Review Report

August 7, 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 840 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	December 21, 2018
Dosage Form/Strength	Injection: Each vial (14.0 mL) contains 840 mg of Atezolizumab (Genetical Recombination).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage, (8) Drug in an additional dosage form (during the reexamination period)
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of PD-L1-positive, hormone-receptor-negative and human epidermal growth factor receptor 2 (HER2)-negative inoperable or recurrent breast cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

PD-L1-positive, hormone-receptor-negative and HER2-negative inoperable or recurrent breast cancer

Dosage and Administration

Atezolizumab in combination with paclitaxel (albumin-bound)

The usual adult dosage is 840 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 2 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

July 3, 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 840 mg
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Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	December 21, 2018
Dosage Form/Strength	Injection: Each vial (14.0 mL) contains 840 mg of Atezolizumab (Genetical Recombination).
Proposed Indication	PD-L1-positive inoperable or recurrent breast cancer

Proposed Dosage and Administration

Atezolizumab in combination with paclitaxel

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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 programmed cell death-ligand 1 (PD-L1) discovered by Genentech (the US). It binds to the extracellular domain of PD-L1, thereby blocking the binding of PD-L1 to programmed cell death-1 (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)/bevacizumab (genetical recombination) (BV) in December 2018, for the treatment of "unresectable advanced or recurrent non-small cell lung cancer."

1.2 Development history etc.

In the clinical development of ATZ/nanoparticle albumin-bound paclitaxel (paclitaxel [albumin-bound]) (nab-PTX) for chemotherapy-naïve patients with hormone-receptor (HR)-negative and human epidermal growth factor receptor 2 (HER2)-negative inoperable or recurrent breast cancer, Roche (Switzerland) and Genentech (the US) initiated a global phase III study in this patient population (IMpassion130 study) in June 2015.

US and EU applications of ATZ in combination with nab-PTX for chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer were filed based mainly on the results from the IMpassion130 study in September 2018. In the US, ATZ was approved for the following indication in March 2019: "TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥1% of the tumor area), as determined by an FDA-approved test." The EU application is under review.

As of May 2019, ATZ has been approved for the indication of breast cancer in 8 countries.

In Japan, the IMpassion130 study initiated patient enrollment in August 2016.

The applicant has filed a partial change application for ATZ/nab-PTX for the treatment of breast cancer, based mainly on the results from the IMpassion130 study.

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

The present application is intended for an additional dosage form as well as a new indication and a new dosage, and data relating to quality have been submitted. Tecentriq Intravenous Infusion 840 mg and the previously approved drug product, Tecentriq Intravenous Infusion 1200 mg, are vials of the same drug solution from different fills, and these two drug products differ only in fill volume and the container and closure system. This report contains a review of the new indication and new dosage only. As a result of its quality review of the additional dosage form, PMDA found no problems.

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

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

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical method

Roche Diagnostics' immunohistochemical (IHC) assay, "VENTANA OptiView PD-L1 (SP142)" was used to measure PD-L1 expression in tumor specimens in the IMpassion130 study. Roche Diagnostics submitted a partial change application for its *in vitro* diagnostic, "VENTANA OptiView PD-L1 (SP142)," as an aid in identifying patients eligible for treatment with ATZ, as of February 25, 2019.

6.2 Clinical pharmacology

The PK of ATZ when administered with nab-PTX were studied in patients with cancer.

6.2.1 Global phase III study (CTD 5.3.5.1-1, IMpassion130 study [ongoing since June 2015 (data cutoff date of April 17, 2018)])

A double-blind, randomized, controlled study was conducted to evaluate the efficacy and safety of ATZ/nab-PTX compared with placebo/nab-PTX in 902 chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer (451 in the ATZ/nab-PTX group, 451 in the placebo/nab-PTX group) (772 included in PK analysis[1)]). Subjects were to receive nab-PTX 100 mg/m^2 intravenously on Days 1, 8, and 15 of each 28-day cycle and ATZ 840 mg or placebo intravenously on Days 1 and 15, and serum ATZ concentrations etc. were determined.

In Japanese and non-Japanese patients (34 Japanese patients and 402 non-Japanese patients included in PK analysis), (a) the C_{max} values of ATZ (mean ± standard deviation [SD]) on Day 1 of Cycle 1, and the C_{min} values of ATZ (mean ± SD) on Day 27 of (b) Cycle 1, of (c) Cycle 2, of (d) Cycle 3, and of (e) Cycle 7 were (a) 411

[1)] Four hundred and thirty-six subjects in the ATZ/nab-PTX group and 336 subjects in the placebo/nab-PTX group were included in PK analysis.

± 98.9 and 321 ± 95.6, respectively, (b) 178 ± 67.5 and 143 ± 50.3, respectively, (c) 264 ± 95.0 and 210 ± 75.1, respectively, (d) 293 ± 116 and 241 ± 86.5, respectively, and (e) 316 ± 162 and 270 ± 104 μg/mL, respectively. The applicant explained that the IMpassion130 study results etc. indicated no pharmacokinetic interactions between ATZ and nab-PTX.

Among 434 subjects tested for the presence of anti-ATZ antibodies after the initiation of ATZ, 57 tested positive for anti-ATZ antibodies. The neutralizing antibody assay was not performed.

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the clinical pharmacology etc. of ATZ is acceptable.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 1 global phase III study presented in Table 1.

Table 1. Efficacy and safety clinical study

Data category	Geographical location	Study Identity	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Global	IMpassion130	III	Chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer	902 (a) 451 (b) 451	nab-PTX 100 mg/m^2 intravenously on Days 1, 8, and 15 of each 28-day cycle and (a) ATZ 840 mg or (b) placebo intravenously on Days 1 and 15	Efficacy Safety

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

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1-1, IMpassion130 study [ongoing since June 2015 (data cutoff date of April 17, 2018)])

A double-blind, randomized, controlled study was conducted at 246 sites in 41 countries or regions, including Japan, to evaluate the efficacy and safety of ATZ/nab-PTX compared with placebo/nab-PTX in chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer (target sample size, 900 subjects[2)]).

Subjects were to receive nab-PTX 100 mg/m^2 intravenously on Days 1, 8, and 15 of each 28-day cycle and ATZ 840 mg or placebo intravenously on Days 1 and 15 until disease progression or a criterion for discontinuation was met.

All of 902 subjects who were enrolled in the study and randomized (451 in the ATZ/nab-PTX group, 451 in

[2)] The study was initially planned to enroll 350 subjects. Subsequently, a protocol amendment (Protocol Version 4 [as of [redacted], 20[redacted]]) increased the sample size to 900 because OS was added as a co-primary endpoint, and the statistical analysis plan was amended accordingly.

the placebo/nab-PTX group) (including 34 Japanese patients in the ATZ/nab-PTX group and 31 Japanese patients in the placebo/nab-PTX group) were included in the intention-to-treat (ITT) population, which was used as the efficacy analysis population. Among the ITT population, 12 subjects (6 in the ATZ/nab-PTX group, 6 in the placebo/nab-PTX group) did not receive study drug, and 7 subjects who were assigned to the placebo/nab-PTX group, but received ATZ/nab-PTX were handled as the ATZ/nab-PTX group. Thus, 890 subjects (452 in the ATZ/nab-PTX group, 438 in the placebo/nab-PTX group) (including 34 Japanese patients in the ATZ/nab-PTX group and 30 Japanese patients in the placebo/nab-PTX group) were included in the safety population.

Initially, the primary endpoint for the study was investigator-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) ver1.1 in the ITT population and in the PD-L1-positive[3)] subpopulation, and the secondary endpoints were overall survival (OS) and the response rate in the ITT population.

The primary analysis of PFS was to take place when 228 PFS events had occurred in the ITT population. However, since the results from the POPLAR study[4)] etc. indicated that OS may be a more appropriate efficacy endpoint for ATZ, OS in the ITT population and in the PD-L1-positive subpopulation was added as a co-primary endpoint, and the testing procedure for the co-primary endpoints and the allocation of alpha were as shown in Figure 1 to control the overall type I error rate at a two-sided significance level of 0.05. Two interim analyses of OS for efficacy evaluation were planned. The primary analysis of PFS and the first interim analysis of OS were to be performed when 600 PFS events had occurred in the ITT population. The second interim analysis of OS and the final analysis of OS were to take place when the pre-planned number of events depending on the outcome of the testing of PFS and the response rate had been observed (Protocol Version 4 [as of [redacted], 20[redacted]]). In order to control for the type I error rate, the boundary for statistical significance at each interim analysis was determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function.

[3)] For analysis of the PD-L1-positive subpopulation, Roche Diagnostics' "VENTANA OptiView PD-L1 (SP142)" was used to measure PD-L1 expression in tumor specimens (IC), and the PD-L1-positive subpopulation was defined as patients whose PD-L1 status was IC1/2/3.

[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

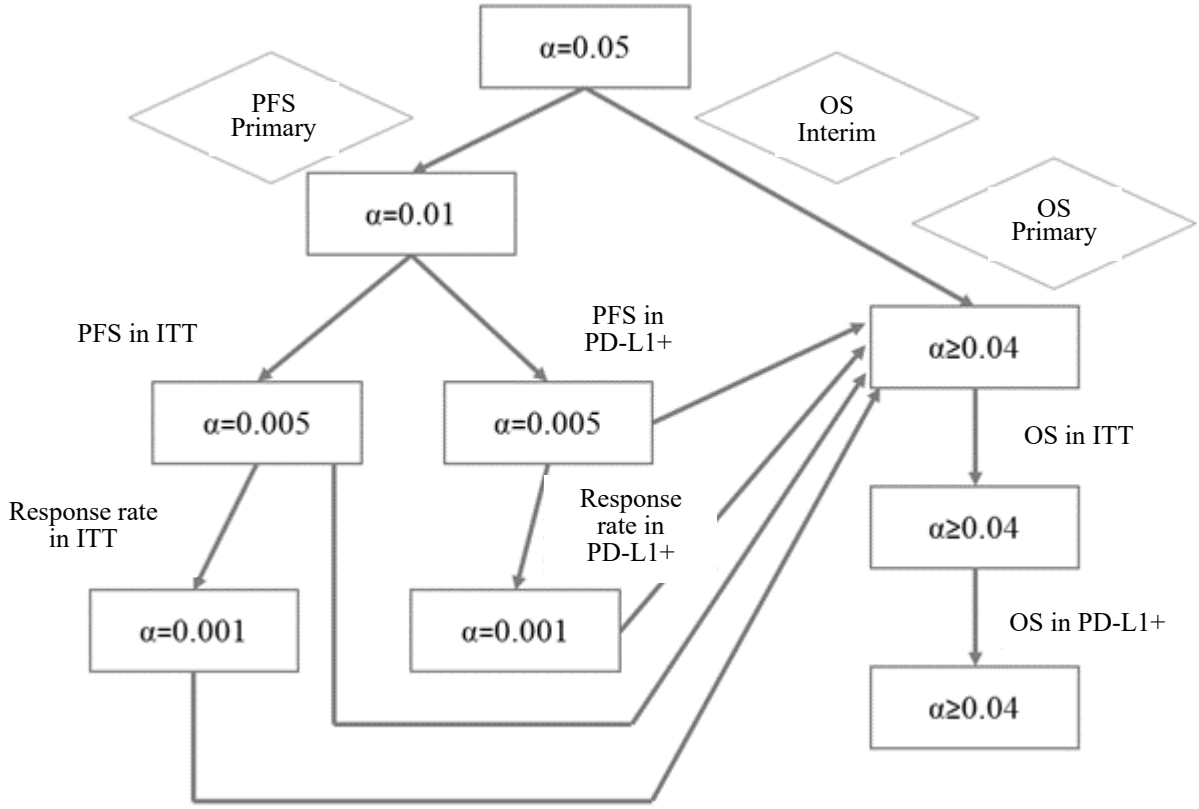


Figure 1. Testing procedure for PFS, response rate, and OS and allocation of alpha (two-sided)

The results of the co-primary efficacy endpoint of PFS in the ITT population and in the PD-L1-positive subpopulation (data cutoff date of April 17, 2018) and the Kaplan-Meier curves for PFS are shown in Table 2 and Figures 2 and 3, respectively, and the superiority of ATZ/nab-PTX over placebo/nab-PTX was demonstrated.

