

Report on the Deliberation Results

December 3, 2025

Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Tecentriq Intravenous Infusion 1,200 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	May 14, 2025

Result of Deliberation

In its meeting held on November 27, 2025, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The re-examination period is 10 years.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

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

Review Report

November 10, 2025

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 1,200 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	May 14, 2025
Dosage Form/Strength	Injection: Each vial (20.0 mL) contains 1,200 mg of Atezolizumab (Genetical Recombination).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 684 of 2025 [R7 *yaku*]; PSB/PED Notification No. 0331-1 dated March 31, 2025 by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of unresectable thymic carcinoma, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indications

- Unresectable advanced or recurrent non-small cell lung cancer
- Postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer
- Extensive-stage small cell lung cancer
- Unresectable hepatocellular carcinoma
- Unresectable alveolar soft part sarcoma

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- Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type
- Unresectable thymic carcinoma

(Single underline denotes additions. Double-underline denotes changes made as of September 19, 2025 after the submission of the present partial change application.)

Dosage and Administration

The initial dose of Atezolizumab (Genetical Recombination) is intravenously infused over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable advanced or recurrent non-small cell lung cancer

Chemotherapy-naïve unresectable advanced or recurrent non-squamous non-small cell lung cancer

Atezolizumab in combination with other anti-neoplastic drugs

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks. Thereafter, when administered as monotherapy, Atezolizumab (Genetical Recombination) is administered at a dose of 1,200 mg every 3 weeks or 1,680 mg every 4 weeks as an intravenous infusion. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Chemotherapy-naïve PD-L1-positive unresectable advanced or recurrent non-small cell lung cancer

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks or 1,680 mg every 4 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks or 1,680 mg every 4 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks or 1,680 mg every 4 weeks for up to 12 months. ~~If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.~~

Extensive-stage small cell lung cancer

Atezolizumab in combination with carboplatin and etoposide

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks for 4 doses. Thereafter, Atezolizumab (Genetical Recombination) is administered at a dose of 1,200 mg every 3 weeks or 1,680 mg every 4 weeks as an intravenous infusion. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable hepatocellular carcinoma

Atezolizumab in combination with bevacizumab (genetical recombination)

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks. ~~If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.~~

Unresectable alveolar soft part sarcoma

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks. The usual dosage for children aged ≥ 2 years is 15 mg/kg (body weight) of Atezolizumab (Genetical Recombination) (up to a maximum of 1,200 mg) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks. ~~If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.~~

Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks. The usual dosage for children aged >12 years is 15 mg/kg (body weight) of Atezolizumab (Genetical Recombination) (up to a maximum of 1,200 mg) administered as an intravenous infusion every 3 weeks.

Unresectable thymic carcinoma

Atezolizumab in combination with carboplatin and paclitaxel

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks.

(Underline denotes additions. Double-underline denotes changes made as of September 19, 2025 after submission of the present marketing approval application.)

Approval Condition

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

Review Report (1)

October 3, 2025

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 1,200 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	May 14, 2025
Dosage Form/Strength	Injection: Each vial (20.0 mL) contains 1,200 mg of Atezolizumab (Genetical Recombination).

Proposed Indications

- Unresectable advanced or recurrent non-small cell lung cancer
- Postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer
- Extensive-stage small cell lung cancer
- Unresectable hepatocellular carcinoma
- Unresectable alveolar soft part sarcoma
- Unresectable thymic carcinoma

(Underline denotes additions.)

Proposed Dosage and Administration

Unresectable advanced or recurrent non-small cell lung cancer

Chemotherapy-naïve unresectable advanced or recurrent non-squamous non-small cell lung cancer

In combination with other anti-neoplastic drugs, the usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Chemotherapy-naïve PD-L1-positive unresectable, advanced or recurrent non-small cell lung cancer

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy
The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks for up to 12 months. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Extensive-stage small cell lung cancer

In combination with carboplatin and etoposide, the usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable hepatocellular carcinoma

In combination with bevacizumab (genetical recombination), the usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable alveolar soft part sarcoma

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. The usual dosage for children aged ≥ 2 years is 15 mg/kg (body weight) of Atezolizumab (Genetical Recombination) (up to a maximum of 1,200 mg) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable thymic carcinoma

In combination with carboplatin and paclitaxel, the usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

(Underline denotes additions.)

