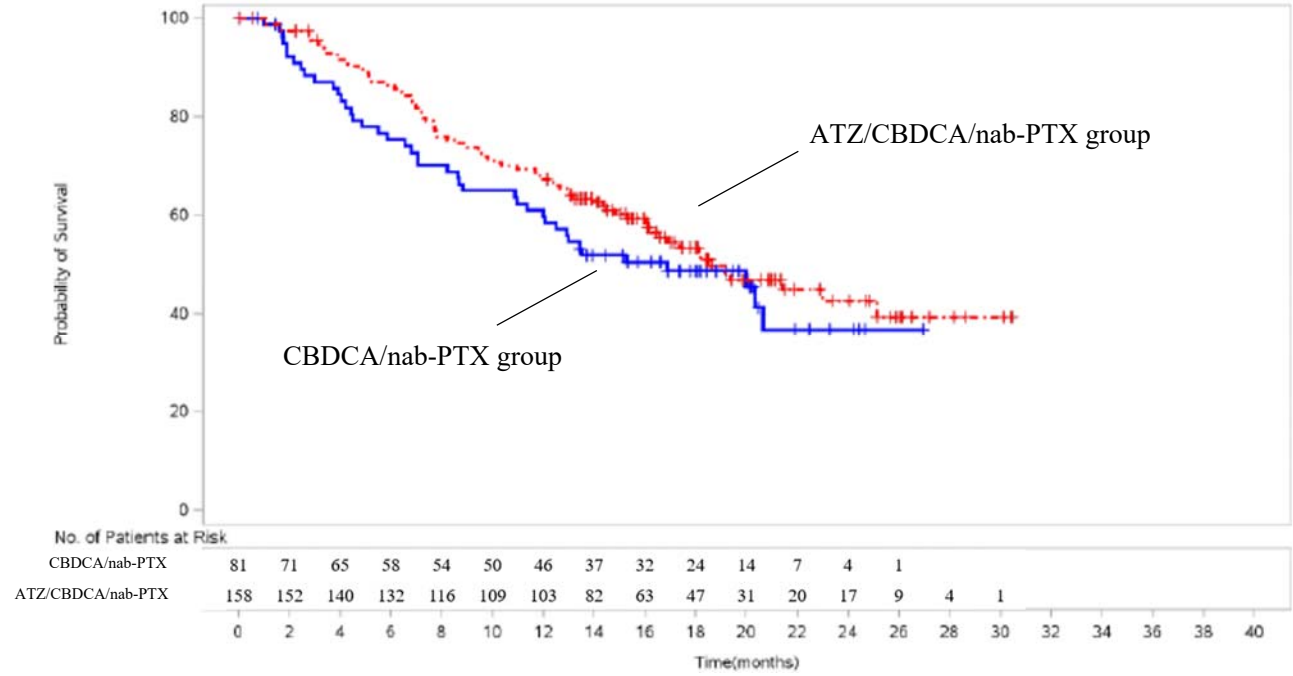

Figure 17. Kaplan-Meier curves for OS at the time of interim analysis by PD-L1 expression status (TC2/3 or IC2/3 subgroup, data cutoff date of March 15, 2018)

