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	Abraxane I.V. Infusion 100 mg
Non-proprietary Name	Paclitaxel (JAN*)
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	November 30, 2018
Dosage Form/Strength	For injectable suspension, lyophilized powder for reconstitution before use: Each vial contains 100 mg of paclitaxel.
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 atezolizumab (genetical recombination) has efficacy in the treatment of breast cancer, and that the combination has acceptable safety in view of its benefits (see Attachment).

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

Indications

Breast cancer, gastric cancer, non-small cell lung cancer, and unresectable pancreatic cancer

(No change)

Dosage and Administration

Use Regimen A or E for breast cancer, Regimen A or D for gastric cancer, Regimen B for non-small cell lung cancer, and Regimen C for unresectable pancreatic cancer.

Regimen A

The usual adult dosage is 260 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes on Day 1 followed by a rest period of at least 20 days. This 21-day cycle should be repeated. The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen B

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks in a 21-day cycle. nab-PTX should be administered at an interval of at least 6 days. This 21-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen C

nab-PTX in combination with gemcitabine

The usual adult dosage is 125 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen D

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen E

nab-PTX in combination with atezolizumab (genetical recombination)

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

(Underline denotes additions.)

**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	Abraxane I.V. Infusion 100 mg
Non-proprietary Name	Paclitaxel
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	November 30, 2018
Dosage Form/Strength	For injectable suspension, lyophilized powder for reconstitution before use: Each vial contains 100 mg of paclitaxel.

Proposed Indications

Breast cancer, gastric cancer, non-small cell lung cancer, and unresectable pancreatic cancer

(No change)

Proposed Dosage and Administration

Use Regimen A or E for breast cancer, Regimen A or D for gastric cancer, Regimen B for non-small cell lung cancer, and Regimen C for unresectable pancreatic cancer.

Regimen A

The usual adult dosage is 260 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes on Day 1 followed by a rest period of at least 20 days. This 21-day cycle should be repeated.
The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen B

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks in a 21-day cycle. nab-PTX should be administered at an interval of at least 6 days. This 21-day cycle should be repeated.
The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen C

nab-PTX in combination with gemcitabine

The usual adult dosage is 125 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.
The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen D

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen E

nab-PTX in combination with other anti-neoplastic drugs

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

(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

Nanoparticle albumin-bound paclitaxel (nab-PTX) is a human serum albumin-bound formulation of paclitaxel discovered by Abraxis BioScience (the US).

In Japan, nab-PTX was approved for the indication of breast cancer in July 2010, for the indications of non-small cell lung cancer and gastric cancer in February 2013, and for the indication of unresectable pancreatic cancer in December 2014. The once-weekly (QW) dosing regimen of nab-PTX was also approved for gastric cancer in August 2017.

1.2 Development history etc.

In Japan, a regimen of nab-PTX 260 mg/m^2 Q3W has been approved for breast cancer.

In the clinical development of atezolizumab (genetical recombination) (ATZ)/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. The applicant has filed a partial change application for an additional dosing regimen for nab-PTX, i.e. nab-PTX 100 mg/m^2 QW in combination with ATZ, for the treatment of breast cancer, based on the results from the IMpassion130 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

Since the present application is intended for a new dosage, no data relating to non-clinical pharmacology 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 nab-PTX, etc., 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 biopharmaceutic data and the clinical pharmacology data were previously evaluated for the initial approval of nab-PTX, etc., and no new study data have been submitted.

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. The applicant also submitted the results from 2 studies (1 Japanese phase I study and 1 Japanese phase II study) as reference data.

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	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
Reference	Japan	J-0102	I	Chemotherapy-naïve patients with HER2-negative inoperable or recurrent breast cancer	6	nab-PTX 150 mg/m^2 intravenously on Days 1, 8, and 15 of each 28-day cycle	Safety PK
	Japan	J-0201	II	Chemotherapy-naïve patients with HER2-negative inoperable or recurrent breast cancer	200 (a) 100 (b) 100	(a) nab-PTX 150 mg/m^2 intravenously on Days 1, 8, and 15 of each 28-day cycle (b) DTX 75 mg/m^2 intravenously every 3 weeks	Efficacy Safety

The clinical studies are summarized below. The main adverse events other than deaths observed in the clinical studies are described in Section "7.3 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[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 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 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,

[1)] 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.

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 programmed cell death-ligand 1 (PD-L1)-positive[2)] 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[3)] 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.

[2)] 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.