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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 (genetical recombination) (hereinafter referred to as 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, blocks the binding of PD-L1 to programmed cell death-1 (PD-1), etc., thereby enhancing tumor antigen-specific cytotoxic T-cell activity and suppressing tumor growth.

In Japan, the 1,200 mg and 840 mg preparations of ATZ have been approved for the indications shown in the table below.

1,200 mg preparation

Approval date	Indications
January 2018	Unresectable advanced or recurrent non-small cell lung cancer*
August 2019	Extensive-stage small cell lung cancer
September 2020	Unresectable hepatocellular carcinoma
May 2022	Postoperative adjuvant treatment for PD-L1–positive non-small cell lung cancer
February 2025	Unresectable alveolar soft part sarcoma
September 2025	Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

* Dosage regimen for monotherapy with ATZ 1,200 mg Q3W in patients previously treated with chemotherapy. The following dosage regimens were additionally approved: In December 2018, the combination therapy with ATZ, carboplatin, paclitaxel, and bevacizumab (ATZ/CBDCA/PTX/BV) for chemotherapy-naïve patients, in November 2019, the combination therapy with ATZ 1,200 mg Q3W and other anti-neoplastic drugs for chemotherapy-naïve patients, and in December 2020, the monotherapy with ATZ 1,200 mg Q3W for chemotherapy-naïve patients with PD-L1–positive.

840 mg preparation

Approval date	Indications
September 2019	PD-L1–positive, hormone receptor–negative and HER2–negative inoperable or recurrent breast cancer
February 2025	Unresectable alveolar soft part sarcoma
September 2025	Unresectable advanced or recurrent non-small cell lung cancer* Postoperative adjuvant treatment for PD-L1–positive non-small cell lung cancer* Extensive-stage small cell lung cancer* Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

* Added following the approval of monotherapy with ATZ 1,680 mg Q4W (September 2025).

1.2 Development history, etc.

In Japan, an investigator-initiated Japanese phase II study (Study JTD2101 [Marble study]) was conducted from June 2022 by Juntendo University Hospital, and other institutions, targeting chemotherapy-naïve patients with unresectable thymic carcinoma.

As of August 2025, no countries or regions have granted approval for ATZ for the indication of unresectable thymic carcinoma.

Based primarily on the results of the Marble study, the applicant submitted a partial change application to add unresectable thymic carcinoma as new indication with dosage regimen.

ATZ has been designated as an orphan drug for the intended indication of “unresectable thymic carcinoma” in March 2025 (Designation No. 684 of 2025 [*R7 yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

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

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

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

5. Toxicology and Outline of the Review Conducted by PMDA

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

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

Although the present application is intended for a new indication and a new dosage, the data on biopharmaceutic studies and associated analytical methods, and clinical pharmacology were previously evaluated for the initial approval of ATZ, 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 shown in Table 1.

Table 1. List of clinical studies on efficacy and safety

Data category	Geographical location	Study identifier	Phase	Study population	Number of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	Marble	II	Chemotherapy-naïve patients with unresectable thymic carcinoma	48	After intravenous administration of ATZ 1,200 mg Q3W for 4–6 cycles in combination with CBDCA* ¹ and PTX,* ² ATZ 1,200 mg was administered intravenously Q3W.	Safety Efficacy

*1 Administered intravenously at an AUC of 6 mg·min/mL equivalent Q3W.

*2 Administered intravenously at 200 mg/m² Q3W.

The summary of the clinical study is as follows. Major adverse events other than death observed in the clinical study are described in Section “7.R.2 Safety.”

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase II study (CTD 5.3.5.2-1, Marble study [ongoing since June 2022 (data cutoff date, July 6, 2024)])

An open-label, uncontrolled study was conducted at 15 study sites in Japan to evaluate the efficacy and safety of ATZ administered in combination with carboplatin and paclitaxel (ATZ/CBDCA/PTX) in chemotherapy-naïve patients with unresectable thymic carcinoma¹⁾ (target sample size, 47 subjects²⁾).

ATZ 1,200 mg was administered intravenously Q3W for 4 to 6 cycles³⁾ in combination with CBDCA at an AUC of 6 mg·min/mL equivalent and PTX at 200 mg/m² administered intravenously Q3W. Thereafter, ATZ 1,200 mg was administered intravenously Q3W. Treatment was continued until disease progression or discontinuation criteria were met (up to a maximum of 2 years).