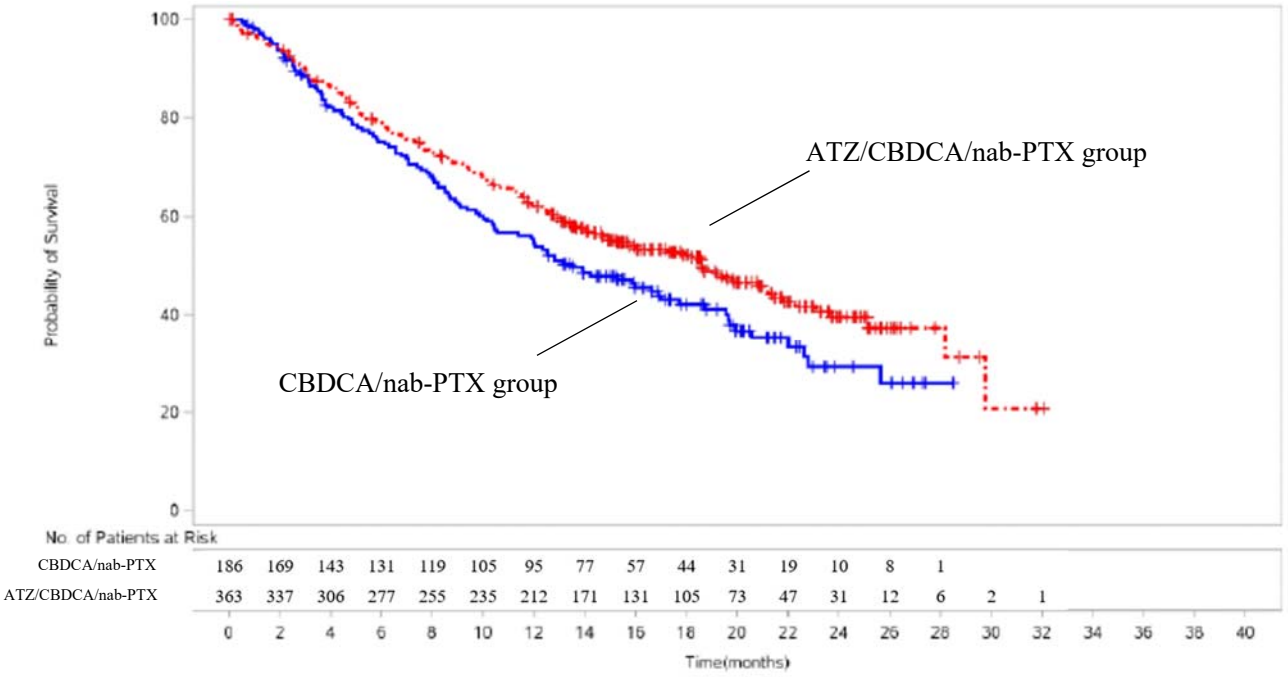

Figure 18. Kaplan-Meier curves for OS at the time of interim analysis by PD-L1 expression status (TC0/1/2 and IC0/1/2 subgroup, data cutoff date of March 15, 2018)

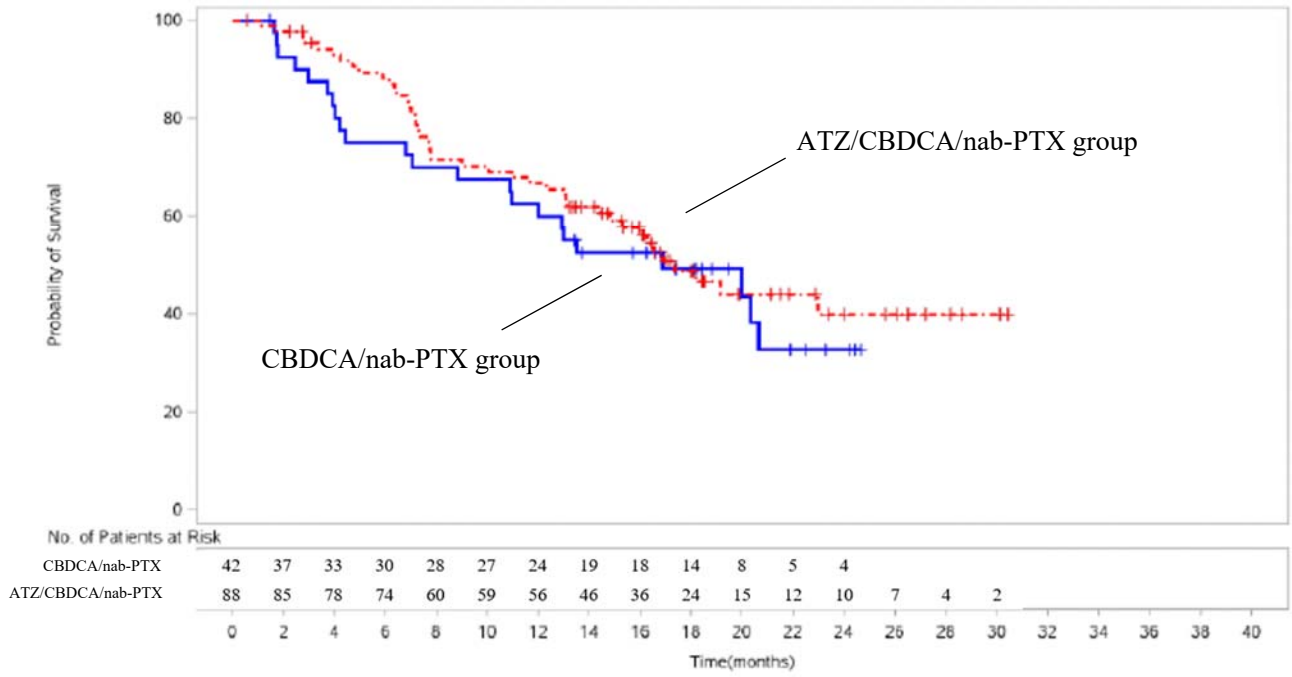

Figure 19. Kaplan-Meier curves for OS at the time of interim analysis by PD-L1 expression status (TC3 or IC 3 subgroup, data cutoff date of March 15, 2018)