[3)] 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

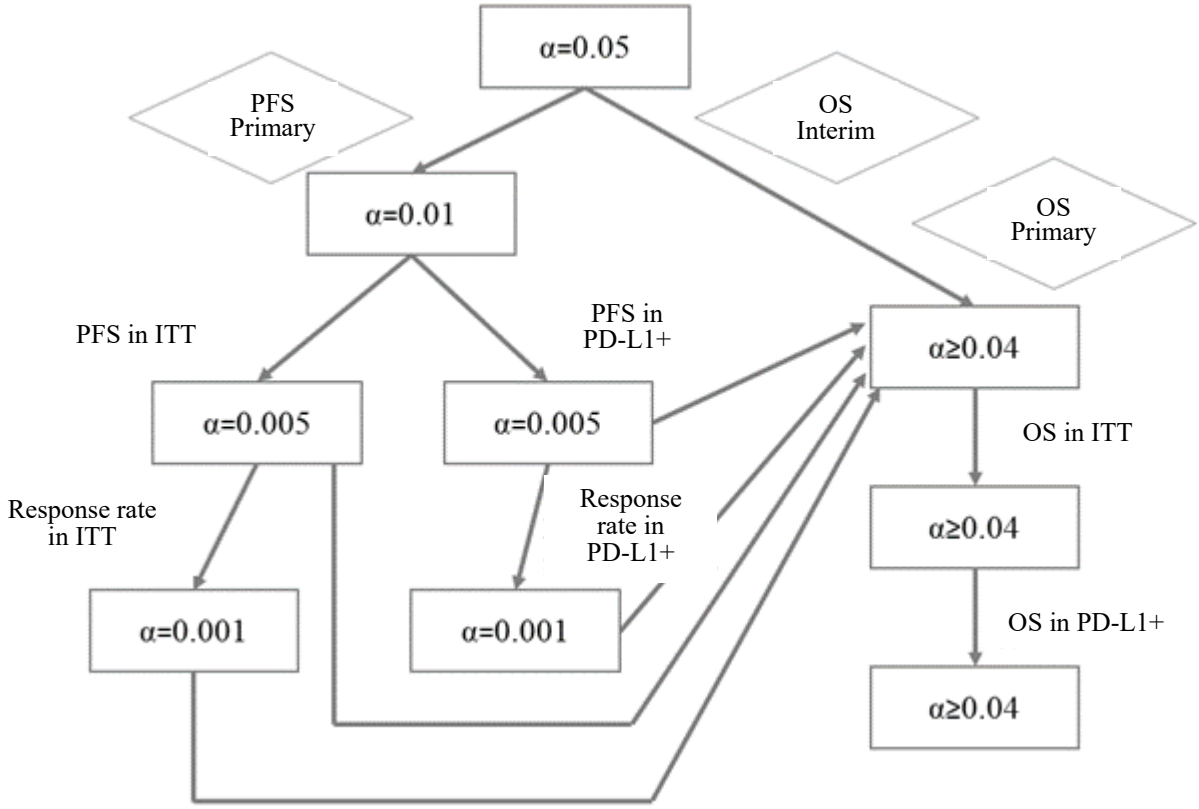

Figure 1. Testing procedure for PFS, response rate, and OS and allocation of alpha (two-sided)