All 48 subjects enrolled in the study received the study drug and were included in the safety analysis set. The efficacy analysis set was defined as all patients in the safety analysis set with measurable lesions identified by central assessment at baseline⁴⁾ and included all 48 subjects.

The primary endpoint of the study was the response rate based on central assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1. The primary analysis was scheduled to be conducted 1 year after the enrollment of the last subject.

Table 2 shows the results of the primary efficacy analysis of the centrally-assessed response rate according to RECIST ver.1.1 (data cutoff, July 6, 2024). The lower limit of the 95% confidence interval (CI) for the response rate exceeded the pre-specified threshold response rate (30%²⁾).

**Table 2. Best overall response and response rate
(RECIST ver.1.1, central assessment, efficacy analysis set, data cutoff on July 6, 2024)**

Best overall response	Number of subjects (%)
	48
CR	0
PR	27 (56.3)
SD	20 (41.7)
PD	1 (2.1)
Response (CR + PR)	27
Response rate [95% CI*] (%)	(56.3 [41.2, 70.5])

* Clopper-Pearson method

¹⁾ Included (a) patients diagnosed with Masaoka stage III, IVa, or IVb thymic carcinoma ineligible for radical surgery or radiotherapy, and (b) patients with recurrent thymic carcinoma after radical surgery or radiotherapy.

²⁾ In clinical studies in chemotherapy-naïve patients with unresectable thymic carcinoma, the response rates to CBDCA/PTX and to combination therapy with amrubicin hydrochloride (amrubicin) and CBDCA were 21.7% to 35.9% (*J Clin Oncol.* 2011;29:2060-5; *Ann Oncol.* 2015;26:363-8, etc.). Based on these data, the threshold response rate was 30%. In clinical studies in chemotherapy-naïve patients with non-small cell lung cancer (NSCLC), the addition of immune checkpoint inhibitors to platinum-based chemotherapy increased the response rate by approximately 20% (*N Engl J Med.* 2018;378:2288-301; *Lancet Oncol.* 2019;20:924-37, etc.). On this basis, the expected response rate was 52%. Under these assumptions, with a two-sided significance level of 0.05 and a power of 80%, the required number of subjects was calculated to be 43. Considering potential dropouts, the target sample size was determined as 47.

³⁾ The number of treatment cycles was determined at the discretion of the investigator.

⁴⁾ Patients who were found not meeting major inclusion criteria, having a measurement error, etc. preventing evaluation, or having serious protocol deviations or violations were excluded.

Safety analyses revealed a death occurring in 1 of 48 subjects (2.1%) during the study treatment period or within 28 days after the treatment completion. The cause of death was sudden death,⁵⁾ for which a causal relationship with the study drug was ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the following considerations, PMDA concluded that a certain level of efficacy of ATZ/CBDCA/PTX was demonstrated in chemotherapy-naïve patients with unresectable thymic carcinoma.

7.R.1.1 Efficacy endpoints and results of evaluation

The applicant's explanation about the primary endpoint in the Marble study and the efficacy of ATZ/CBDCA/PTX in chemotherapy-naïve patients with unresectable thymic carcinoma:

Patients with unresectable thymic carcinoma responding to the treatment are expected to have improved clinical symptoms such as chest pain and respiratory symptoms caused by the tumors. Therefore, the response rate was selected as the primary endpoint of the Marble study.

In the Marble study, the efficacy of ATZ/CBDCA/PTX was evaluated in chemotherapy-naïve patients with unresectable thymic carcinoma for the reasons below. The threshold response rate was specified based on the results of clinical studies of CBDCA/PTX, etc. reported at the time of study planning.²⁾

- CBDCA/PTX was recommended for chemotherapy-naïve patients with unresectable thymic carcinoma in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Thymomas and Thymic Carcinomas (NCCN Guidelines) (v.1.2021) and the Guidelines for Diagnosis and Treatment of Lung Cancer/Malignant Pleural Mesothelioma/Thymic Tumors (Japanese clinical practice guidelines) (2020 edition).
- The combination of cytotoxic anti-neoplastic drugs and immune checkpoint inhibitors is thought to induce immunogenic cell death and enhance the antitumor effect of immune checkpoint inhibitors (*Nat Rev Clin Oncol.* 2016;13:143-58). Immune checkpoint inhibitors have been reported to have a certain level of efficacy against thymic carcinoma (*Lancet Oncol.* 2018;19:347-55; *J Clin Oncol.* 2019;37:2162-70). Thus, ATZ/CBDCA/PTX was expected to have greater antitumor effects.