In the ATZ/CBDCA/nab-PTX group, the incidences of adverse events of any grade in the TC0 and IC0 subgroup and the TC1/2/3 or IC1/2/3 subgroup were 99.2% and 100%, respectively, the incidences of Grade ≥3 adverse events were 84.3% and 87.5%, respectively, and the incidences of serious adverse events were 50.2% and 51.3%, respectively. The incidences of adverse events of any grade in the TC0/1 and IC0/1 subgroup and the TC2/3 or IC2/3 subgroup were 99.3% and 100%, respectively, the

incidences of Grade ≥3 adverse events were 85.2% and 86.9%, respectively, and the incidences of serious adverse events were 49.5% and 53.0%, respectively. The incidences of adverse events of any grade in the TC0/1/2 and IC0/1/2 subgroup and the TC3 or IC3 subgroup were 99.5% and 100%, respectively, the incidences of Grade ≥3 adverse events were 86.1% and 84.6%, respectively, and the incidences of serious adverse events were 50.5% and 51.6%, respectively. There was no clear difference in the safety of ATZ on the basis of PD-L1 expression status in tumor specimens.

PMDA's discussion:
PMDA largely accepted the above explanation by the applicant, but considers that it is necessary to continue to collect information on the predictive factors for response to ATZ, including factors other than PD-L1, and appropriately provide any new information to healthcare professionals in clinical practice.

7.R.5 Dosage and administration

The proposed dosage and administration statement for ATZ was "For chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer; *Atezolizumab in combination with other anti-neoplastic drugs;* 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 PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the current package insert for unresectable advanced or recurrent non-small cell lung cancer was unchanged, and the following statements were included in this section of the proposed package insert.

- In patients with unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy, the efficacy and safety of ATZ in combination with other anti-neoplastic drugs have not been established.
- Infusion solution preparation procedure
- Recommended ATZ dosage modifications for adverse reactions

Based on Sections "7.R.1 Efficacy" and "7.R.2 Safety" and the considerations in the following section, 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 (Underline denotes additions made in the present partial change application).

- <u>In chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer, other anti-neoplastic drugs for combination with ATZ should be selected with a full understanding of the information presented in the CLINICAL STUDIES section.</u>
- In patients with unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy, the efficacy and safety of ATZ in combination with other anti-neoplastic drugs have not been established.
- Infusion solution preparation procedure

- Recommended ATZ dosage modifications for adverse reactions

7.R.5.1 Dosage and administration for ATZ

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

The dosing regimen for the IMpower132 study and the IMpower130 study was selected based on the following study results etc., and these studies demonstrated the clinical usefulness of ATZ in combination with platinum/PEM or CBDCA/nab-PTX in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC. Thus, the proposed dosing regimen for ATZ was selected based on these 2 studies.

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

The IMpower132 study and the IMpower130 study were conducted according to the ATZ dosage modification guidelines for adverse events, which are similar to those in the approved package insert, and the clinical usefulness of ATZ/platinum/PEM in the patient population of the IMpower132 study and that of ATZ/CBDCA/nab-PTX in the patient population of the IMpower130 study were demonstrated. Thus, recommended ATZ dosage modifications in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the current package insert are unchanged in the present partial change application.

PMDA's discussion:

PMDA largely accepted the above explanation by the applicant. However, as there are no clinical study data from chemotherapy-naïve patients with NSQ-NSCLC treated with ATZ in combination with anti-neoplastic drugs other than platinum/PEM, CBDCA/nab-PTX, and CBDCA/PTX/BV, information on other anti-neoplastic drugs for combination with ATZ should be included in the CLINICAL STUDIES section of the package insert, and then the following statement should also be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

- In chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer, other anti-neoplastic drugs for combination with ATZ should be selected with a full understanding of the information presented in the CLINICAL STUDIES section.