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

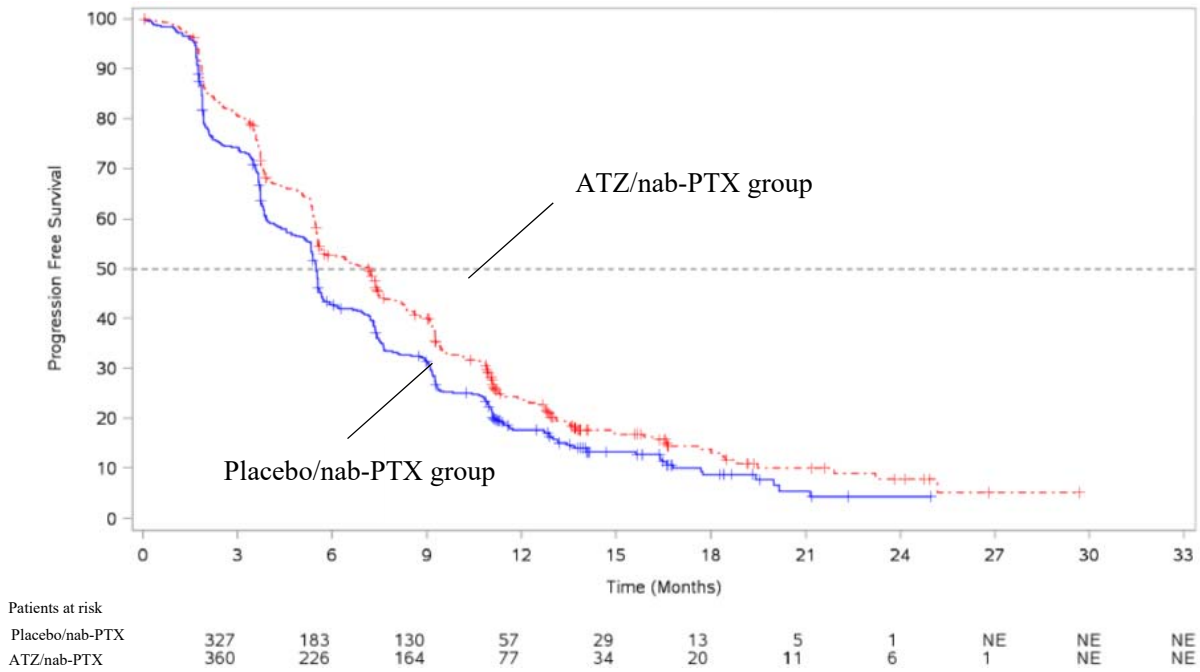

Figure 2. Kaplan-Meier curves for PFS at the time of primary analysis (investigator assessment, ITT population, data cutoff date of April 17, 2018)

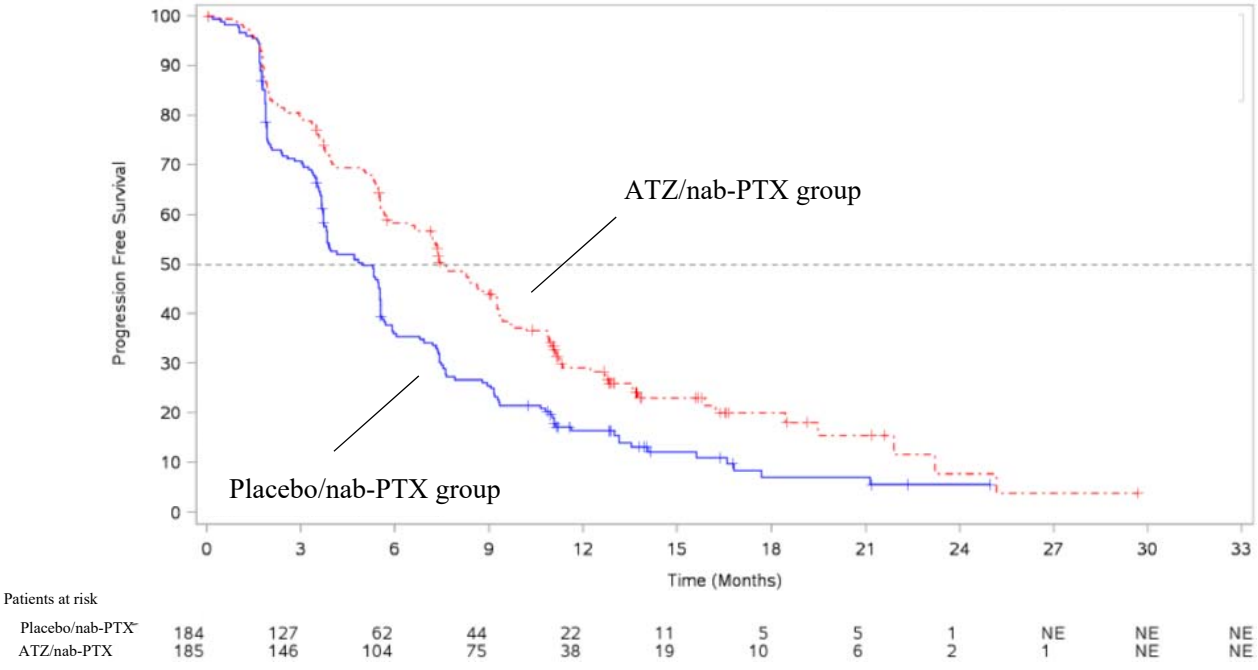

Figure 3. Kaplan-Meier curves for PFS at the time of primary analysis (investigator assessment, PD-L1-positive subpopulation, data cutoff date of April 17, 2018)

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)