In the Marble study, the centrally-assessed response rate (%) [95% CI], the primary endpoint, was 56.3% [41.2%, 70.5%] (27 of 48 subjects), and the lower limit of the 95% confidence interval exceeded the threshold response rate of 30% [see Section 7.1.1.1].

Figure 1 shows the centrally-assessed best percentage change in the sum of diameters of target lesions in the Marble study. The centrally-assessed median duration of response⁶⁾ [95% CI] (months), a secondary endpoint, was 6.4 [4.1, not reached].

⁵⁾ After receiving ATZ/CBDCA/PTX ■ times, the subject died before the ■th dose of monotherapy with ATZ that had been postponed due to an adverse event (hyperglycemia) (■ days after the ■th dose of ATZ alone). No autopsy was conducted. The investigator assessed the death as not related to the study drug.

⁶⁾ For subjects with a confirmed response (complete response [CR] or partial response [PR]), the response duration was defined as the time from the first documentation of response to progressive disease (PD) or death, whichever came first.

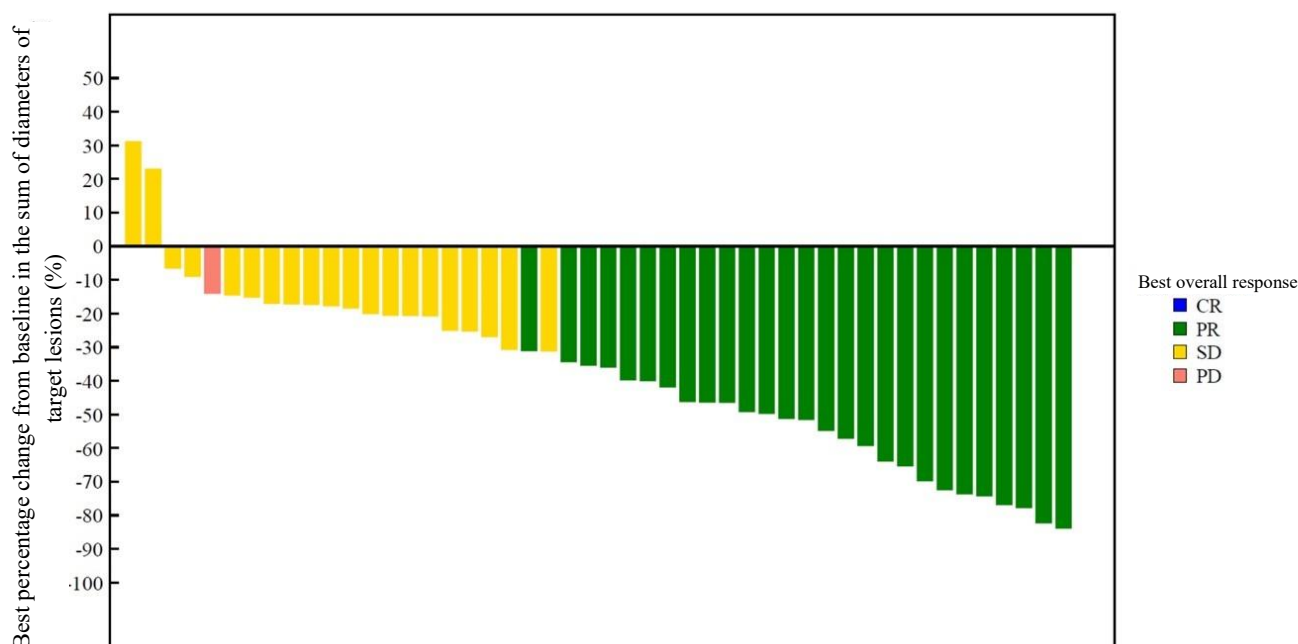


Figure 1. Best percentage change from baseline in the sum of diameters of target lesions (RECIST ver.1.1, central assessment, efficacy analysis set, data cutoff on July 6, 2024)

Table 3 shows the response rates by histopathological subtype in the Marble study. No clear differences were observed among histopathological subtypes.