Table 2. Results of primary analysis of PFS (investigator assessment, data cutoff date of April 17, 2018)

	ITT population		PD-L1-positive subpopulation	
	ATZ/nab-PTX	Placebo/nab-PTX	ATZ/nab-PTX	Placebo/nab-PTX
N	451	451	185	184
No. of events (%)	358 (79.4)	378 (83.8)	138 (74.6)	157 (85.3)
Median [95% CI] (months)	7.16 [5.59, 7.46]	5.49 [5.32, 5.59]	7.46 [6.70, 9.23]	4.96 [3.81, 5.55]
Hazard ratio [95% CI]	0.80 [0.69, 0.92] *1		0.62 [0.49, 0.78] *2	
P-value (two-sided)	0.0025*3		<0.0001*4	

*1: Cox regression stratified by liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3)
*2: Cox regression stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no)
*3: Log-rank test stratified by liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3), a significance level (two-sided) of 0.005
*4: Log-rank test stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no), a significance level (two-sided) of 0.005

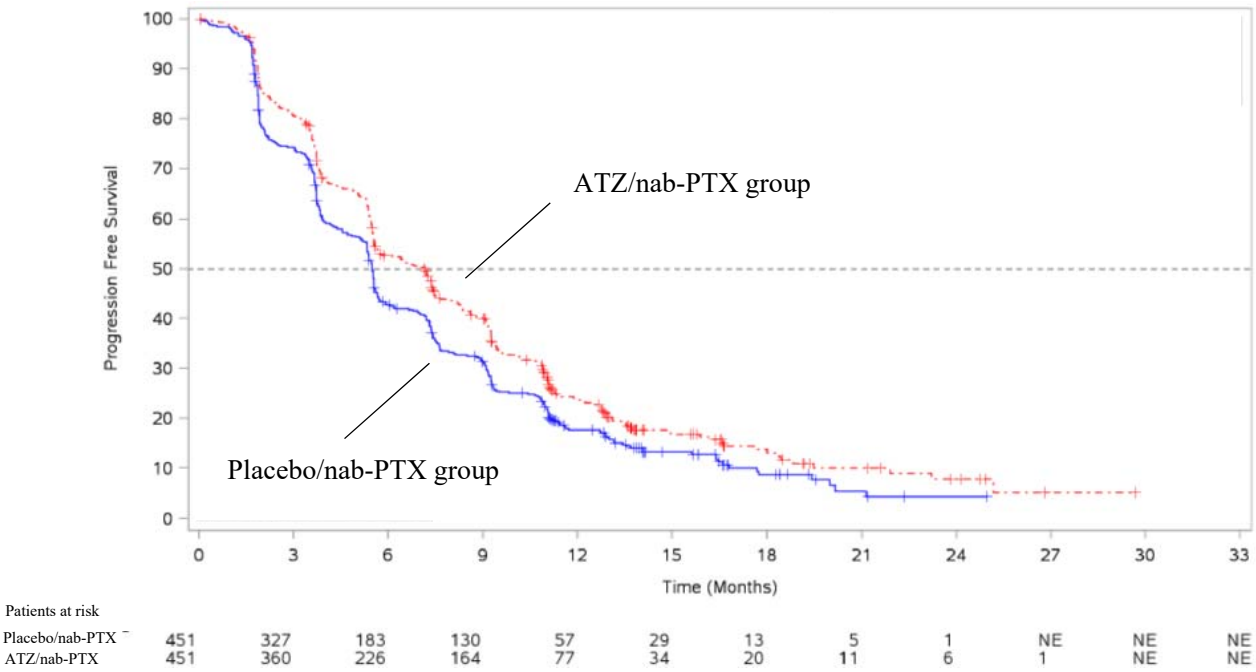


Figure 2. Kaplan-Meier curves for PFS at the time of primary analysis (investigator assessment, ITT population, data cutoff date of April 17, 2018)

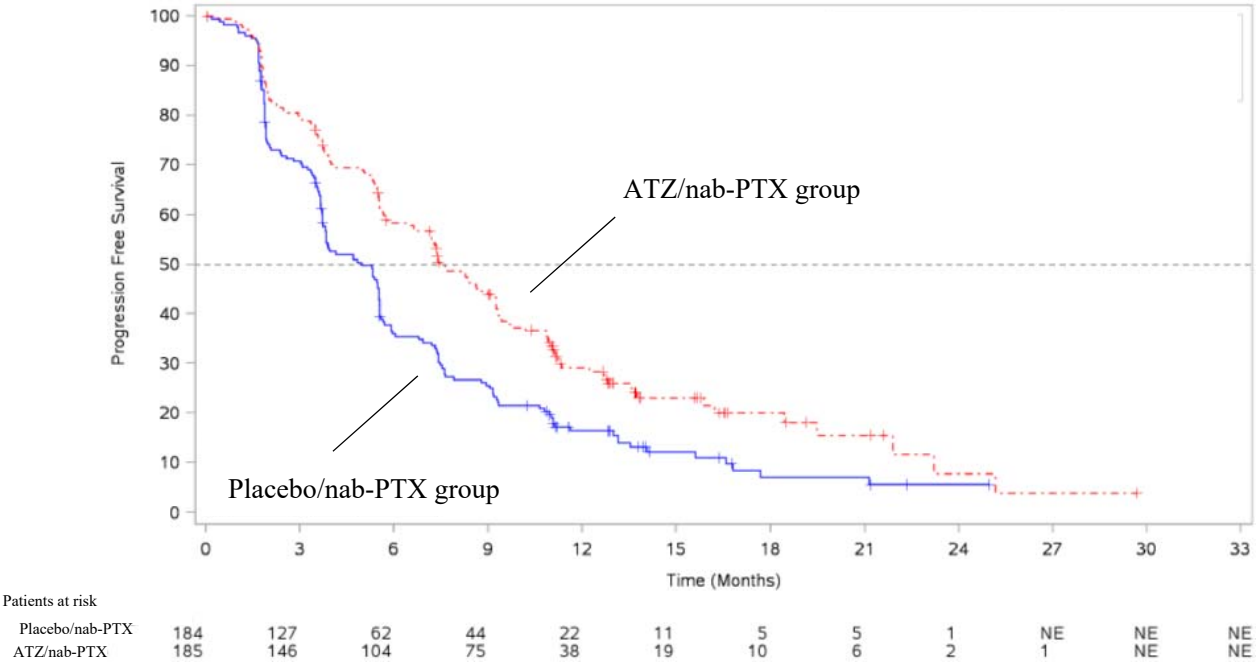


Figure 3. Kaplan-Meier curves for PFS at the time of primary analysis (investigator assessment, PD-L1-positive subpopulation, data cutoff date of April 17, 2018)

The results of the first interim analysis of the co-primary endpoint of OS in the ITT population and in the PD-L1-positive subpopulation (data cutoff date of April 17, 2018) and the Kaplan-Meier curves for OS are shown in Table 3 and Figures 4 and 5, respectively, and the superiority of ATZ/nab-PTX over placebo/nab-PTX in terms of OS in the ITT population and in the PD-L1-positive subpopulation was not demonstrated.

Table 3. Results of first interim analysis of OS (data cutoff date of April 17, 2018)

	ITT population		PD-L1-positive subpopulation	
	ATZ/nab-PTX	Placebo/nab-PTX	ATZ/nab-PTX	Placebo/nab-PTX
N	451	451	185	184
No. of events (%)	181 (40.1)	208 (46.1)	64 (34.6)	88 (47.8)
Median [95% CI] (months)	21.26 [17.25, 23.43]	17.58 [15.93, 20.01]	25.03 [22.60, NE]	15.47 [13.14, 19.35]
Hazard ratio [95% CI]	0.84 [0.69, 1.02] *1		0.62 [0.45, 0.86] *2	
P-value (two-sided)	0.0840*3		0.0035*4	

*1: Cox regression stratified by liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3)
*2: Cox regression stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no)
*3: Log-rank test stratified by liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3), a significance level (two-sided) of 0.0065
*4: Log-rank test stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no)