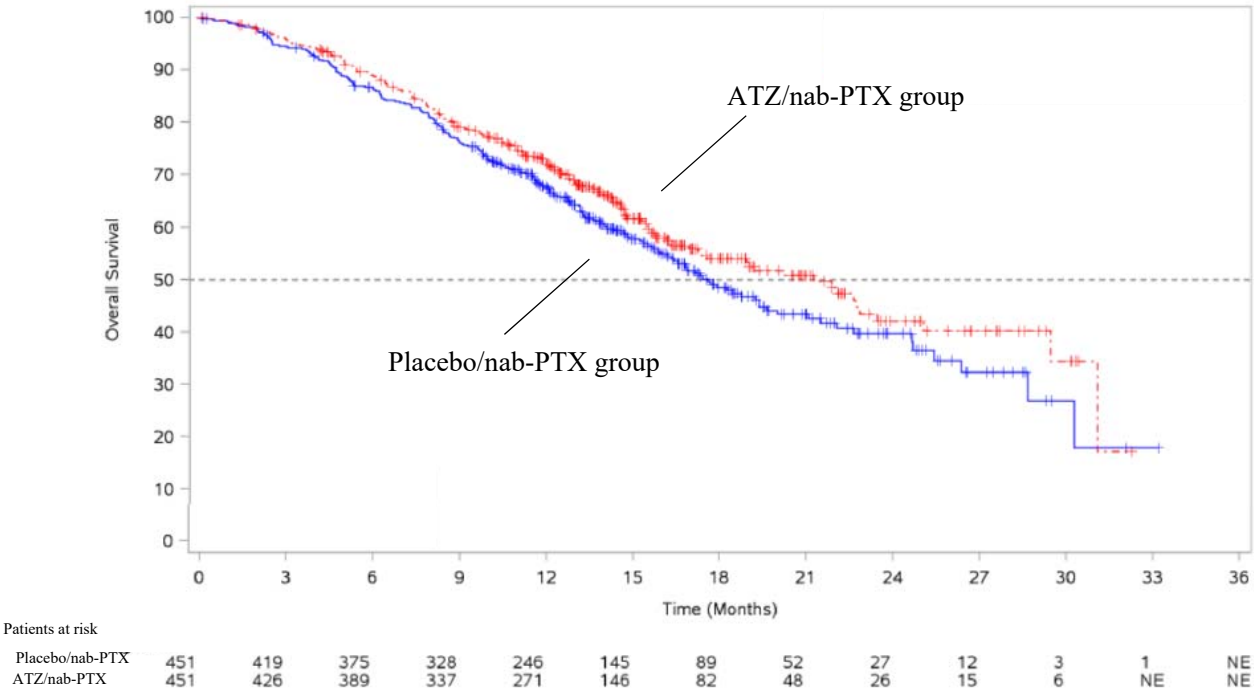

Figure 4. Kaplan-Meier curves for OS at the time of first interim analysis (ITT population, data cutoff date of April 17, 2018)

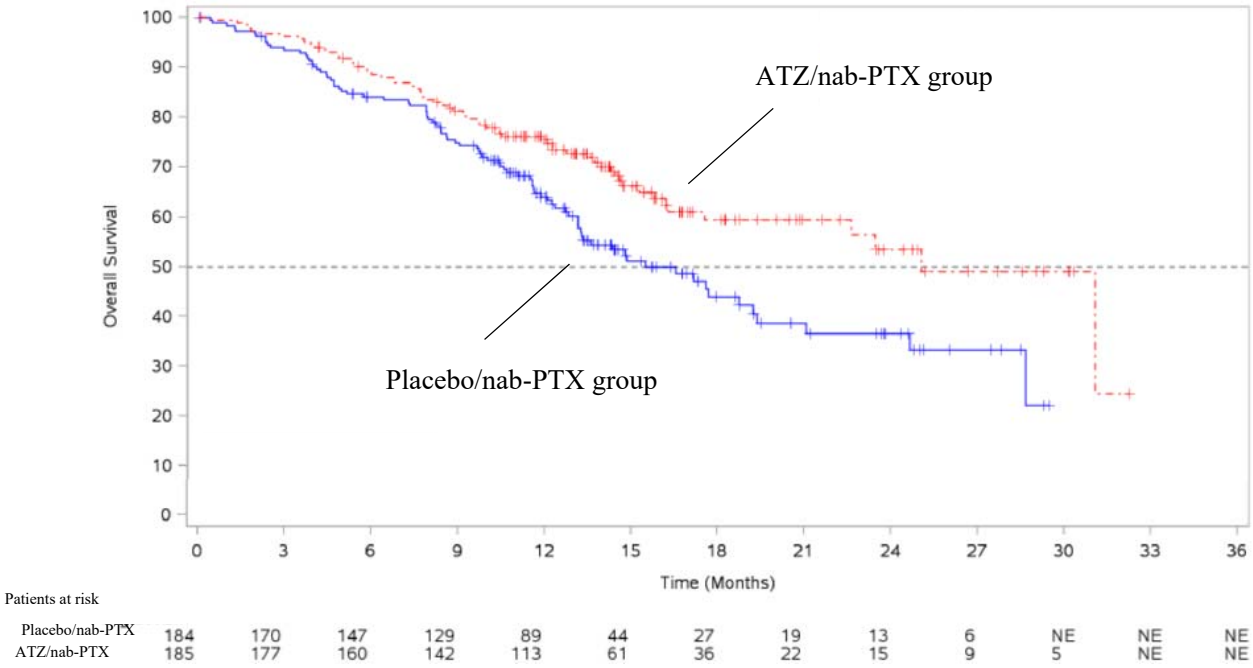

Figure 5. Kaplan-Meier curves for OS at the time of first interim analysis (PD-L1-positive subpopulation, data cutoff date of April 17, 2018)

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).