7.R.6 Post-marketing investigations

The applicant's explanation:

No new safety concerns have been identified in the present partial change application, and there is no need to conduct post-marketing surveillance to investigate the safety etc. of ATZ/platinum/PEM and ATZ/CBDCA/nab-PTX, immediately after obtaining approval, for the following reasons etc.

- There were no clear differences between the safety profile of (a) ATZ/platinum/PEM in the IMpower132 study/(b) ATZ/CBDCA/nab-PTX in the IMpower130 study and the previously approved regimen of ATZ/CBDCA/PTX/BV [see Section 7.R.3.1].

- There were no clear differences in the safety profile of ATZ/platinum/PEM in the IMpower132 study between the Japanese and non-Japanese subgroups [see Section 7.R.3.2].
- Given that adverse events reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup in the ATZ/CBDCA/nab-PTX group of the IMpower131 study were all known adverse events etc., no new events requiring attention have been observed in Japanese patients treated with ATZ/CBDCA/nab-PTX [see Section 7.R.3.2].

PMDA's discussion:
Taking account of the above explanation by the applicant, and given that a certain amount of safety information from Japanese patients with unresectable advanced or recurrent NSCLC has been available etc., there is little need to conduct post-marketing surveillance to investigate the safety etc. of ATZ/platinum/PEM and ATZ/CBDCA/nab-PTX, immediately after obtaining approval, and the applicant may collect ATZ safety information through routine pharmacovigilance activities.

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 III study (IMpower132 study)

Adverse events occurred in 286 of 291 subjects (98.3%) in the ATZ/platinum/PEM group and 266 of 274 subjects (97.1%) in the platinum/PEM group, and those for which a causal relationship to study drug could not be ruled out occurred in 267 of 291 subjects (91.8%) in the ATZ/platinum/PEM group and 239 of 274 subjects (87.2%) in the platinum/PEM group. Adverse events reported by ≥10% of subjects in either group are shown in Table 14.

Table 14. Adverse events reported by ≥10% of subjects in either group

SOC PT (MedDRA ver.21.0)	n (%)			
	ATZ/platinum/PEM N = 291		Platinum/PEM N = 274	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	286 (98.3)	202 (69.4)	266 (97.1)	161 (58.8)
Gastrointestinal disorders				
Nausea	108 (37.1)	8 (2.7)	115 (42.0)	2 (0.7)
Constipation	87 (29.9)	3 (1.0)	78 (28.5)	3 (1.1)
Diarrhoea	59 (20.3)	8 (2.7)	48 (17.5)	5 (1.8)
Vomiting	60 (20.6)	10 (3.4)	47 (17.2)	2 (0.7)
Stomatitis	34 (11.7)	5 (1.7)	23 (8.4)	1 (0.4)
General disorders and administration site conditions				
Fatigue	69 (23.7)	13 (4.5)	67 (24.5)	8 (2.9)
Asthenia	81 (27.8)	18 (6.2)	54 (19.7)	8 (2.9)
Pyrexia	62 (21.3)	5 (1.7)	37 (13.5)	3 (1.1)
Oedema peripheral	40 (13.7)	2 (0.7)	30 (10.9)	0
Blood and lymphatic system disorders				
Anaemia	131 (45.0)	46 (15.8)	117 (42.7)	44 (16.1)
Neutropenia	49 (16.8)	29 (10.0)	39 (14.2)	16 (5.8)
Thrombocytopenia	46 (15.8)	19 (6.5)	24 (8.8)	14 (5.1)
Investigations				
Neutrophil count decreased	43 (14.8)	28 (9.6)	51 (18.6)	27 (9.9)
Platelet count decreased	39 (13.4)	14 (4.8)	38 (13.9)	11 (4.0)
White blood cell count decreased	20 (6.9)	9 (3.1)	29 (10.6)	9 (3.3)
AST increased	53 (18.2)	4 (1.4)	28 (10.2)	2 (0.7)
ALT increased	56 (19.2)	8 (2.7)	24 (8.8)	2 (0.7)
Blood creatinine increased	31 (10.7)	3 (1.0)	17 (6.2)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	40 (13.7)	4 (1.4)	39 (14.2)	5 (1.8)
Cough	39 (13.4)	0	27 (9.9)	1 (0.4)
Metabolism and nutrition disorders				
Decreased appetite	78 (26.8)	6 (2.1)	66 (24.1)	3 (1.1)
Nervous system disorders				
Headache	32 (11.0)	1 (0.3)	23 (8.4)	0
Taste abnormality	31 (10.7)	0	23 (8.4)	0
Musculoskeletal and connective tissue disorders				
Back pain	30 (10.3)	1 (0.3)	25 (9.1)	2 (0.7)
Arthralgia	30 (10.3)	1 (0.3)	15 (5.5)	0
Skin and subcutaneous tissue disorders				
Rash	37 (12.7)	2 (0.7)	21 (7.7)	0