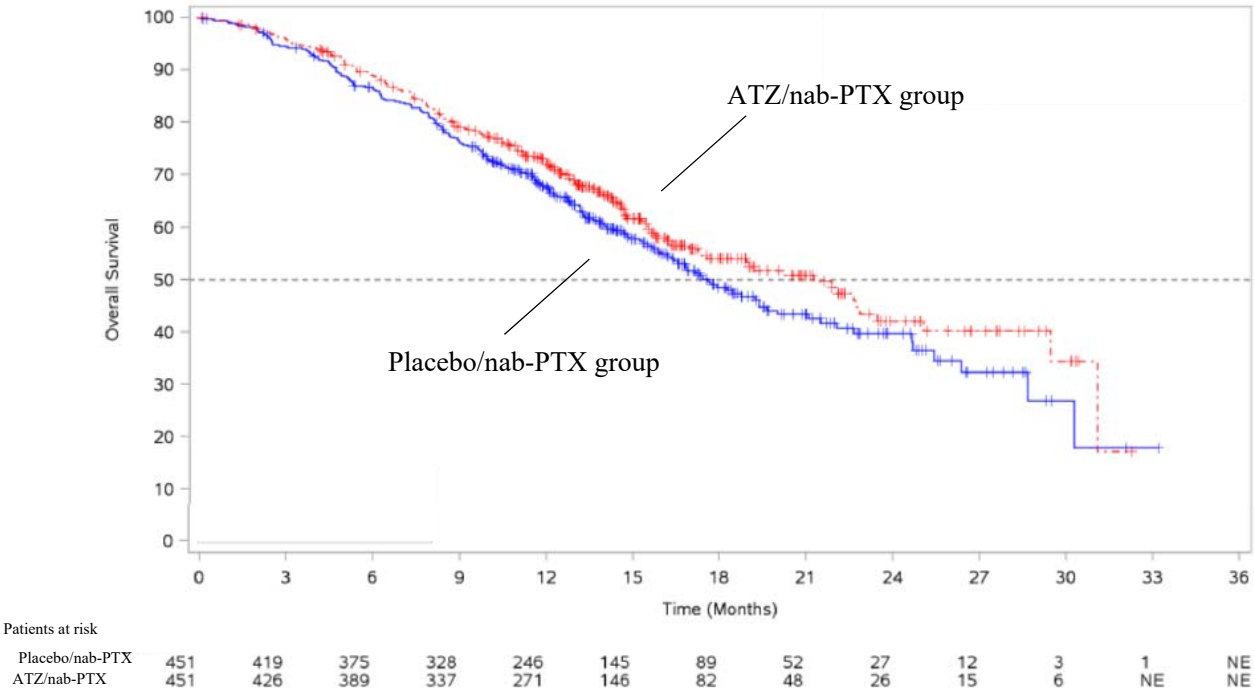


Figure 4. Kaplan-Meier curves for OS at the time of first interim analysis (ITT population, data cutoff date of April 17, 2018)

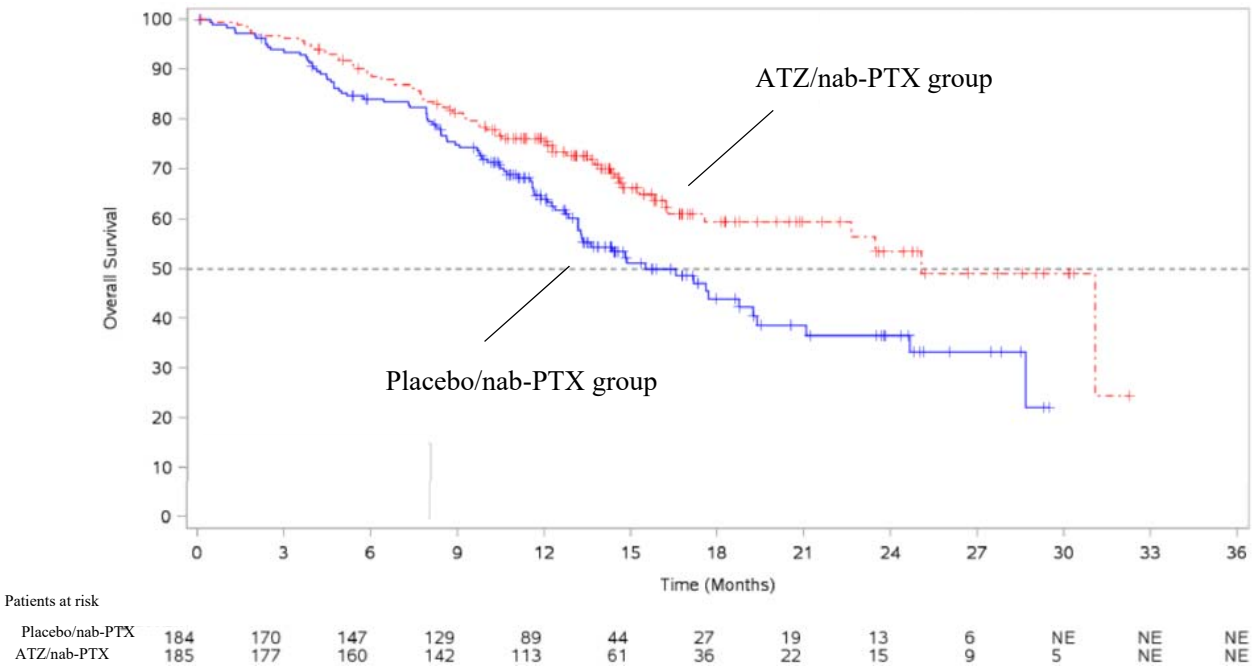


Figure 5. Kaplan-Meier curves for OS at the time of first interim analysis (PD-L1-positive subpopulation, data cutoff date of April 17, 2018)

For the secondary efficacy endpoint of investigator-assessed response rate per RECIST ver.1.1 in the ITT population and in the PD-L1-positive subpopulation [95% CI] (%) (data cutoff date of April 17, 2018), there was no statistically significant difference between the treatment groups.

Regarding safety, 181 of 452 subjects (40.0%) in the ATZ/nab-PTX group and 203 of 438 subjects (46.3%) in the placebo/nab-PTX group died during the study treatment period or within 30 days after the last dose of study drug. The causes of deaths other than disease progression (157 in the ATZ/nab-PTX group, 186 in the placebo/nab-PTX group) were unknown (12 subjects); pneumonia; and pulmonary embolism (2 subjects each); and aspiration; autoimmune hepatitis; death; septic shock; staphylococcus aureus bacteraemia and acute kidney injury; acute renal failure; pulmonary sepsis; and symptomatic aggravation (1 subject each) in the ATZ/nab-PTX group and unknown (11 subjects); and hepatic failure; acute myocardial infarction; death; fall and subarachnoid haemorrhage; intra-cerebral haemorrhage; and hemorrhagic shock and encephalopathy (1 subject each) in the placebo/nab-PTX group. A causal relationship to study drug could not be ruled out for autoimmune hepatitis; and septic shock (1 subject each) in the ATZ/nab-PTX group and hepatic failure (1 subject) in the placebo/nab-PTX group (the causes of deaths in Japanese patients [6 in the ATZ/nab-PTX group, 10 in the placebo/nab-PTX group] were all disease progression, and their causal relationship to study drug was denied).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA decided to focus its review on the overall population of the IMpassion130 study submitted, and evaluated the efficacy of ATZ/nab-PTX in Japanese patients in terms of the consistency of the results between the overall population and the Japanese subgroup, based on "Basic Principles on Global Clinical Trials"

(PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)" (PFSB/ELD Administrative Notice dated September 5, 2012), “Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials” (PSEHB/PED Notification No. 0612-1 dated June 12, 2018), etc.

Based on the following considerations, PMDA concluded that the efficacy of ATZ/nab-PTX in chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer was demonstrated.

7.R.1.1 Choice of control group

The applicant's explanation:

Given that the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Breast Cancer (NCCN guidelines) (v.3.2014), etc., at the time of planning the IMpassion130 study, recommended a taxane as a standard of care for the patient population of the IMpassion130 study, and taking account of the following point, nab-PTX was chosen as a comparator in the IMpassion130 study.

- Unlike other taxanes, nab-PTX can be administered without corticosteroid premedication. Thus, immunosuppressive effects from the concurrent corticosteroid use can be avoided.

PMDA asked the applicant to explain the appropriateness of nab-PTX 100 mg/m^2 QW (the dosing regimen unapproved for breast cancer in Japan) selected for the IMpassion130 study.

The applicant's response:

Although the NCCN guidelines (v.3.2014) recommended nab-PTX 260 mg/m^2 Q3W, 100 mg/m^2 QW, or 150 mg/m^2 QW for breast cancer, 100 mg/m^2 QW was selected, taking account of the following points etc.

- In a foreign phase II study in chemotherapy-naïve patients with inoperable or recurrent breast cancer (Study CA-024), the response rates in the nab-PTX 100 mg/m^2 QW, 150 mg/m^2 QW, and 300 mg/m^2 Q3W groups were 45%, 49%, and 37%, respectively, showing a higher response rate for patients receiving nab-PTX QW compared with Q3W (*J Clin Oncol*. 2009;27:3611-9).
- In Study CA-024, the incidences of adverse events of Grade 3 or 4 neutropenia and Grade 3 sensory neuropathy were lower in the 100 mg/m^2 QW group than in the 150 mg/m^2 QW group, suggesting the favorable safety profile of 100 mg/m^2 QW (*J Clin Oncol*. 2009;27:3611-9).
- nab-PTX 260 mg/m^2 Q3W has been approved for the patient population of the IMpassion130 study in Japan, and there have been no clear differences in the efficacy and safety of nab-PTX 100 mg/m^2 QW in the previously approved indications of non-small cell lung cancer (NSCLC) and gastric cancer between the Japanese and non-Japanese populations.

PMDA accepted the applicant's explanation.

7.R.1.2 Efficacy endpoint and results of evaluation

The IMpassion130 study demonstrated the superiority of ATZ/nab-PTX over placebo/nab-PTX in the co-

primary endpoint of PFS in the ITT population and in the PD-L1-positive subpopulation [see Section 7.1.1.1].

At the first interim analysis of OS, the co-primary endpoint for the IMpassion130 study, ATZ/nab-PTX did not demonstrate a statistically significant improvement in OS compared with placebo/nab-PTX in the ITT population or in the PD-L1-positive subpopulation, while there was no trend towards shorter OS in the ATZ/nab-PTX group than in the placebo/nab-PTX group in either the ITT population or the PD-L1-positive subpopulation [see Section 7.1.1.1].

The results of primary analysis of PFS and the first interim analysis of OS, and the Kaplan-Meier curves for PFS and OS in the Japanese subgroup of the IMpassion130 study are shown in Tables 4 and 5 and Figures 6, 7, 8, and 9, respectively.