7.2 Reference data

7.2.1 Japanese clinical studies

7.2.1.1 Japanese phase I study (CTD 5.3.5.2-1, Study J-0102 [February 2008-March 2010])

An open-label, uncontrolled study was conducted at 1 site in Japan to evaluate the safety etc. of nab-PTX in chemotherapy-naïve patients with HER2-negative inoperable or recurrent breast cancer (target sample size, 6 subjects).

All of 6 subjects enrolled in the study received nab-PTX, and were included in the safety population.

Regarding safety, no subjects died during the nab-PTX treatment period or within 28 days after the last dose of nab-PTX.

7.2.1.2 Japanese phase II study (CTD 5.3.5.1-3, Study J-0201 [November 2009-June 2014])

An open-label, randomized, controlled study was conducted at 21 sites in Japan to evaluate the efficacy and safety of nab-PTX compared with docetaxel hydrate (DTX) in chemotherapy-naïve patients with HER2-negative inoperable or recurrent breast cancer (target sample size, 192 subjects).

All of 200 subjects who were enrolled in the study and randomized (100 in the nab-PTX group, 100 in the DTX group) received study drug, and were included in the safety population.

Regarding safety, 1 of 100 subjects (1.0%) in the DTX group died during the study treatment period or within 28 days after the last dose of study drug. The cause of death was disease progression, and its causal relationship to study drug was denied.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning and efficacy

The applicant's explanation about the efficacy of ATZ in combination with nab-PTX in chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer:

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].

ATZ/nab-PTX 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.

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Breast Cancer (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's 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.

Given the above study results etc., the efficacy of ATZ in combination with nab-PTX was demonstrated in chemotherapy-naïve patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer.

PMDA accepted the applicant's explanation.

7.R.2 Safety (for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies")

PMDA's conclusion:

Based on the following considerations, although there are adverse events that require 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, ATZ/nab-PTX is tolerable in these patients 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 dose interruption/reduction and discontinuation of ATZ and nab-PTX.

Adverse events that require particular attention following administration of ATZ/nab-PTX in patients with breast cancer are 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). Attention should be paid to the possible occurrence of these adverse events during treatment with ATZ/nab-PTX as well.

(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.)

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 4.

Table 4. 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.

PMDA's discussion:
Attention should be paid to the possible occurrence of adverse events that were reported at a higher incidence in the ATZ/nab-PTX group than in the placebo/nab-PTX group in the IMpassion130 study. However, since all events were known adverse events associated with nab-PTX or ATZ, it is considered that no new adverse events to which attention should be paid have occurred during treatment with ATZ/nab-PTX at present.

Based on the above, ATZ/nab-PTX is tolerable in chemotherapy-naïve patients with 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. management of and monitoring for adverse events and interruption of ATZ and nab-PTX.

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 5.

Table 5. 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%]).

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 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.

7.R.3 Dosage and administration

The proposed dosage and administration statement for nab-PTX in the present partial change application was "*nab-PTX in combination with other anti-neoplastic drugs;* The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated. The dosage should be reduced, as appropriate, according to the patient's condition." The following statements were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert (Underline denotes additions in the present partial change application).

- <u>The efficacy and safety of nab-PTX in combination with anti-neoplastic drugs other than ATZ have not been established. Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the efficacy and safety of nab-PTX</u>.
- nab-PTX dose interruption/reduction recommendations

PMDA's conclusion:

Based on Sections "7.R.1 Clinical positioning and efficacy" and "7.R.2 Safety", and the following considerations, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the current package insert for nab-PTX should be unchanged (the above underlined statement should not be added),

and the proposed dosage and administration statement for nab-PTX should be amended as follows.

Dosage and Administration

nab-PTX in combination with atezolizumab (genetical recombination)

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

7.R.3.1 Dosage and administration for nab-PTX

The applicant's explanation about the dosing rationale for nab-PTX for combination with ATZ in patients with breast cancer:

Since the IMpassion130 study in chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer demonstrated the clinical usefulness of ATZ/nab-PTX in the PD-L1-positive subpopulation, the proposed dosing regimen for nab-PTX (100 mg/m^2 QW) was selected based on the IMpassion130 study.

The IMpassion130 study was conducted according to the nab-PTX 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, nab-PTX dose interruption/reduction recommendations in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the current package insert will be unchanged in the present application.

PMDA's discussion:

Since the clinical usefulness of nab-PTX in combination with ATZ only was demonstrated in the patient population of the IMpassion130 study, and the clinical usefulness of nab-PTX in combination with anti-neoplastic drugs other than ATZ is unknown, it is necessary to specify the anti-neoplastic drug for combination with nab-PTX in the DOSAGE AND ADMINISTRATION section for nab-PTX in the present partial change application.