Table 3. Response rate by histopathological type (RECIST ver.1.1, central assessment, efficacy analysis set, data cutoff on July 6, 2024)

Histopathological type	Number of subjects	Response rate (%)
All histological types	48	56.3
Squamous cell carcinoma (NOS)	34	58.8
Thymic carcinoma (NOS)	9	33.3
Enteric adenocarcinoma	1	100
Adenocarcinoma NOS	1	100
Adenosquamous cell carcinoma	1	100
Unknown	2	50.0

PMDA's view:

The Marble study did not evaluate overall survival (OS), a critical endpoint. Although the life-extending effect of ATZ/CBDCA/PTX cannot be assessed based on the results of the response rate selected as the primary endpoint, the applicant's explanation about the selection of the primary endpoint is yet understandable. Based on the results of the Marble study submitted, and taking the following points into account, the study demonstrated a certain level of efficacy of ATZ/CBDCA/PTX in chemotherapy-naïve patients with unresectable thymic carcinoma:

- The lower limit of the 95% confidence interval for the response rate exceeded the threshold response rate. The following outcome is also suggestive of the clinical significance of the response rates in the Marble study:

- The Japanese clinical practice guidelines (2024 edition) “weakly recommend ⁷⁾” the administration of CBDCA/PTX or the combination therapy with CBDCA and amrubicin hydrochloride (amrubicin). The response rates of these treatments in chemotherapy-naïve patients with unresectable thymic carcinoma have been reported to be 21.7% to 42% (*J Clin Oncol.* 2011;29:2060-5; *J Thorac Oncol.* 2014;9:1805-9, etc.).
- Patients in the Marble study responded to the treatment, regardless of their histopathological types of thymic carcinoma.

7.R.2 Safety

PMDA’s view:

Based on the following review, the adverse events of special attention during the treatment with ATZ/CBDCA/PTX in chemotherapy-naïve patients with unresectable thymic carcinoma are those identified as such at the time of approval for the previously approved indications.⁸⁾

Despite these known adverse events of attention in the treatment with ATZ, the administration of ATZ/CBDCA/PTX is tolerable in chemotherapy-naïve patients with unresectable thymic carcinoma, as long as treating physicians with adequate knowledge and experience in cancer chemotherapy continue to take appropriate measures such as patient monitoring, adverse event management including adverse drug reactions due to excessive immune responses, and treatment interruption or dose reduction of ATZ, CBDCA, or PTX.

7.R.2.1 Safety profile

The applicant’s explanation about the safety profile of ATZ/CBDCA/PTX based on the safety data from the Marble study:

Table 4 is a summary of safety in the Marble study. Table 5 shows adverse events with an incidence above a certain level in the Marble study.

Table 4. Summary of safety^{*1} (safety analysis set, data cutoff on July 6, 2024)

	Number of subjects (%)
	48
All adverse events	48 (100)
Grade ≥ 3 adverse events	37 (77.1)
Adverse events resulting in death	1 (2.1)
Serious adverse events	20 (41.7)
Adverse events leading to treatment discontinuation ^{*2}	6 (12.5)
Adverse events leading to treatment interruption ^{*2}	20 (41.7)

*1 Dose reduction of ATZ was not permitted.

*2 Adverse events leading to the discontinuation or interruption of any study drug

⁷⁾ The recommendation level was determined by voting after evidence-based discussions in the concerned subcommittee. The intervention was “strongly recommended” when either one of 2 directions of the intervention, i.e., “to perform” or “not to perform, gained $\geq 60\%$ approval, while it was “weakly recommended” with $<60\%$ approval for 1 consistent direction. When the voting result failed to show consistency in the direction of recommendation, it was interpreted as “no clear justification for recommending the intervention.”

⁸⁾ Interstitial lung disease (ILD), hepatic dysfunction/hepatitis/cholangitis sclerosing, colitis/severe diarrhea, pancreatitis, type 1 diabetes mellitus, endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction), encephalitis/meningitis/myelitis, neuropathy (including Guillain-Barré syndrome), myasthenia gravis, severe skin disorders, renal dysfunction (including tubulointerstitial nephritis), myositis/rhabdomyolysis, myocarditis, hemophagocytic syndrome, immune thrombocytopenia, infusion reaction, hemolytic anemia, pericarditis/pericardial effusion/cardiac tamponade, hematologic toxicity when combined with chemotherapy (neutropenia, febrile neutropenia), and infections when combined with chemotherapy (see “Review Report on Tecentriq Intravenous Infusion 840 mg and 1,200 mg, dated August 8, 2025,” etc.)