Table 4. Results of primary analysis of PFS in Japanese subgroup (investigator assessment, data cutoff date of April 17, 2018)

	ITT population		PD-L1-positive subpopulation	
	ATZ/nab-PTX	Placebo/nab-PTX	ATZ/nab-PTX	Placebo/nab-PTX
N	34	31	12	13
No. of events (%)	26 (76.5)	28 (90.3)	9 (75.0)	13 (100)
Median [95% CI] (months)	7.36 [5.39, 10.84]	4.63 [3.71, 7.20]	10.84 [5.62, 10.91]	3.84 [3.25, 5.49]
Hazard ratio [95% CI]	0.47 [0.25, 0.90] *1		0.04 [<0.01, 0.35] *2	
P-value (two-sided)	0.0206*3		<0.0001*4	

*1: Cox regression stratified by liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3)
*2: Cox regression stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no)
*3: Log-rank test stratified by liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3)
*4: Log-rank test stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no)

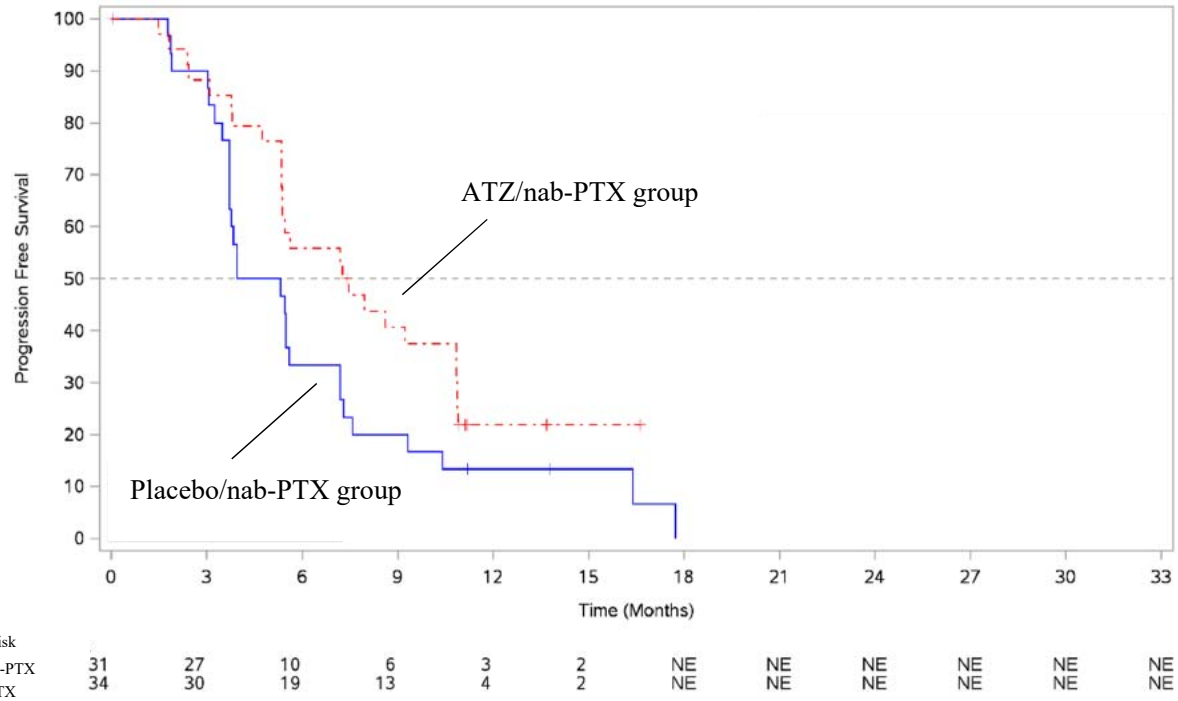


Figure 6. Kaplan-Meier curves for PFS at the time of primary analysis in Japanese subgroup (investigator assessment, ITT population, data cutoff date of April 17, 2018)

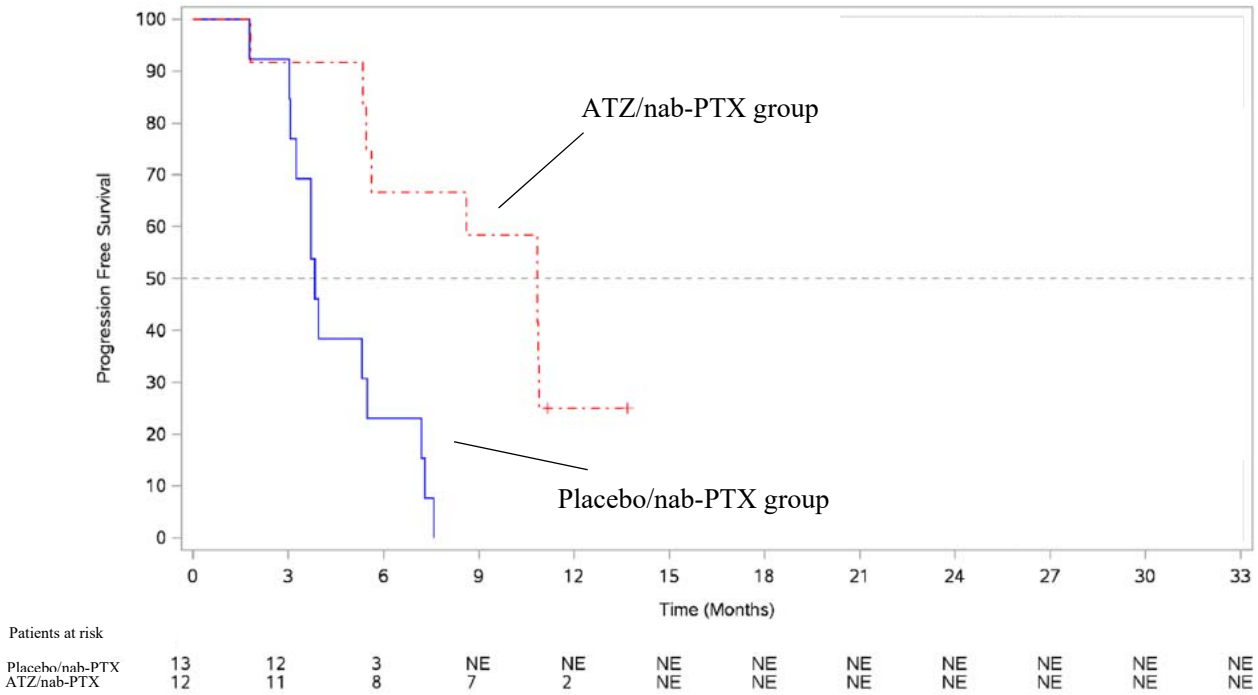


Figure 7. Kaplan-Meier curves for PFS at the time of primary analysis in Japanese subgroup (investigator assessment, PD-L1-positive subpopulation, data cutoff date of April 17, 2018)

Table 5. Results of first interim analysis of OS in Japanese subgroup (data cutoff date of April 17, 2018)

	ITT population		PD-L1-positive subpopulation	
	ATZ/nab-PTX	Placebo/nab-PTX	ATZ/nab-PTX	Placebo/nab-PTX
N	34	31	12	13
No. of events (%)	6 (17.6)	10 (32.3)	1 (8.3)	6 (46.2)
Median [95% CI] (months)	NE [NE, NE]	16.82 [13.27, NE]	NE [NE, NE]	13.27 [11.56, 13.31]
Hazard ratio [95% CI]	0.44 [0.16, 1.24] *1		0.12 [0.01, 0.99] *2	
P-value (two-sided)	0.1121*3		0.0202*4	

*1: Cox regression stratified by liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3)
*2: Cox regression stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no)
*3: Log-rank test stratified by liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3)
*4: Log-rank test stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no)

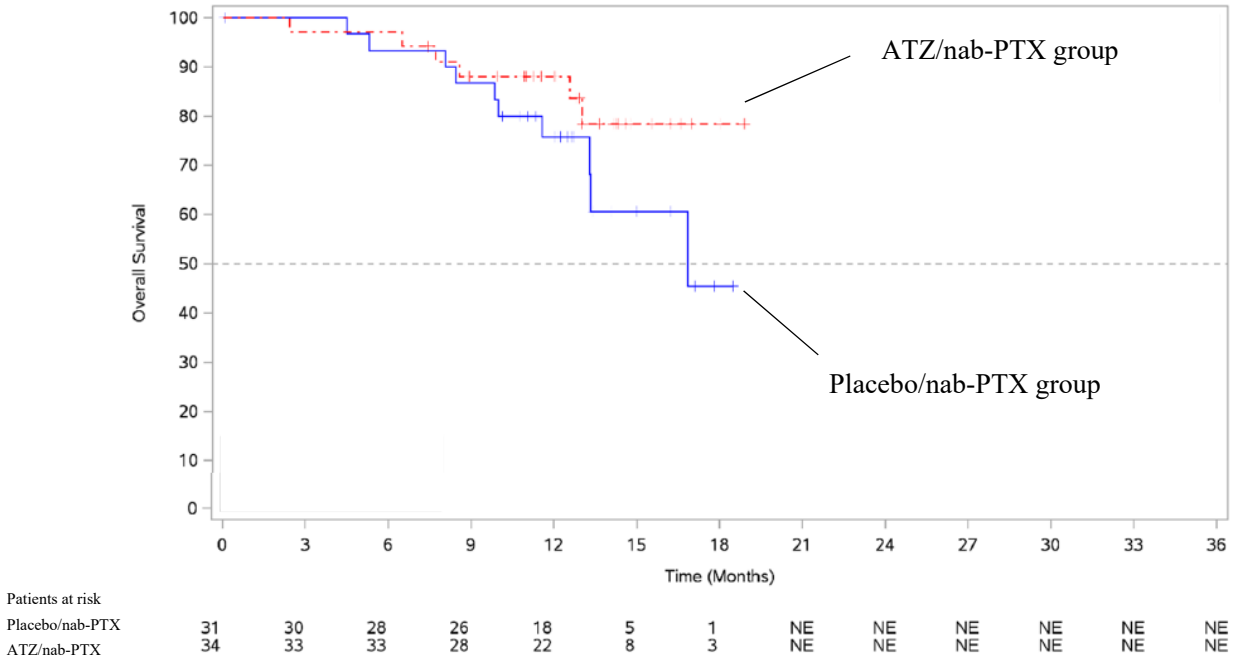


Figure 8. Kaplan-Meier curves for OS at the time of first interim analysis in Japanese subgroup (ITT population, data cutoff date of April 17, 2018)