Based on the above, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the current package insert for nab-PTX should be unchanged, and the proposed dosage and administration statement for nab-PTX should be amended as follows.

Dosage and Administration

nab-PTX in combination with atezolizumab (genetical recombination)

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

7.R.4 Post-marketing investigations

The applicant's explanation:

At present, there is no need to conduct another post-marketing surveillance for patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer, immediately after obtaining approval, for the following reasons etc.

- In the IMpassion130 study, there were adverse events reported at a higher incidence in the ATZ/nab-PTX group than in the placebo/nab-PTX group, but all events were known adverse events associated with nab-PTX or ATZ, and no new safety concerns about ATZ/nab-PTX were identified [see Section 7.R.2.1].
- A use-results survey etc. in patients with breast cancer (the previously approved indication) has been conducted, and a certain amount of nab-PTX safety information from Japanese patients is available.

PMDA accepted the applicant's explanation.

7.3 Adverse events etc. observed in clinical studies

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

7.3.1 Global phase 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 6.

Table 6. 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.

7.3.2 Japanese phase I study (Study J-0102)

Adverse events occurred in 6 of 6 subjects (100%), and those for which a causal relationship to nab-PTX could not be ruled out occurred in all subjects. Adverse events reported by ≥3 subjects were neutrophil count decreased; white blood cell count decreased; haemoglobin decreased; haematocrit decreased; red blood cell count decreased; diarrhoea; decreased appetite; peripheral sensory neuropathy; alopecia; nail disorder; and rash (6 subjects each [100%]); arthralgia; myalgia; taste abnormality; and pigmentation disorder (5 subjects each [83.3%]); monocyte count decreased; C-reactive protein increased; nausea; asthenia; and peripheral motor neuropathy (4 subjects each [66.7%]); and lymphocyte count decreased; ALT increased; stomatitis; oedema; oedema peripheral; weight decreased; and rhinorrhoea (3 subjects each [50.0%]).

Serious adverse events occurred in 2 of 6 subjects (33.3%). None of those events were reported by ≥2 subjects.

Adverse events leading to nab-PTX discontinuation occurred in 2 of 6 subjects (33.3%). None of those events were reported by ≥2 subjects.

7.3.3 Japanese phase II study (Study J-0201)

Adverse events occurred in 100 of 100 subjects (100%) in the nab-PTX group and 100 of 100 subjects (100%) in the DTX group, and those for which a causal relationship to study drug could not be ruled out occurred in all subjects in the nab-PTX and DTX groups. Adverse events reported by ≥50% of subjects in each group were neutrophil count decreased (97 subjects [97.0%]); white blood cell count decreased (96 subjects [96.0%]); alopecia (95 subjects [95.0%]); peripheral sensory neuropathy (88 subjects [88.0%]); rash (61 subjects [61.0%]); nail disorder (57 subjects [57.0%]); and anaemia (51 subjects [51.0%]) in the nab-PTX group and neutrophil count decreased; and white blood cell count decreased (99 subjects each [99.0%]); alopecia (91 subjects [91.0%]); peripheral sensory neuropathy (69 subjects [69.0%]); taste abnormality (67 subjects [67.0%]); nail disorder (57 subjects [57.0%]); oedema (51 subjects [51.0%]); and rash (50 subjects [50.0%]) in the DTX group.

Serious adverse events occurred in 17 of 100 subjects (17.0%) in the nab-PTX group and 14 of 100 subjects (14.0%) in the DTX group. Those reported by ≥2 subjects in each group were vomiting; decreased appetite; and dehydration (2 subjects each [2.0%]) in the nab-PTX group and ILD (3 subjects [3.0%]) in the DTX group. A causal relationship to study drug could not be ruled out for decreased appetite; and dehydration (2 subjects each); and vomiting (1 subject) in the nab-PTX group and ILD (3 subjects) in the DTX group.

Adverse events leading to study drug discontinuation occurred in 34 of 100 subjects (34.0%) in the nab-PTX group and 37 of 100 subjects (37.0%) in the DTX group. Those reported by ≥2 subjects in each group were peripheral sensory neuropathy (8 subjects [8.0%]); oedema (4 subjects [4.0%]); macular oedema; and VIIth nerve paralysis (3 subjects each [3.0%]); and vomiting; oedema peripheral; and decreased appetite (2 subjects each [2.0%]) in the nab-PTX group and oedema (10 subjects [10.0%]); peripheral sensory neuropathy (7 subjects [7.0%]); oedema peripheral (6 subjects [6.0%]); ILD (4 subjects [4.0%]); and hypersensitivity (3

subjects [3.0%]) in the DTX group. A causal relationship to study drug could not be ruled out for peripheral sensory neuropathy (8 subjects); oedema (4 subjects); macular oedema; and VIIth nerve paralysis (3 subjects each); oedema peripheral; and decreased appetite (2 subjects each); and vomiting (1 subject) in the nab-PTX group and oedema (10 subjects); peripheral sensory neuropathy (7 subjects); oedema peripheral (6 subjects); ILD (4 subjects); and hypersensitivity (3 subjects) in the DTX group.