Serious adverse events occurred in 134 of 291 subjects (46.0%) in the ATZ/platinum/PEM group and 84 of 274 subjects (30.7%) in the platinum/PEM group. Those reported by ≥5 subjects in each group were pneumonia; and pyrexia (12 subjects each [4.1%]); thrombocytopenia (11 subjects [3.8%]); anaemia; and febrile neutropenia (10 subjects each [3.4%]); pneumonitis (9 subjects [3.1%]); diarrhoea (8 subjects [2.7%]); urinary tract infection; and vomiting (6 subjects each [2.1%]); and asthenia (5 subjects [1.7%]) in the ATZ/platinum/PEM group and pneumonia (11 subjects [4.0%]); anaemia (6 subjects [2.2%]); and febrile neutropenia (5 subjects [1.8%]) in the platinum/PEM group. A causal relationship to study drug could not be ruled out for thrombocytopenia (11 subjects); anaemia; and febrile neutropenia (10 subjects each); pneumonitis (9 subjects); diarrhoea (7 subjects); pyrexia (6 subjects); pneumonia; and vomiting (4 subjects each); asthenia (3 subjects); and urinary tract infection

(1 subject) in the ATZ/platinum/PEM group and anaemia (5 subjects); pneumonia (4 subjects); and febrile neutropenia (3 subjects) in the platinum/PEM group.

Adverse events leading to discontinuation of any study drug occurred in 69 of 291 subjects (23.7%) in the ATZ/platinum/PEM group and 48 of 274 subjects (17.5%) in the platinum/PEM group. Those reported by ≥5 subjects in each group were pneumonitis (7 subjects [2.4%]); and fatigue (5 subjects [1.7%]) in the ATZ/platinum/PEM group and anaemia (8 subjects [2.9%]) in the platinum/PEM group. A causal relationship to study drug could not be ruled out for pneumonitis (7 subjects); and fatigue (4 subjects) in the ATZ/platinum/PEM group and anaemia (8 subjects) in the platinum/PEM group.

7.2.2 Foreign phase III study (IMpower130 study)

Adverse events occurred in 471 of 473 subjects (99.6%) in the ATZ/CBDCA/nab-PTX group and 230 of 232 subjects (99.1%) in the CBDCA/nab-PTX group, and those for which a causal relationship to study drug could not be ruled out occurred in 455 of 473 subjects (96.2%) in the ATZ/CBDCA/nab-PTX group and 215 of 232 subjects (92.7%) in the CBDCA/nab-PTX group. Adverse events reported by ≥15% of subjects in either group are shown in Table 15.