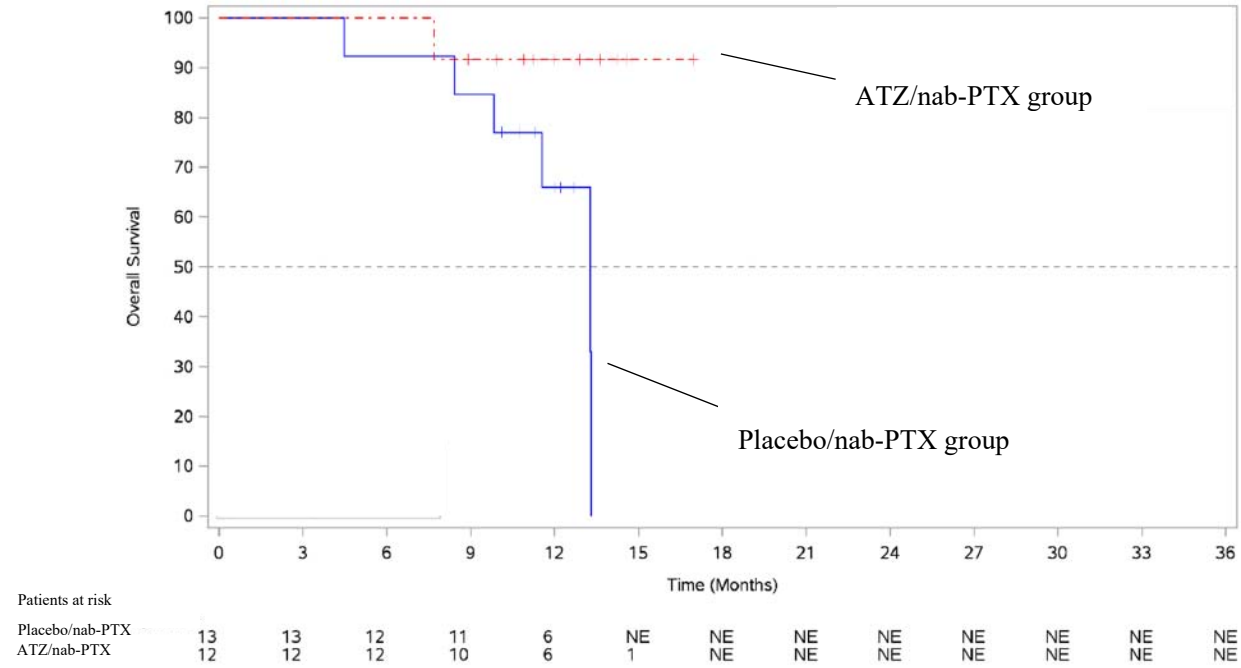


Figure 9. Kaplan-Meier curves for OS at the time of first interim analysis in Japanese subgroup (PD-L1-positive subpopulation, data cutoff date of April 17, 2018)

PMDA's discussion:

For the following reasons etc., PMDA concluded that the efficacy of ATZ/nab-PTX in patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer was demonstrated.

- The superiority of ATZ/nab-PTX over placebo/nab-PTX in the co-primary endpoint of PFS in the PD-L1-positive subpopulation 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/nab-PTX group than in the placebo/nab-PTX group in the PD-L1-positive subpopulation.
- While the number of Japanese patients and the number of events in Japanese patients in the IMpassion130 study were limited, and there are limitations to evaluate the efficacy of ATZ/nab-PTX in Japanese patients based on the PFS results from the Japanese subgroup, there was no trend towards clear differences in the results between the Japanese subgroup and the overall population.

7.R.2 Safety (for adverse events, see Section "7.2 Adverse events etc. observed in clinical studies")

PMDA's conclusion:

Based on the following considerations, adverse events that require particular attention following administration of ATZ/nab-PTX in chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer are the following events that were considered to require attention at the time of the previous approvals of (a) ATZ and (b) nab-PTX (use in the previously approved indications). Attention should be paid to the possible occurrence of these adverse events during treatment with ATZ/nab-PTX.

(a) gastrointestinal disorders, skin disorders, hepatic dysfunction, neuropathies, thyroid dysfunction, adrenal dysfunction, pituitary dysfunction, diabetes mellitus (especially, type 1 diabetes mellitus), interstitial lung disease (ILD), infusion related reaction (IRR), encephalitis/meningitis, pancreatitis, renal dysfunction, myositis/dermatomyositis/rhabdomyolysis, myasthenia gravis, and febrile neutropenia (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of October 23, 2017" etc.)

(b) myelosuppression, infections, neurologic adverse events, cardiovascular adverse events, ILD, cutaneous adverse events, etc. (see Review Report on Abraxane I.V. Infusion 100 mg as of November 11, 2009" etc.)

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

7.R.2.1 Safety profile

The applicant's explanation about the safety profile of ATZ/nab-PTX based on safety information from the IMpassion130 study:

Safety data from the IMpassion130 study are summarized in Table 6.

Table 6. Summary of safety data (IMpassion130 study)

	n (%)	
	ATZ/nab-PTX N = 452	Placebo/nab-PTX N = 438
All adverse events	449 (99.3)	429 (97.9)
Grade ≥3 adverse events	223 (49.3)	186 (42.5)
Adverse events leading to death	6 (1.3)	3 (0.7)
Serious adverse events	103 (22.8)	80 (18.3)
Adverse events leading to treatment discontinuation		
ATZ or Placebo	29 (6.4)	6 (1.4)
nab-PTX	72 (15.9)	36 (8.2)
Adverse events leading to dose interruption		
ATZ or Placebo	139 (30.8)	103 (23.5)
nab-PTX	170 (37.6)	151 (34.5)
Adverse events leading to dose reduction		
nab-PTX	48 (10.6)	39 (8.9)

Adverse events of any grade reported at a ≥5% higher incidence in the ATZ/nab-PTX group than in the placebo/nab-PTX group were nausea (208 subjects [46.0%] in the ATZ/nab-PTX group, 167 subjects [38.1%] in the placebo/nab-PTX group), cough (112 subjects [24.8%], 83 subjects [18.9%]), neutropenia (94 subjects [20.8%], 67 subjects [15.3%]), pyrexia (85 subjects [18.8%], 47 subjects [10.7%]), and hypothyroidism (62 subjects [13.7%], 15 subjects [3.4%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in the ATZ/nab-PTX group than in the placebo/nab-PTX group were peripheral neuropathy (25 subjects [5.5%], 12 subjects [2.7%]). Adverse events leading to study drug discontinuation reported at a ≥2% higher incidence in the ATZ/nab-PTX group than in the placebo/nab-PTX group were peripheral neuropathy (20 subjects [4.4%], 6 subjects [1.4%]). There were no adverse events leading to death, serious adverse events, or adverse events leading to dose interruption or reduction of study drug reported at a ≥2% higher incidence in the ATZ/nab-PTX group than in the placebo/nab-PTX group.

The applicant's explanation about differences in the safety profile between chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer (IMpassion130 study) and chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous (NSQ)-NSCLC (IMpower150 study) (the previously approved indication for which ATZ was used in combination with other anti-neoplastic drugs):

Table 7 shows the results of comparison of the incidence of adverse events between the ATZ/nab-PTX group of the IMpassion130 study and the ATZ/CBDCA/PTX/BV group of the IMpower150 study.

Table 7. Summary of safety data from patients with breast cancer or NSQ-NSCLC (IMpassion130 study and IMpower150 study)

	n (%)	
	Patients with breast cancer	Patients with NSQ-NSCLC
	ATZ/nab-PTX N = 452	ATZ/CBDCA/PTX/BV N = 393
All adverse events	449 (99.3)	386 (98.2)
Grade ≥3 adverse events	223 (49.3)	274 (69.7)
Adverse events leading to death	6 (1.3)	24 (6.1)
Serious adverse events	103 (22.8)	174 (44.3)
Adverse events leading to ATZ discontinuation	29 (6.4)	59 (15.0)
Adverse events leading to ATZ interruption	139 (30.8)	188 (47.8)

Adverse events of any grade reported at a ≥5% higher incidence in patients with breast cancer than in patients with NSQ-NSCLC were alopecia (breast cancer, 255 subjects [56.4%]; NSQ-NSCLC, 187 subjects [47.6%]), fatigue (211 subjects [46.7%], 130 subjects [33.1%]), nausea (208 subjects [46.0%], 154 subjects [39.2%]), cough (112 subjects [24.8%], 77 subjects [19.6%]), headache (105 subjects [23.2%], 61 subjects [15.5%]), oedema peripheral (66 subjects [14.6%], 28 subjects [7.1%]), dizziness (63 subjects [13.9%], 27 subjects [6.9%]), taste abnormality (62 subjects [13.7%], 31 subjects [7.9%]), chills (40 subjects [8.8%], 12 subjects [3.1%]), nail discolouration (34 subjects [7.5%], 0 subjects), hot flush (30 subjects [6.6%], 3 subjects [0.8%]), dry eye (29 subjects [6.4%], 3 subjects [0.8%]), lymphoedema (27 subjects [6.0%], 1 subject [0.3%]), and breast pain (26 subjects [5.8%], 0 subjects). Grade ≥3 adverse events reported at a ≥2% higher incidence in patients with breast cancer than in patients with NSQ-NSCLC were peripheral neuropathy (25 subjects [5.5%], 6 subjects [1.5%]). There were no adverse events leading to death, serious adverse events, or adverse events leading to discontinuation or interruption of ATZ reported at a ≥2% higher incidence in patients with breast cancer than in patients with NSQ-NSCLC.

PMDA's discussion:
In the IMpassion130 study, many of the adverse events reported at a higher incidence in the ATZ/nab-PTX group than in the placebo/nab-PTX group were known adverse events associated with ATZ. Adverse events reported at a higher incidence in patients with breast cancer than in patients with NSQ-NSCLC were known adverse events associated with nab-PTX, and there was no trend towards a higher incidence of serious adverse events.

Based on the above, ATZ is tolerable also in chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for and management of adverse events and interruption of ATZ.

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

The applicant's explanation about differences in the safety of ATZ/nab-PTX between Japanese and non-Japanese populations:
Safety data from Japanese and non-Japanese patients in the IMpassion130 study are summarized in Table 8.

Table 8. Summary of safety data from Japanese and non-Japanese patients (IMpassion130 study)

	n (%)			
	Japanese patients		Non-Japanese patients	
	ATZ/nab-PTX N = 34	Placebo/nab-PTX N = 30	ATZ/nab-PTX N = 418	Placebo/nab-PTX N = 408
All adverse events	34 (100)	30 (100)	415 (99.3)	399 (97.8)
Grade ≥3 adverse events	13 (38.2)	12 (40.0)	210 (50.2)	174 (42.6)
Adverse events leading to death	0	0	6 (1.4)	3 (0.7)
Serious adverse events	4 (11.8)	3 (10.0)	99 (23.7)	77 (18.9)
Adverse events leading to treatment discontinuation				
ATZ	0	0	29 (6.9)	6 (1.5)
nab-PTX	2 (5.9)	0	70 (16.7)	36 (8.8)
Adverse events leading to dose interruption				
ATZ	17 (50.0)	10 (33.3)	122 (29.2)	93 (22.8)
nab-PTX	18 (52.9)	12 (40.0)	152 (36.4)	139 (34.1)
Adverse events leading to dose reduction				
nab-PTX	8 (23.5)	9 (30.0)	40 (9.6)	30 (7.4)

In the ATZ/nab-PTX group, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were alopecia (29 subjects [85.3%] in the Japanese subgroup, 226 subjects [54.1%] in the non-Japanese subgroup), peripheral sensory neuropathy (20 subjects [58.8%], 52 subjects [12.4%]), neutrophil count decreased (15 subjects [44.1%], 42 subjects [10.0%]), nasopharyngitis (11 subjects [32.4%], 38 subjects [9.1%]), rash (10 subjects [29.4%], 68 subjects [16.3%]), white blood cell count decreased (10 subjects [29.4%], 27 subjects [6.5%]), stomatitis (9 subjects [26.5%], 35 subjects [8.4%]), taste abnormality (8 subjects [23.5%], 54 subjects [12.9%]), nail discolouration (7 subjects [20.6%], 27 subjects [6.5%]), paronychia (7 subjects [20.6%], 2 subjects [0.5%]), and malaise (5 subjects [14.7%], 13 subjects [3.1%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (6 subjects [17.6%], 15 subjects [3.6%]) and white blood cell count decreased (4 subjects [11.8%], 4 subjects [1.0%]). Adverse events leading to ATZ interruption reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (7 subjects [20.6%], 5 subjects [1.2%]), leukopenia (2 subjects [5.9%], 3 subjects [0.7%]), and peripheral sensory neuropathy (2 subjects [5.9%], 0 subjects). There were no adverse events leading to death, serious adverse events, or adverse events leading to ATZ discontinuation reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup. Grade ≥3 adverse events and adverse events leading to ATZ interruption reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup, i.e., neutrophil count decreased, white blood cell count decreased, leukopenia, and peripheral sensory neuropathy will not become a particular problem in Japanese patients, given that no serious cases were reported and that none of these events led to ATZ discontinuation, etc.