8. Results of Compliance Assessment Concerning the 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 in combination with nab-PTX has efficacy in the treatment of PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer, and that the combination has acceptable safety in view of its benefits. ATZ in combination with 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 efficacy, dosage and administration, etc. need to be further discussed.

PMDA has concluded that the dosing regimen of nab-PTX in combination with ATZ for the treatment of PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer may be approved if it 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	Abraxane I.V. Infusion 100 mg
Non-proprietary Name	Paclitaxel
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	November 30, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

PMDA's conclusion:

Based on the considerations in Section "7.R.1 Clinical positioning and efficacy" in the Review Report (1), given the results from the IMpassion130 study that evaluated the efficacy and safety of ATZ/nab-PTX in chemotherapy-naïve patients with HR-negative and HER2-negative inoperable or recurrent breast cancer, etc., PMDA concluded that the efficacy of ATZ in combination with 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), following administration of 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 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.3 Dosage and administration" in the Review Report (1), the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the current package insert for nab-PTX should be unchanged, and the proposed dosage and administration statement for nab-PTX should be amended as follows.

Dosage and Administration

nab-PTX in combination with atezolizumab (genetical recombination)

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.

The dosage should be reduced, as appropriate, according to the patient's condition.

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

1.4 Risk management plan (draft)

PMDA's conclusion:

Based on the considerations in Section "7.R.4 Post-marketing investigations" in the Review Report (1), there is little need to conduct another post-marketing surveillance for patients with PD-L1-positive, HR-negative and HER2-negative inoperable or recurrent breast cancer, immediately after obtaining approval, and the applicant may collect safety information through routine pharmacovigilance activities.

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

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 indications and dosage and administration shown below, 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.

Indications (No change)

Breast cancer, gastric cancer, non-small cell lung cancer, and unresectable pancreatic cancer

Dosage and Administration (Underline denotes additions.)

Use Regimen A or E for breast cancer, Regimen A or D for gastric cancer, Regimen B for non-small cell lung cancer, and Regimen C for unresectable pancreatic cancer.

Regimen A

The usual adult dosage is 260 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes on Day 1 followed by a rest period of at least 20 days. This 21-day cycle should be repeated. The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen B

The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks in a 21-day cycle. nab-PTX should be administered at

an interval of at least 6 days. This 21-day cycle should be repeated.
The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen C
nab-PTX in combination with gemcitabine
The usual adult dosage is 125 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.
The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen D
The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.
The dosage should be reduced, as appropriate, according to the patient's condition.

Regimen E
nab-PTX in combination with atezolizumab (genetical recombination)
The usual adult dosage is 100 mg/m^2 (body surface area) of paclitaxel administered as an intravenous infusion over 30 minutes once weekly for 3 consecutive weeks followed by a rest period of 1 week. nab-PTX should be administered at an interval of at least 6 days. This 28-day cycle should be repeated.
The dosage should be reduced, as appropriate, according to the patient's condition.

Warnings (No change)
1. Chemotherapy including nab-PTX should be administered only to patients eligible for this 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. Since serious adverse reactions such as myelosuppression (mainly neutropenia) may occur, patients should be closely monitored, e.g. frequent laboratory tests (hematology tests, liver function test, renal function test, etc.).
3. Prior to the use of nab-PTX, read the package insert carefully, and administer nab-PTX with an understanding that its administration method, indications, pharmacokinetics, etc. are different from those of other paclitaxel formulations.

Contraindications (No change)
1. Patients with serious myelosuppression [Myelosuppression is a dose-limiting toxicity, and infections associated with myelosuppression may become serious.]
2. Patients with infections [Infections may be exacerbated by myelosuppression.]

3. Patients with a history of hypersensitivity to nab-PTX or paclitaxel/albumin
4. Pregnant women or women who may be pregnant

Precautions Concerning Indications (No change)

1. The efficacy and safety of nab-PTX as adjuvant or neoadjuvant chemotherapy have not been established.
2. In the treatment of unresectable pancreatic cancer, eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the disease stage, performance status, etc. of patients, and of the efficacy and safety of nab-PTX.

Precautions Concerning Dosage and Administration (Underline denotes additions, and strikethrough denotes deletions.)

~~1. The efficacy and safety of nab-PTX in combination with other anti-neoplastic drugs in the treatment of breast cancer have not been established.~~

1~~2~~. Note the following during administration of nab-PTX, and interrupt or reduce the dose of nab-PTX as needed.