Table 15. Adverse events reported by ≥15% of subjects in either group

SOC PT (MedDRA ver.21.0)	n (%)			
	ATZ/CBDCA/nab-PTX N = 473		CBDCA/nab-PTX N = 232	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	471 (99.6)	406 (85.8)	230 (99.1)	177 (76.3)
Blood and lymphatic system disorders				
Anaemia	265 (56.0)	151 (31.9)	124 (53.4)	56 (24.1)
Neutropenia	220 (46.5)	153 (32.3)	105 (45.3)	66 (28.4)
Thrombocytopenia	133 (28.1)	47 (9.9)	60 (25.9)	16 (6.9)
Gastrointestinal disorders				
Nausea	234 (49.5)	16 (3.4)	107 (46.1)	5 (2.2)
Diarrhoea	201 (42.5)	25 (5.3)	73 (31.5)	14 (6.0)
Constipation	171 (36.2)	5 (1.1)	72 (31.0)	0
Vomiting	128 (27.1)	13 (2.7)	45 (19.4)	5 (2.2)
General disorders and administration site conditions				
Fatigue	223 (47.1)	36 (7.6)	109 (47.0)	14 (6.0)
Asthenia	87 (18.4)	16 (3.4)	38 (16.4)	5 (2.2)
Pyrexia	82 (17.3)	1 (0.2)	23 (9.9)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	133 (28.1)	22 (4.7)	47 (20.3)	2 (0.9)
Cough	126 (26.6)	3 (0.6)	39 (16.8)	0
Metabolism and nutrition disorders				
Decreased appetite	142 (30.0)	10 (2.1)	60 (25.9)	5 (2.2)
Hypomagnesaemia	95 (20.1)	10 (2.1)	39 (16.8)	4 (1.7)
Hypokalaemia	74 (15.6)	22 (4.7)	26 (11.2)	6 (2.6)
Nervous system disorders				
Dizziness	76 (16.1)	1 (0.2)	25 (10.8)	1 (0.4)
Headache	77 (16.3)	1 (0.2)	23 (9.9)	0
Investigations				
Platelet count decreased	108 (22.8)	37 (7.8)	39 (16.8)	14 (6.0)
Neutrophil count decreased	95 (20.1)	59 (12.5)	35 (15.1)	20 (8.6)
Skin and subcutaneous tissue disorders				
Alopecia	151 (31.9)	0	63 (27.2)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	72 (15.2)	8 (1.7)	24 (10.3)	0
Back pain	82 (17.3)	8 (1.7)	16 (6.9)	1 (0.4)

Serious adverse events occurred in 240 of 473 subjects (50.7%) in the ATZ/CBDCA/nab-PTX group and 88 of 232 subjects (37.9%) in the CBDCA/nab-PTX group. Those reported by ≥5 subjects in each group were pneumonia (28 subjects [5.9%]); pulmonary embolism; neutropenia; diarrhoea; and lung infection (14 subjects each [3.0%]); anaemia (13 subjects [2.7%]); chronic obstructive pulmonary disease (12 subjects [2.5%]); dyspnoea (11 subjects [2.3%]); febrile neutropenia (9 subjects [1.9%]); pyrexia; and pleural effusion (8 subjects each [1.7%]); pneumonitis (7 subjects [1.5%]); vomiting; sepsis; thrombocytopenia; neutrophil count decreased; and pericardial effusion (6 subjects each [1.3%]); and nausea; haemoptysis; renal failure; septic shock; influenza; bronchitis; and chest pain (5 subjects each [1.1%]) in the ATZ/CBDCA/nab-PTX group and pneumonia (14 subjects [6.0%]); anaemia (8 subjects [3.4%]); and pulmonary embolism; and febrile neutropenia (5 subjects each [2.2%]) in the CBDCA/nab-PTX group. A causal relationship to study drug could not be ruled out for neutropenia (14 subjects); diarrhoea (12 subjects); anaemia (11 subjects); febrile neutropenia (9 subjects); pneumonitis (7 subjects); thrombocytopenia; and neutrophil count decreased (6 subjects each); pneumonia; and pyrexia (5 subjects each); nausea; and lung infection (4 subjects each); vomiting; renal failure; and septic shock (3 subjects each); and sepsis; dyspnoea; pericardial effusion; influenza; bronchitis; and chest pain

(1 subject each) in the ATZ/CBDCA/nab-PTX group and anaemia (6 subjects); febrile neutropenia (5 subjects); pneumonia (3 subjects); and pulmonary embolism (1 subject) in the CBDCA/nab-PTX group.

Adverse events leading to discontinuation of any study drug occurred in 125 of 473 subjects (26.4%) in the ATZ/CBDCA/nab-PTX group and 51 of 232 subjects (22.0%) in the CBDCA/nab-PTX group. Those reported by ≥5 subjects in each group were thrombocytopenia (17 subjects [3.6%]); neutropenia (14 subjects [3.0%]); platelet count decreased; anaemia; and neutrophil count decreased (8 subjects each [1.7%]); fatigue (7 subjects [1.5%]); and pneumonia; and dyspnoea (6 subjects each [1.3%]) in the ATZ/CBDCA/nab-PTX group and neutropenia (6 subjects [2.6%]) in the CBDCA/nab-PTX group. A causal relationship to study drug could not be ruled out for thrombocytopenia (15 subjects); neutropenia (14 subjects); platelet count decreased; and neutrophil count decreased (8 subjects each); anaemia (7 subjects); fatigue (6 subjects); and pneumonia; and dyspnoea (1 subject each) in the ATZ/CBDCA/nab-PTX group and neutropenia (6 subjects) in the CBDCA/nab-PTX group.