The incidence of events related to infections resulting from neutropenia[5)] was higher in Japanese patients (64.7%, 22 of 34 patients) than in non-Japanese patients (56.9%, 238 of 418 patients). However, given the following points etc., this finding will not become a particular problem in Japanese patients, though it is difficult to draw a definitive conclusion on the impact of nab-PTX in combination with ATZ on the occurrence

[5)] Events in the MedDRA SOC "infections and infestations"

of these events, etc.

- Most of the events related to infections observed in Japanese patients were of Grade ≤2.
- These events are known adverse events associated with nab-PTX.

PMDA's discussion:

Although the number of Japanese patients included in the IMpassion130 study was limited, and there are limitations to compare the safety between the Japanese and non-Japanese subgroups, given the following points, ATZ/nab-PTX is tolerable also in Japanese patients as long as physicians take appropriate measures, e.g. dose interruption/reduction and discontinuation of ATZ and nab-PTX.

- 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.

Though the number of Japanese patients treated was limited, the incidences of neutropenia, infections, etc., with ATZ/nab-PTX were higher in the Japanese subgroup than in the non-Japanese subgroup. Thus, it is necessary to watch for the occurrence of these events, etc. after the market launch and appropriately provide any new information to healthcare professionals in clinical practice.

7.R.3 Clinical positioning and indication

The proposed indication for ATZ was "PD-L1-positive inoperable or recurrent breast cancer." The following statements were included in the PRECAUTIONS CONCERNING INDICATION section of the proposed package insert.

- The efficacy and safety of ATZ as adjuvant or neoadjuvant chemotherapy have not been established.
- ATZ should be used in patients with PD-L1 expression as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic should be used for testing.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning HR and HER2 status etc. in patients enrolled in the clinical study, and of the efficacy and safety of ATZ.

PMDA's conclusion:

Based on Sections "7.R.1 Efficacy" and "7.R.2 Safety" and the following considerations, the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section, and then the proposed indication for ATZ should be amended to "PD-L1-positive, hormone-receptor-negative and HER2-negative inoperable or recurrent breast cancer."

- The efficacy and safety of ATZ as pre-operative systemic therapy or systemic adjuvant therapy have not been established.
- ATZ should be used in patients with PD-L1 expression as detected by testing performed by a pathologist or laboratory with adequate experience in determination of the proportion of tumor area occupied by

PD-L1-expressing tumor-infiltrating immune cells. The approved *in vitro* diagnostic should be used for testing.

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

ATZ for chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer is described as follows in the major Japanese/foreign clinical practice guidelines and textbook of clinical oncology.

- NCCN guidelines (v.1.2019)
  ATZ/nab-PTX is recommended as a treatment option for chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer.
- US National Cancer Institute Physician Data Query (NCI PDQ) (Updated: March 15, 2019)
  In the IMpassion130 study in chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer, ATZ/nab-PTX significantly prolonged PFS compared with placebo/nab-PTX in the PD-L1-positive subpopulation. In this subpopulation, OS was longer with ATZ/nab-PTX compared with placebo/nab-PTX.

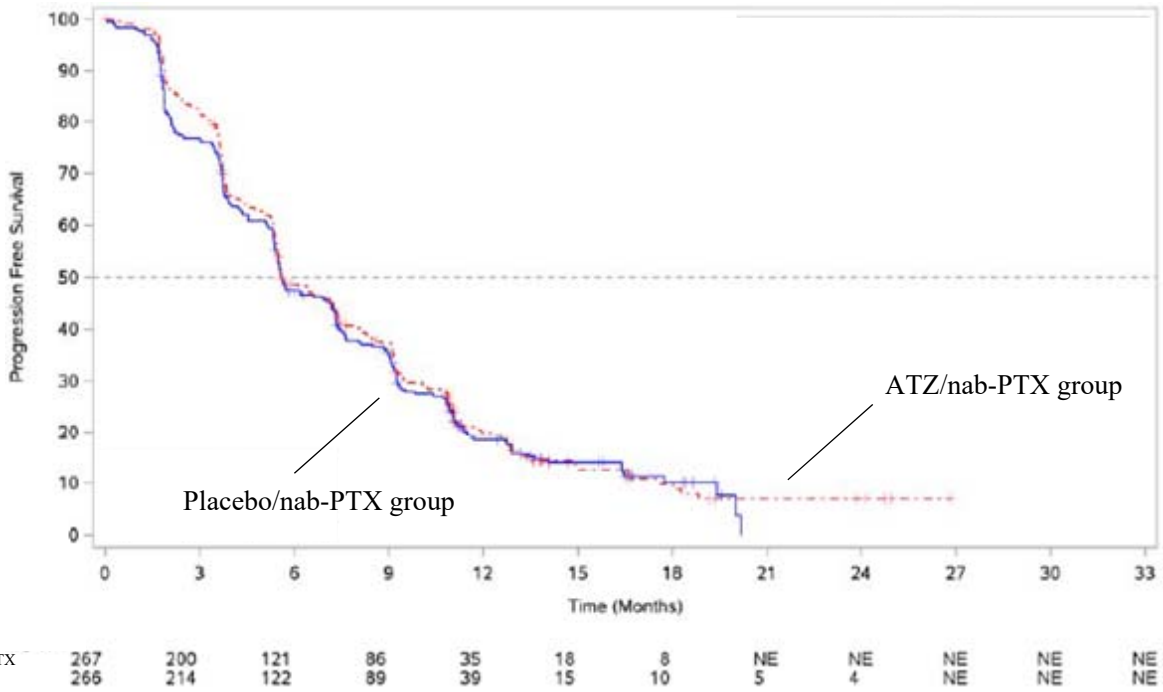
The applicant's explanation about the clinical positioning of ATZ and the indication:
The IMpassion130 study demonstrated the superiority of ATZ/nab-PTX over placebo/nab-PTX in the co-primary endpoint of PFS in the ITT population and in the PD-L1-positive subpopulation [see Section 7.1.1.1]. On the other hand, the results of primary analysis of PFS and the Kaplan-Meier curves for PFS by PD-L1 expression status in the ITT population of the study are shown in Table 9 and Figures 10 and 11, respectively, and higher efficacy was suggested in the PD-L1-positive subpopulation than in the PD-L1-negative[6)] subpopulation. Thus, the target population for ATZ/nab-PTX should be patients with PD-L1-positive inoperable or recurrent breast cancer.

Table 9. Results of primary analysis of PFS by PD-L1 expression status (investigator assessment, data cutoff date of April 17, 2018)

PD-L1 expression	Treatment group	N	PFS		
			Median [95% CI] (months)	Hazard ratio* [95% CI]	*P*-value for interaction
PD-L1-negative	ATZ/nab-PTX	266	5.59 [5.45, 7.26]	0.94 [0.78, 1.13]	0.0052
	Placebo/nab-PTX	267	5.59 [5.39, 7.20]		
PD-L1-positive	ATZ/nab-PTX	185	7.46 [6.70, 9.23]	0.62 [0.49, 0.78]	
	Placebo/nab-PTX	184	4.96 [3.81, 5.55]		

*: Proportional hazard model stratified by liver metastases (yes vs. no) and prior taxane treatment (yes vs. no)

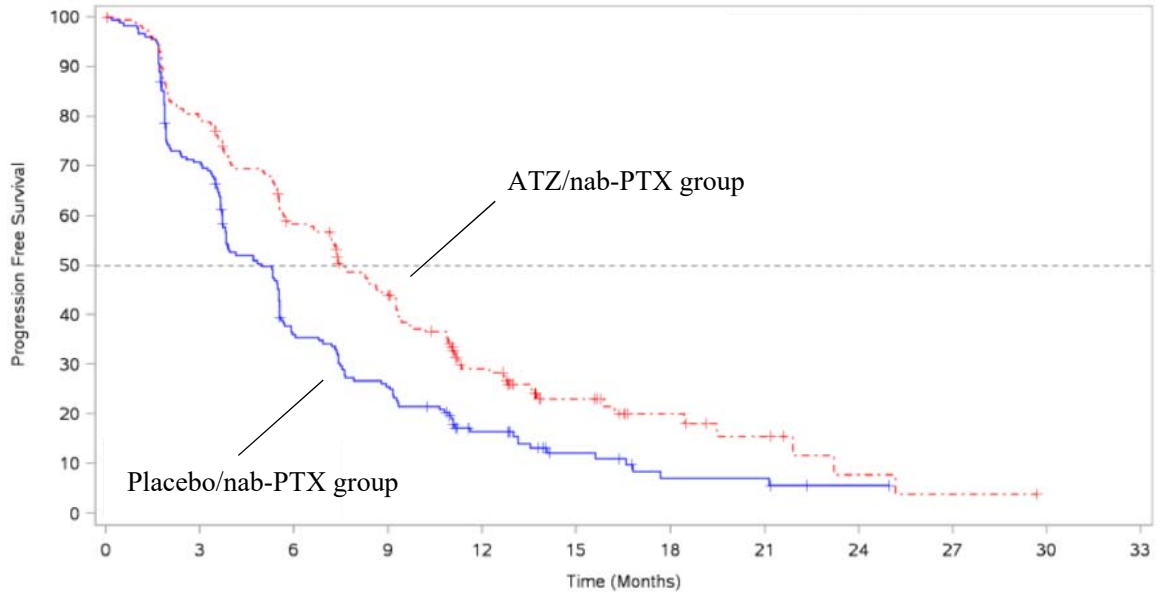
6) The PD-L1-negative subpopulation was defined as patients whose PD-L1 status was IC0.