1) Regimen A ~~or~~, B, or E

Closely monitor the changes in neutrophil and platelet counts. If neutrophil count is <1,500/mm^3 or platelet count is <100,000/mm^3 at predose on Day 1 of the next cycle, delay doses until recovery of bone marrow function. Within a cycle of Regimen B or E, if neutrophil count is <500/mm^3 or platelet count is <50,000/mm^3 at predose, withhold doses until recovery of bone marrow function. In the case of neutrophil count <500/mm^3 for ≥7 days, platelet count <50,000/mm^3, or febrile neutropenia during a course of therapy, reduce the dose in subsequence courses. In Regimen B or E, also in the case of the next cycle delayed by ≥7 days for neutropenia, reduce the dose in subsequent courses.

For severe (Grade 3) peripheral neuropathy, withhold treatment until improvement or resolution (Grade ≤1), followed by a dose reduction.

2) Regimen C

[Day 1 (at the start of a cycle)]

Closely monitor the changes in neutrophil and platelet counts. If neutrophil count is <1,500/mm^3 or platelet count is <100,000/mm^3 at predose, delay doses until recovery of bone marrow function.

[Days 8 and 15]

Day 8		
Predose hematology (/mm^3)		Recommended action
(1)	Neutrophil count >1,000 and Platelet count ≥75,000	No dose changes
(2)	Neutrophil count ≥500 but ≤1,000 or Platelet count ≥50,000 but <75,000	Reduce 1 dose level
(3)	Neutrophil count <500 or Platelet count <50,000	Withhold doses

Day 15		
Predose hematology (/mm^3)	Day 8 hematology	Recommended action
Neutrophil count >1,000 and Platelet count ≥75,000	(1)	No dose changes
	(2)	Return to the Day 1 dose levels
	(3)	Reduce 1 dose level
Neutrophil count ≥500 but ≤1,000 or Platelet count ≥50,000 but <75,000	(1)	No dose changes
	(2)	Treat with Day 8 dose levels
	(3)	Reduce 1 dose level
Neutrophil count <500 or Platelet count <50,000	(1) (2) (3)	Withhold doses

In the case of neutrophil count <500/mm^3 for ≥7 days, platelet count <50,000/mm^3, or febrile neutropenia during a course of therapy, reduce the subsequent dose.
For severe (Grade 3) peripheral neuropathy, withhold treatment until improvement or resolution (Grade ≤1), followed by a dose reduction.

3) Regimen D
Closely monitor the changes in neutrophil and platelet counts. If neutrophil count is <1,000/mm^3 or platelet count is <75,000/mm^3 at predose, delay doses until recovery of bone marrow function. In patients treated with nab-PTX in combination with other anti-neoplastic drugs, if neutrophil count is <1,500/mm^3 or platelet count is <100,000/mm^3 at predose on Day 1 of a cycle, delay doses until recovery of bone marrow function. In the case of neutrophil count <500/mm^3, platelet count <25,000/mm^3, or febrile neutropenia during a course of therapy, reduce the subsequent dose.
For severe (Grade 3) peripheral neuropathy, withhold treatment until improvement or resolution (Grade ≤2), followed by a dose reduction.

4) Dose level reductions

Dose level	Regimen A	Regimen B or E	Regimen C	Regimen D
Full dose	260 mg/m^2	100 mg/m^2	125 mg/m^2	100 mg/m^2
1st dose reduction	220 mg/m^2	75 mg/m^2	100 mg/m^2	80 mg/m^2
2nd dose reduction	180 mg/m^2	50 mg/m^2	75 mg/m^2	60 mg/m^2

23. In the treatment of gastric cancer and non-small cell lung cancer, other anti-neoplastic drugs for combination with nab-PTX should be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the efficacy and safety of nab-PTX.
34. In the treatment of gastric cancer, the dosing regimen for nab-PTX should be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the efficacy and safety of nab-PTX. Especially, the use of Regimen D should also be considered prior to the use of Regimen A.

Appendix

List of Abbreviations

ALT	alanine aminotransferase
a partial change application	an application for partial change of marketing approval
ATZ	atezolizumab (genetical recombination)
ATZ/nab-PTX	the combination of ATZ and nab-PTX
CI	confidence interval
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
ILD	interstitial lung disease
IMpassion130 study	Study WO29522
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
NE	not estimable
OS	overall survival
PD-L	programmed cell death-ligand
PFS	progression free survival
PK	pharmacokinetics
placebo/nab-PTX	the combination of placebo and nab-PTX
PMDA	Pharmaceuticals and Medical Devices Agency
QW	dosing on Days 1, 8, and 15 of each 28-day cycle
Q3W	quaque 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SOC	system organ class