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

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

The 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 since the clinical studies as a whole were performed in compliance with GCP, there were no obstacles to conducting its review based on the application documents submitted. Though the outcome of the overall assessment of the studies was not affected significantly, the inspection revealed the following findings at some of the study sites used by the applicant, and the heads of the relevant study sites were notified of these findings requiring corrective action.

Findings requiring corrective action

Study sites

- Protocol deviations (non-compliance with the concomitant medication restrictions)
- Failure to properly obtain new consent from some subjects, using the revised written information

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

On the basis of the data submitted, PMDA has concluded that ATZ/platinum/PEM and ATZ/CBDCA/nab-PTX have efficacy in the treatment of chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous NSCLC, and that the combinations have acceptable safety in view of their benefits. The combinations are clinically meaningful because they offer treatment options for chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous NSCLC. PMDA considers that dosage and administration etc. need to be further discussed.

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

Review Report (2)

October 10, 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	January 23, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

PMDA's conclusion:

Based on the considerations in Section "7.R.2 Efficacy" in the Review Report (1), the results from the following 2 clinical studies etc. demonstrated the efficacy of ATZ in combination with platinum-containing chemotherapy in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC.

- IMpower132 study

A global phase III study in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC (IMpower132 study) demonstrated the superiority of ATZ/platinum/PEM over platinum/PEM in the co-primary endpoint of PFS. The results of the final analysis of OS were submitted after the preparation of the Review Report (1). The hazard ratio [95% CI] was [redacted] [[redacted], [redacted]], and the median OS was [redacted] months in the ATZ/platinum/PEM group and [redacted] months in the platinum/PEM group.

- IMpower130 study

A foreign phase III study in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC (IMpower130 study) demonstrated the superiority of ATZ/CBDCA/nab-PTX over CBDCA/nab-PTX in the co-primary endpoint of OS.

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

1.2 Safety

PMDA's conclusion:

Based on the considerations in Section "7.R.3 Safety" in the Review Report (1), adverse events that require attention following administration of ATZ in combination with platinum-containing chemotherapy in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC are the events that were considered to require attention at the time of the previous approval of ATZ (use in the previously approved indications).[13)]

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

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

1.3 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement ("For chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer; *Atezolizumab in combination with other anti-neoplastic drugs*; 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

- In chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous NSCLC, other anti-neoplastic drugs for combination with ATZ should be selected with a full understanding of the information presented in the CLINICAL STUDIES section.
- In patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy, the efficacy and safety of ATZ in combination with other anti-neoplastic drugs have not been established.
- Infusion solution preparation procedure
- Recommended ATZ dosage modifications for adverse reactions

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

13) 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, febrile neutropenia, and myocarditis (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of October 23, 2017," "Review Report on Tecentriq Intravenous Infusion 1200 mg as of November 12, 2018," and "Review Report on Tecentriq Intravenous Infusion 1200 mg as of July 24, 2019")

Based on the above, PMDA instructed the applicant to amend the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section accordingly. The applicant agreed.

1.4 Risk management plan (draft)

PMDA's conclusion:

Based on the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1), there is little need to conduct post-marketing surveillance to investigate the safety etc. of ATZ/platinum/PEM and ATZ/CBDCA/nab-PTX, immediately after obtaining approval, and the applicant may collect ATZ safety information through routine pharmacovigilance activities.

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

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for ATZ should include the safety specification presented in Table 16, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 17.

Table 16. 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) • Infections when combined with chemotherapy	None
Efficacy specification		
None		

Table 17. 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
• 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, febrile neutropenia)] • Post-marketing database survey in patients with PD-L1-positive, hormone-receptor-negative and HER2-negative inoperable or recurrent breast cancer (infections when combined with chemotherapy) • Post-marketing clinical studies (extension studies of OAK, BIRCH, IMpower133, IMpassion130, and IMpower132) • Post-marketing clinical study (Study BO39633-01)	None	• Develop information materials to be distributed to healthcare professionals. • Develop information materials to be distributed to patients.

Underline denotes planned activities for the additional regimens in the present application.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed 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. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until January 18, 2026).

Indications (No change made in the present partial change application. Double underline denotes additions made as of August 22, 2019 after submission of the present partial change application.)