Patients at risk

Placebo/nab-PTX	267	200	121	86	35	18	8	NE	NE	NE	NE	NE
ATZ/nab-PTX	266	214	122	89	39	15	10	5	4	NE	NE	NE

Figure 10. Kaplan-Meier curves for PFS at the time of primary analysis by PD-L1 expression status (investigator assessment, PD-L1-negative population, data cutoff date of April 17, 2018)



Patients at risk

Placebo/nab-PTX	184	127	62	44	22	11	5	5	1	NE	NE	NE
ATZ/nab-PTX	185	146	104	75	38	19	10	6	2	1	NE	NE

Figure 11. Kaplan-Meier curves for PFS at the time of primary analysis by PD-L1 expression status (investigator assessment, PD-L1-positive subpopulation, data cutoff date of April 17, 2018)

In the IMpassion130 study, Roche Diagnostics' "VENTANA OptiView PD-L1 (SP142)" was used to measure PD-L1 expression in tumor specimens. Patients whose PD-L1 status was assessed with this assay were enrolled in the study [see Section 7.1.1.1], and the efficacy and safety of ATZ were demonstrated. Thus, also after the market launch, "VENTANA OptiView PD-L1 (SP142)" should be used to select patients, and the relevant statement should be included in the PRECAUTIONS CONCERNING INDICATION section.

Based on the above, the information on the patient population of the IMpassion130 study (HR-negative, HER2-negative) was included in the CLINICAL STUDIES section of the proposed package insert, and the following statements were included in the PRECAUTIONS CONCERNING INDICATION section. Then, the indication of "PD-L1-positive inoperable or recurrent breast cancer" was proposed.

- The efficacy and safety of ATZ as adjuvant or neoadjuvant chemotherapy have not been established.
- ATZ should be used in patients with PD-L1 expression as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic should be used for testing.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning HR and HER2 status etc. in patients enrolled in the clinical study, and of the efficacy and safety of ATZ.

PMDA's discussion:
The patient population of the IMpassion130 study was patients with HR-negative and HER2-negative breast cancer. The Japanese and foreign clinical practice guidelines make a clear distinction between the treatment paradigms for HR-positive/HER2-positive and HR-negative/HER2-negative breast cancer, and given that these treatment paradigms are widely accepted in clinical practice, etc., the INDICATION section should clarify that the target population for ATZ is patients with HR-negative and HER2-negative breast cancer.

Based on the above, the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section, and then the appropriate indication for ATZ is "PD-L1-positive, hormone-receptor-negative and HER2-negative inoperable or recurrent breast cancer."

- The efficacy and safety of ATZ as pre-operative systemic therapy or systemic adjuvant therapy have not been established.
- ATZ should be used in patients with PD-L1 expression as detected by testing performed by a pathologist or laboratory with adequate experience in determination of the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells. The approved *in vitro* diagnostic should be used for testing.

7.R.4 Dosage and administration

The proposed dosage and administration statement for ATZ in the present application was "*Atezolizumab in combination with paclitaxel*; The usual adult dosage is 840 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 2 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes." The following statements were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert.

- Treatment with ATZ should be initiated with paclitaxel. Other anti-neoplastic drugs for combination with ATZ should be selected with a full understanding of the information presented in the CLINICAL STUDIES section.
- If ATZ is used in combination with other anti-neoplastic drugs, carefully read the package inserts for the concomitant drugs.

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

PMDA's conclusion:
Based on Sections "7.R.1 Efficacy" and "7.R.2 Safety" and the following considerations, the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement for ATZ should be amended to "*Atezolizumab in combination with paclitaxel (albumin-bound);* The usual adult dosage is 840 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 2 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes."
- Infusion solution preparation procedure
- Recommended ATZ dosage modifications for adverse reactions

7.R.4.1 Dosage and administration of ATZ
The applicant's explanation about the dosing rationale for ATZ:
The dosing regimen for the IMpassion130 study was selected based on the following study results etc., and the IMpassion130 study demonstrated the clinical usefulness of ATZ in combination with nab-PTX in chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer. Thus, the proposed dosing regimen for ATZ was selected based on the IMpassion130 study.
- Taking account of the considerations based on the results from a Japanese phase I study (Study JO28944) and a foreign phase I study (Study PCD4989g), the fixed dosing regimen of 1200 mg Q3W was selected (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of October 23, 2017").
- Since ATZ exposure was generally dose-proportional over the dose range of 1 to 20 mg/kg (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of October 23, 2017"), there should be no differences in the total exposure to ATZ between 1200 mg Q3W and 800 mg Q2W. However, ATZ is formulated at a concentration of 60 mg/mL, and in the interest of simplifying administration, 840 mg Q2W was considered appropriate.

With respect to the infusion time of ATZ, based on the infusion time specified in the IMpassion130 study, the following statements will be included in the DOSAGE AND ADMINISTRATION section: Administer the initial infusion of ATZ over 60 minutes; and if the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes. Furthermore, as there are no clinical study data from chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer treated with ATZ in combination with anti-neoplastic drugs other than nab-PTX, the following statements will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section: Other anti-neoplastic drugs for combination with ATZ should be selected with a full understanding of the information presented in the CLINICAL STUDIES section; and if ATZ is used in combination with other anti-neoplastic drugs, carefully read the package inserts for the concomitant drugs.

The IMpassion130 study was conducted according to the ATZ dosage modification guidelines for adverse

events, which are similar to those in the approved package insert, and the study demonstrated the clinical usefulness of ATZ/nab-PTX in the PD-L1-positive subpopulation. Thus, recommended ATZ dosage modifications in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the current package insert will be unchanged in the present application.

PMDA's discussion:
The dosing regimen of ATZ for the IMpassion130 study needed more consideration because there were no clinical study data on the PK etc. of ATZ Q2W at the time of initiating the study. Meanwhile, taking also into account that the study demonstrated the clinical usefulness of ATZ at the selected dosing regimen of 840 mg Q2W, PMDA accepted the applicant's explanation (ATZ 840 mg Q2W was proposed). However, as the IMpassion130 study demonstrated the clinical usefulness of ATZ/nab-PTX only, this information needs to be specified in the DOSAGE AND ADMINISTRATION section.

Based on the above, the proposed dosage and administration statement for ATZ in chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer should be amended as shown below. (1) "Other anti-neoplastic drugs for combination with ATZ should be selected with a full understanding of the information presented in the CLINICAL STUDIES section" and (2) "if ATZ is used in combination with other anti-neoplastic drugs, carefully read the package inserts for the concomitant drugs" in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert in the present application are unnecessary because (1) this information will be specified in the DOSAGE AND ADMINISTRATION section, and (2) this is general information, and not the point that should be noted specifically for administration of ATZ.

Dosage and Administration
Atezolizumab in combination with paclitaxel (albumin-bound)
The usual adult dosage is 840 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 2 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

7.R.5 Post-marketing investigations

Taking account of the occurrence of adverse events etc. in the IMpassion130 study, the applicant included the safety of ATZ when administered with chemotherapy in the safety specification, and is planning to conduct a post-marketing database survey in patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer to compare the incidence of severe infections (pneumonia, etc.) with ATZ/nab-PTX with that with nab-PTX or PTX in clinical practice, after considering the feasibility etc. of the survey and choosing nab-PTX or PTX as comparators.

PMDA's discussion:
Given the considerations in Section "7.R.2 Safety," and since the results of a use-results survey in patients with unresectable advanced or recurrent NSCLC (the previously approved indication) have not become available,

and information concerning neutropenia is useful for investigating the cause of severe infections, etc., neutropenia, in addition to severe infections, should be included in the safety specification, and it is necessary to investigate the occurrence of these events after the market launch.

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

7.2 Adverse events etc. observed in clinical studies

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

7.2.1 Global phase III study (IMpassion130 study)

Adverse events occurred in 449 of 452 subjects (99.3%) in the ATZ/nab-PTX group and 429 of 438 subjects (97.9%) in the placebo/nab-PTX group, and those for which a causal relationship to study drug could not be ruled out occurred in 436 of 452 subjects (96.5%) in the ATZ/nab-PTX group and 410 of 438 subjects (93.6%) in the placebo/nab-PTX group. Adverse events reported by ≥15% of subjects in either group are shown in Table 10.

Table 10. Adverse events reported by ≥15% of subjects in either group

SOC PT (MedDRA/J ver.21.0)	n (%)			
	ATZ/nab-PTX N = 452		Placebo/nab-PTX N = 438	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	449 (99.3)	223 (49.3)	429 (97.9)	186 (42.5)
General disorders and administration site conditions				
Fatigue	211 (46.7)	18 (4.0)	196 (44.7)	15 (3.4)
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0
Oedema peripheral	66 (14.6)	1 (0.2)	68 (15.5)	6 (1.4)
Skin and subcutaneous tissue disorders				
Alopecia	255 (56.4)	3 (0.7)	252 (57.5)	1 (0.2)
Rash	78 (17.3)	2 (0.4)	72 (16.4)	2 (0.5)
Gastrointestinal disorders				
Nausea	208 (46.0)	5 (1.1)	167 (38.1)	8 (1.8)
Diarrhoea	147 (32.5)	6 (1.3)	150 (34.2)	9 (2.1)
Constipation	113 (25.0)	3 (0.7)	108 (24.7)	1 (0.2)
Vomiting	88 (19.5)	4 (0.9)	74 (16.9)	5 (1.1)
Nervous system disorders				
Headache	105 (23.2)	2 (0.4)	96 (21.9)	4 (0.9)
Neuropathy peripheral	98 (21.7)	25 (5.5)	97 (22.1)	12 (2.7)
Peripheral sensory neuropathy	72 (15.9)	9 (2.0)	52 (11.9)	8 (1.8)
Musculoskeletal and connective tissue disorders				
Arthralgia	81 (17.9)	1 (0.2)	70 (16.0)	1 (0.2)
Back pain	69 (15.3)	6 (1.3)	58 (13.2)	2 (0.5)
Myalgia	64 (14.2)	2 (0.4)	67 (15.3)	3 (0.7)
Respiratory, thoracic and mediastinal disorders				
Cough	112 (24.8)	0	83 (18.9)	0
Dyspnoea	72 (15.9)	4 (0.9)	64 (14.6)	3 (0.7)
Blood and lymphatic system disorders				
Anaemia	125 (27.7)	13 (2.9)	115 (26.3)	13 (3.0)
Neutropenia	94 (20.8)	37 (8.2)	67 (15.3)	36 (8.2)
Metabolism and nutrition disorders				
Decreased appetite	91 (20.1)	3 (0.7)	79 (18.0)	3 (0.7)

Serious adverse events occurred in 103 of 452 subjects (22.8%) in the ATZ/nab-PTX group and 80 of 438 subjects (18.3%) in the placebo/nab-PTX group. Those reported by ≥5 subjects in each group were pneumonia (10 subjects [2.2%]); and pyrexia; dyspnoea; and urinary tract infection (5 subjects each [1.1%]) in the ATZ/nab-PTX group and pneumonia (5 subjects [1.1%]) in the placebo/nab-PTX group. A causal relationship to study drug could not be ruled out for pneumonia (5 subjects); dyspnoea (4 subjects); and pyrexia (1 subject) in the ATZ/nab-PTX group and pneumonia (2 subjects) in the placebo/nab-PTX group.