**Table 5. Adverse events with an incidence above a certain level*
(safety analysis set data cutoff on July 6, 2024)**

PT (MedDRA ver.27.0)	Number of subjects (%)
	48
All adverse events	
Peripheral sensory neuropathy	42 (87.5)
Alopecia	41 (85.4)
Constipation	33 (68.8)
Anaemia	26 (54.2)
White blood cell count decreased	22 (45.8)
Nausea	20 (41.7)
Rash maculo-papular	20 (41.7)
Neutropenia	19 (39.6)
Neutrophil count decreased	18 (37.5)
Decreased appetite	18 (37.5)
Malaise	15 (31.3)
Arthralgia	15 (31.3)
ALT increased	14 (29.2)
Diarrhoea	13 (27.1)
Stomatitis	13 (27.1)
AST increased	13 (27.1)
Platelet count decreased	12 (25.0)
Febrile neutropenia	11 (22.9)
Pyrexia	11 (22.9)
Hiccups	11 (22.9)
Grade ≥ 3 adverse events	
White blood cell count decreased	14 (29.2)
Neutrophil count decreased	14 (29.2)
Neutropenia	13 (27.1)
Febrile neutropenia	11 (22.9)
Rash maculo-papular	6 (12.5)
Lymphocyte count decreased	5 (10.4)
Serious adverse events	
Febrile neutropenia	8 (16.7)
Rash maculo-papular	4 (8.3)
Adverse events leading to interruption of the study drug	
Pneumonitis	3 (6.3)
Rash maculo-papular	3 (6.3)
Anaemia	3 (6.3)

* All adverse events occurred at an incidence of $\geq 20\%$, Grade ≥ 3 adverse events occurred at an incidence of $\geq 10\%$, and other adverse events occurred at an incidence of $\geq 5\%$

In a clinical study of pembrolizumab monotherapy, an anti-PD-1 antibody, targeting patients with thymic epithelial tumors previously treated with chemotherapy including platinum-based anti-neoplastic drugs, Grade ≥ 3 immune-related adverse events were reported in 5 patients⁹⁾ (19.2%), including myasthenia gravis in 2 patients (7.7%) with thymic carcinoma (*J Clin Oncol.* 2018;37:2162-70). PMDA requested the applicant to explain the necessity of cautionary advice on the occurrence of immune-related adverse events including myasthenia gravis and the manifestation of autoimmune diseases associated with the administration of ATZ.

The applicant's response:

Although immune-related adverse events were observed in the Marble study, there was no clear trend toward a higher incidence of immune-related adverse events¹⁰⁾ in the study compared with the clinical

⁹⁾ Myasthenia gravis and hepatitis in 2 patients each, and subacute myoclonus in 1 patient

¹⁰⁾ In the Marble study, the following were defined as immune-related adverse events: ILD, hepatic dysfunction/hepatitis/cholangitis sclerosing, colitis/severe diarrhoea, pancreatitis, type 1 diabetes mellitus, endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction), encephalitis/meningitis/myelitis, neuropathy (including Guillain-Barré syndrome), myasthenia gravis, severe skin disorders, renal dysfunction (including tubulointerstitial nephritis), myositis/rhabdomyolysis, myocarditis, haemophagocytic syndrome, immune thrombocytopenia, infusion reaction, haemolytic anaemia, pericarditis/pericardial effusion/cardiac tamponade, hematologic toxicity when combined with chemotherapy (neutropenia, febrile neutropenia), and infections when combined with chemotherapy.

studies for the previously approved indications,¹¹⁾ or no manifestation of autoimmune diseases was observed. Therefore, additional cautionary advice on immune-related adverse events including myasthenia gravis is considered unnecessary.

PMDA's view:

The events occurring in the Marble study listed in Table 5 are known events of ATZ, CBDCA, or PTX. The applicant's view of no need for additional cautionary advice concerning immune-related adverse events is understandable.