Unresectable advanced or recurrent non-small cell lung cancer

Extensive-stage small cell lung cancer

Dosage and Administration (Single underline denotes new additions, and strikethrough denotes deletions. Double underline denotes additions made as of August 22, 2019 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)~~ other anti-neoplastic drugs

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. ATZ should be administered only to patients eligible for ATZ 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, ATZ 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 ATZ.

Precautions Concerning Indications (No change made in the present partial change application. Double underline denotes additions made as of August 22, 2019 after submission of the present partial change application.)
Unresectable advanced or recurrent non-small cell lung cancer
1. The efficacy and safety of ATZ in chemotherapy-naïve patients with squamous disease have not been established.
2. The efficacy and safety of ATZ 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 ATZ.

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 ATZ.

Precautions Concerning Dosage and Administration (Single underline denotes new additions, and strikethrough denotes deletions. Double underline denotes additions made as of August 22, 2019 after submission of the present partial change application.)

1. In chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer, other anti-neoplastic drugs for combination with ATZ should be selected with a full understanding of the information presented in the CLINICAL STUDIES section.

~~1~~2. In patients with unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy, the efficacy and safety of ATZ in combination with other anti-neoplastic drugs have not been established.

~~2~~3. ATZ 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.

~~3~~4. Twenty mL of the product 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.

~~4~~5. In the event of adverse reactions to ATZ, ATZ 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	Withhold dose until resolution.

	• Symptomatic hyperthyroidism, or asymptomatic hyperthyroidism with thyroid stimulating hormone <0.1 mU/L	
	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 myositis	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

List of Abbreviations

ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
a partial change application	an application for partial change of marketing approval
AST	aspartate aminotransferase
ATZ	atezolizumab (genetical recombination)
ATZ/CBDCA/ETP	the combination of ATZ, CBDCA, and ETP
ATZ/CBDCA/nab-PTX	the combination of ATZ, CBDCA, and nab-PTX
ATZ/CBDCA/PTX	the combination of ATZ, CBDCA, and PTX
ATZ/CBDCA/PTX/BV	the combination of ATZ, CBDCA, PTX, and BV
ATZ/platinum/PEM	the combination of ATZ, platinum, and PEM
AUC	area under the blood concentration-time curve
BV	bevacizumab (genetical recombination)
CBDCA	carboplatin
CBDCA/nab-PTX	the combination of CBDCA and nab-PTX
CBDCA/PTX/BV	the combination of CBDCA, PTX, and BV
CDDP	cisplatin
CI	confidence interval
CXCL9	chemokine ligand 9
DTX	docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
erlotinib	erlotinib hydrochloride
ESMO guidelines	Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
ETP	etoposide
IC0	<1% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC0/1	<5% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC0/1/2	<10% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC1/2/3	≥1% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC2/3	≥5% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC3	≥10% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IFN-γ	interferon-γ
ILD	interstitial lung disease
IMpower130 study	Study GO29537
IMpower131 study	Study GO29437
IMpower132 study	Study GO29438
IMpower150 study	Study GO29436
IRF	independent review facility
IRR	infusion related reaction
ITT	intention-to-treat
ITT-WT	intention-to-treat wild type (the ITT population excluding patients with an *EGFR* or *ALK* genetic alteration)
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid

nab-PTX	paclitaxel (albumin-bound)
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NE	not estimable
NSCLC	non-small cell lung cancer
NSQ	non-squamous
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
PEM	pemetrexed sodium hydrate
pembrolizumab	pembrolizumab (genetical recombination)
PFS	progression free survival
platinum	platinum agent (CBDCA or CDDP)
platinum/PEM	the combination of platinum and PEM
PMDA	Pharmaceuticals and Medical Devices Agency
POPLAR study	Study GO28753
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
SQ-NSCLC	squamous non-small cell lung cancer
TC0	<1% of tumor area occupied by PD-L1-expressing tumor cells
TC0/1	<5% of tumor area occupied by PD-L1-expressing tumor cells
TC0/1/2	<50% of tumor area occupied by PD-L1-expressing tumor cells
TC1/2/3	≥1% of tumor area occupied by PD-L1-expressing tumor cells
TC2/3	≥5% of tumor area occupied by PD-L1-expressing tumor cells
TC3	≥50% of tumor area occupied by PD-L1-expressing tumor cells
Teff-high	T-effector high (patients with Teff signature score ≥ −1.91)
Teff-high-WT	T-effector high wild type (the Teff-high population excluding patients with an *EGFR* or *ALK* genetic alteration)