Adverse events leading to study drug discontinuation occurred in 72 of 452 subjects (15.9%) in the ATZ/nab-PTX group and 36 of 438 subjects (8.2%) in the placebo/nab-PTX group. Those reported by ≥5 subjects in each group were peripheral neuropathy (20 subjects [4.4%]); peripheral sensory neuropathy (9 subjects [2.0%]); fatigue (6 subjects [1.3%]); and polyneuropathy (5 subjects [1.1%]) in the ATZ/nab-PTX group and peripheral sensory neuropathy (8 subjects [1.8%]); and peripheral neuropathy; and fatigue (6 subjects each [1.4%]) in the placebo/nab-PTX group. A causal relationship to study drug could not be ruled out for peripheral neuropathy (20 subjects); peripheral sensory neuropathy (9 subjects); fatigue (6 subjects); and polyneuropathy (5 subjects) in the ATZ/nab-PTX group and peripheral sensory neuropathy (8 subjects); and peripheral neuropathy; and fatigue (6 subjects each) in the placebo/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 inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

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

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

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

On the basis of the data submitted, PMDA has concluded that ATZ/nab-PTX has efficacy in the treatment of PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer, and that ATZ/nab-PTX has acceptable safety in view of its benefits. ATZ/nab-PTX is clinically meaningful because it offers a treatment option for patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer. PMDA considers that the indication etc. need to be further discussed.

PMDA has concluded that ATZ/nab-PTX may be approved for the treatment of PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer if ATZ/nab-PTX is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 7, 2019

Product Submitted for Approval

Brand Name	Tecentriq Intravenous Infusion 840 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	December 21, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

A global phase III study in chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer (IMpassion130 study) demonstrated the superiority of ATZ/nab-PTX over placebo/nab-PTX in the co-primary endpoint of PFS in the PD-L1-positive subpopulation.

PMDA's conclusion:

Based on the considerations in Section "7.R.1 Efficacy" in the Review Report (1), given the above results etc., the efficacy of ATZ/nab-PTX was demonstrated in chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer.

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

1.2 Safety

PMDA's conclusion:

Based on the considerations in Section 7.R.2 Safety" in the Review Report (1), attention should be paid to the possible occurrence of the following events that were considered to require attention at the time of the previous approval of (a) ATZ and (b) nab-PTX (use in the previously approved indications), during treatment with ATZ/nab-PTX in chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer.

(a) gastrointestinal disorders, skin disorders, hepatic dysfunction, neuropathies, thyroid dysfunction, adrenal dysfunction, pituitary dysfunction, diabetes mellitus (especially, type 1 diabetes mellitus), ILD, IRR, encephalitis/meningitis, pancreatitis, renal dysfunction, myositis/dermatomyositis/rhabdomyolysis, myasthenia gravis, and febrile neutropenia
(b) myelosuppression, infections, neurologic adverse events, cardiovascular adverse events, ILD, cutaneous adverse events, etc.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with ATZ/nab-PTX, ATZ/nab-PTX 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 and nab-PTX.

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

1.3 Clinical positioning and indication

PMDA's conclusion:

Based on the considerations in Section "7.R.3 Clinical positioning and indication" in the Review Report (1), the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section, and then the appropriate indication for ATZ is "PD-L1-positive, hormone-receptor-negative and HER2-negative inoperable or recurrent breast cancer."

Precautions Concerning Indication

- The efficacy and safety of ATZ as pre-operative systemic therapy or systemic adjuvant therapy have not been established.
- ATZ should be used in patients with PD-L1 expression as detected by testing performed by a pathologist or laboratory with adequate experience in determination of the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells. The approved *in vitro* diagnostic should be used for testing.

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

Based on the above, PMDA instructed the applicant to amend the INDICATION and PRECAUTIONS CONCERNING INDICATION sections accordingly. The applicant agreed.

1.4 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.4 Dosage and administration" in the Review Report (1), the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement for ATZ should be

amended to "*Atezolizumab in combination with paclitaxel (albumin-bound);* The usual adult dosage is 840 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 2 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes."

Precautions Concerning Dosage and Administration

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

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

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

1.5 Risk management plan (draft)

Taking account of the occurrence of adverse events etc. in the IMpassion130 study, the applicant included the safety of ATZ when administered with chemotherapy in the safety specification, and then is planning to conduct a post-marketing database survey in patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer to compare the incidence of severe infections (pneumonia, etc.) with ATZ/nab-PTX with that with nab-PTX or PTX.

PMDA's conclusion:
Based on the considerations in Section "7.R.5 Post-marketing investigations" in the Review Report (1), given that information concerning neutropenia is useful for investigating the cause of severe infections, neutropenia, in addition to severe infections, should be included in the safety specification, and it is necessary to investigate the occurrence of these 2 events with ATZ/nab-PTX and that with nab-PTX or PTX in patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer after the market launch.

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

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

The applicant's response:

- A post-marketing database survey will be conducted to investigate the occurrence of severe infections in patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer treated with ATZ/nab-PTX.
- Infections when combined with chemotherapy will be included in the safety specification, and the relationship of severe infections, and neutropenia, which is considered to result in severe infections, to ATZ, etc., in patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast

cancer, will be assessed by comparing the incidence of severe infections/neutropenia with ATZ/nab-PTX with that with nab-PTX or PTX.

PMDA accepted the applicant's response.

In view of the discussion above and the considerations in Section "7.R.2 Safety" in the Review Report (1), PMDA has concluded that the risk management plan (draft) for ATZ should include the safety specification presented in Table 11, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 12.

Table 11. 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		

Underline denotes new additions.
Wavy line denotes additions expected to be made in the review for SCLC (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of July 24, 2019").

Table 12. Summary of additional pharmacovigilance activities, surveillance/studies for efficacy, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillance/studies for efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy • Use-results survey in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy (all-case surveillance) • Post-marketing database survey in chemotherapy-naïve patients with unresectable advanced or recurrent NSQ-NSCLC (hematologic toxicity when combined with chemotherapy [febrile neutropenia]) • Post-marketing database survey in patients with extensive-stage SCLC (hematologic toxicity when combined with chemotherapy [neutropenia, 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, and IMpassion130) • Post-marketing clinical study (Study BO39633-01)	None	• Disseminate data gathered during early post-marketing phase vigilance. • Develop information materials to be distributed to healthcare professionals. • Develop information materials to be distributed to patients.

Underline denotes planned activities for the additional dosage regimen in the present application.
Wavy line denotes planned activities for SCLC (see "Review Report on Tecentriq Intravenous Infusion 1200 mg as of July 24, 2019").

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

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

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

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

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

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following 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 reexamination period for the present application is the remainder of the reexamination period for the initial approval of the product (until January 18, 2026).

Indication

PD-L1-positive, hormone-receptor-negative and HER2-negative inoperable or recurrent breast cancer

Dosage and Administration

Atezolizumab in combination with paclitaxel (albumin-bound)

The usual adult dosage is 840 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 2 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

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

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

Precautions Concerning Indication

1. The efficacy and safety of ATZ as pre-operative systemic therapy or systemic adjuvant therapy have not been established.
2. ATZ should be used in patients with PD-L1 expression as detected by testing performed by a pathologist or laboratory with adequate experience in determination of the proportion of tumor area occupied by

PD-L1-expressing tumor-infiltrating immune cells. The approved *in vitro* diagnostic should be used for testing.

Precautions Concerning Dosage and Administration

1. Fourteen mL of ATZ 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.
2. 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 • Symptomatic hyperthyroidism, or asymptomatic hyperthyroidism with thyroid stimulating hormone <0.1 mU/L	Withhold dose until resolution.
	Grade ≥2 adrenal insufficiency	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	• Grade 2 or 3 hypophysitis • Grade 2 or 3 hypopituitarism	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	• Grade 4 or recurrent hypophysitis • Grade 4 or recurrent hypopituitarism	Permanently discontinue
Encephalitis, Meningitis	All Grades	Permanently discontinue
Neuropathies	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue
	Any grade of Guillain-Barre syndrome	Permanently discontinue
Myasthenia gravis	All Grades	Permanently discontinue
Skin disorders	Grade 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade 4	Permanently discontinue
Nephritis	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue

Ophthalmopathies	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks.
	Grade ≥3	Permanently discontinue
Infusion reaction	Grade 1	Reduce the infusion rate by 50%. Monitor for 30 minutes after symptoms have improved, and if the event does not recur, the infusion rate may be increased back to baseline.
	Grade 2	Interrupt infusion, and resume infusion at a 50% reduction in rate after symptoms have improved.
	Grade ≥3	Discontinue infusion immediately

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

Appendix

List of Abbreviations

a partial change application	an application for partial change of marketing approval
ATZ	atezolizumab (genetical recombination)
ATZ/CBDCA/PTX/BV	the combination of ATZ, CBDCA, PTX, and BV
ATZ/nab-PTX	the combination of ATZ and nab-PTX
BIRCH study	Study GO28754
BV	bevacizumab (genetical recombination)
CBDCA	carboplatin
CI	confidence interval
C_{min}	minimum serum concentration
DTX	docetaxel hydrate
HER	human epidermal growth factor receptor
HR	hormone receptor (estrogen receptor or progesterone receptor)
IC	the proportion of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC0	<1% 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
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IMpassion130 study	Study WO29522
IMpower133 study	Study GO30081
IMpower150 study	Study GO29436
IRR	infusion related reaction
ITT	intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
nab-PTX	paclitaxel (albumin-bound)
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Breast Cancer
NCI PDQ	National Cancer Institute Physician Data Query
NE	not estimable
NSCLC	non-small cell lung cancer
NSQ-NSCLC	non-squamous non-small cell lung cancer
OAK study	Study GO28915
OS	overall survival
PD-L	programmed cell death-ligand
PD-1	programmed cell death-1
PFS	progression free survival
PK	pharmacokinetics
placebo/nab-PTX	the combination of placebo and nab-PTX
PMDA	Pharmaceuticals and Medical Devices Agency
PTX	paclitaxel
QW dosing	dosing on Days 1, 8, and 15 of each 28-day cycle
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	small cell lung cancer
SOC	system organ class