In the Marble study, the serious adverse events with an incidence of $\geq 5\%$ were maculopapular rash and febrile neutropenia. Although maculopapular rash warrants careful attention, additional measures are considered unnecessary for the present application when caution is advised for severe skin disorders. The package insert raises a caution about febrile neutropenia during the treatment with the combination of ATZ, CBDCA, PTX, and BV (ATZ/CBDCA/PTX/BV),¹²⁾ and given this, healthcare professionals should be properly informed of the occurrence of febrile neutropenia associated with the administration of ATZ/CBDCA/PTX and how it was managed in the clinical study, via the package insert and other materials. Adverse events other than maculopapular rash and febrile neutropenia observed at high incidences in the Marble study also warrant careful attention. Nevertheless, the treatment with ATZ/CBDCA/PTX is tolerable in chemotherapy-naïve patients with unresectable thymic carcinoma, with appropriate measures taken, such as patient monitoring, adverse event management with adverse drug reactions after excessive immune responses in mind, and treatment interruption of ATZ, CBDCA, or PTX, by physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.3 Clinical positioning and indication

The indication of ATZ pertaining to the present partial change application was “unresectable thymic carcinoma.” In addition, the PRECAUTIONS CONCERNING INDICATION section provided the following notes:

- The efficacy and safety of ATZ as pre-operative adjuvant therapy have not been established.
- Eligible patients must be selected by physicians based on a full understanding of the information presented in the CLINICAL STUDIES section and the efficacy and safety of ATZ.

Based on the results of the review in Sections “7.R.1 Efficacy,” “7.R.2 Safety,” and the sections below, PMDA concluded that the PRECAUTIONS CONCERNING INDICATION section should provide the following cautionary note and that the Indication for ATZ should be specified as proposed by the applicant.

- The efficacy and safety of ATZ as pre-operative adjuvant therapy have not been established.

¹¹⁾ Grade ≥ 3 immune-related adverse events were observed in 32 subjects (66.7%).

¹²⁾ Among the clinical studies evaluated at the time of approval for the previously approved indications, in a global Phase III study (Study GO29436 [IMpower150 study]) in which ATZ/CBDCA/PTX/BV was administered to chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous NSCLC, the incidence of febrile neutropenia in the Japanese population in the ATZ/CBDCA/PTX/BV group was 19.4% (7 of 36 subjects) for all grades* and 16.7% (6 of 36 subjects) for Grade ≥ 3 events (*, including cases reported as Grade 2 based on the investigator's assessment).

7.R.3.1 Clinical positioning and indication of ATZ

In Japanese and foreign clinical practice guidelines and major textbooks of clinical oncology,¹³⁾ there was no mention of the administration of ATZ for unresectable thymic carcinoma.

The applicant's explanation about the clinical positioning and indication of ATZ:

In the Japanese clinical practice guidelines (2024 edition), the administration of CBDCA/PTX or concomitant use of CBDCA with amrubicin is “weakly recommended⁷⁾” as the first-line treatment for unresectable thymic carcinoma. The efficacy and safety of lenvatinib, approved for the indication of “unresectable thymic carcinoma,” were evaluated in a clinical study targeting patients with unresectable thymic carcinoma previously treated with chemotherapy including platinum-based anti-neoplastic drugs. In the Japanese clinical practice guidelines (2024 edition), the administration of lenvatinib is “weakly recommended” for thymic carcinoma refractory to first-line treatment.⁷⁾”

Based on the results of the Marble study in chemotherapy-naïve patients with unresectable thymic carcinoma, which demonstrated the clinical usefulness of ATZ/CBDCA/PTX in this patient population [see Sections “7.R.1 Efficacy” and “7.R.2 Safety”], the applicant considers that ATZ/CBDCA/PTX can be acknowledged as one of the options in first-line therapies for these patients.

At the same time, in view of the lack of efficacy/safety data from clinical studies, the package insert should note in its CLINICAL STUDIES section that the efficacy and safety of ATZ have yet to be established for ATZ as pre-operative adjuvant therapy for thymic carcinoma, along with the details of the patients enrolled in the Marble study. Also, familiarity with such information and a full understanding of the efficacy and safety of ATZ should be required for the selection of eligible patients.

Accordingly, the Indication was defined as “unresectable thymic carcinoma,” and cautionary notes were provided in the PRECAUTIONS CONCERNING INDICATION section as follows:

- The efficacy and safety of ATZ as pre-operative adjuvant therapy have not been established.
- Eligible patients must be selected with a full understanding of the efficacy and safety of ATZ and a good knowledge of the information in the CLINICAL STUDIES section.

PMDA's view:

The applicant's explanation has been generally accepted. However, the proposed cautionary note that “eligible patients must be selected with a full understanding of the efficacy and safety of ATZ and a good knowledge of the information in the CLINICAL STUDIES section” does not deserve particular mention. The description thus need not be added in the PRECAUTIONS CONCERNING INDICATION section.

¹³⁾ NCCN Guidelines (v.2.2025), National Cancer Institute Physician Data Query (NCI-PDQ) (version dated October 25, 2024), Japanese clinical practice guidelines (2024 edition), and Clinical oncology update-essentials for medical oncologists (seventh revised edition, Nankodo Co., Ltd.)

7.R.3.2 Efficacy and safety of ATZ/CBDCA/PTX by PD-L1 expression status and target population

PMDA asked the applicant to explain the efficacy and safety of ATZ/CBDCA/PTX by the expression of PD-L1, which is the target of ATZ as an antibody drug, and the target population for the treatment with ATZ.

The applicant's explanation:

The (a) efficacy and (b) safety of ATZ/CBDCA/PTX by PD-L1 expression status (the proportion of tumor cells expressing PD-L1 in all tumor cells [TC] or the proportion of tumor-infiltrating immune cells expressing PD-L1 in tumor tissue [IC]) in tumor tissue specimens in the Marble study are as follows. In the Marble study, efficacy and safety by PD-L1 expression status were exploratory endpoints, and the collection of tumor tissue specimens for PD-L1 testing was not mandatory.¹⁴⁾ PD-L1 expression results were obtained from 33 subjects.

(a) Efficacy

Table 6 shows the response rates by PD-L1 expression status in the Marble study. Although the reason remains unknown for the trend toward a lower response rate in the population with unknown PD-L1 expression status, 3 of 15 subjects (20%) in this population responded with no tendency of disease progression. Patients with confirmed PD-L1 expression showed no clear differences in the response rates by PD-L1 expression status. Based on these outcomes, the treatment with ATZ/CBDCA/PTX is expected to have efficacy regardless of PD-L1 expression status.

**Table 6. Response rates by PD-L1 expression status
(RECIST ver.1.1, central assessment, efficacy analysis set, data cutoff on July 6, 2024)**

Best overall response	Number of subjects (%)			
	TC0 or IC0 12	TC1/2 or IC1/2 15	TC3 or IC3 6	Unknown 15
CR	0	0	0	0
PR	9 (75.0)	11 (73.3)	4 (66.7)	3 (20.0)
SD	2 (16.7)	4 (26.7)	2 (33.3)	12 (80.0)
PD	1 (8.3)	0	0	0
Response (CR+PR) (response rate [95% CI*] [%])	9 (75.0 [42.8, 94.5])	11 (73.3 [44.9, 92.2])	4 (66.7 [22.3, 95.7])	3 (20.0 [4.3, 48.1])

TC0, TC <1%; TC 1/2, TC ≥1% and <50%; TC3, TC ≥50%; IC0, IC <1%; IC1/2, IC ≥1% and <10%; IC3, IC ≥10%

* Clopper-Pearson method

(b) Safety

Table 7 is a summary of safety by PD-L1 expression status in the Marble study. No clear differences were observed in the safety profile of ATZ/CBDCA/PTX by PD-L1 expression status.

¹⁴⁾ According to the Marble study protocol, tumor tissue specimens for biomarker analysis were to be "submitted if residual specimens collected in routine clinical practice before the start of treatment are available."

**Table 7. Summary of safety by PD-L1 expression status
(safety analysis set, data cutoff on July 6, 2024)**

	Number of subjects (%)			
	TC0 or IC0	TC1/2 or IC1/2	TC3 or IC3	Unknown
	12	15	6	15
All adverse events	12 (100)	15 (100)	6 (100)	15 (100)
Grade ≥ 3 adverse events	6 (50.0)	12 (80.0)	6 (100)	13 (86.7)
Adverse events resulting in death	0	0	0	1 (6.7)
Serious adverse events	3 (25.0)	5 (33.3)	2 (33.3)	10 (66.7)

TC0, TC <1%; TC1/2, TC $\geq 1\%$ and <50%; TC3, TC $\geq 50\%$; IC0, IC <1%; IC1/2, IC $\geq 1\%$ and <10%; IC3, IC $\geq 10\%$

Based on the results of (a) and (b) above, the administration of ATZ/CBDCA/PTX is recommended for patients with unresectable thymic carcinoma, regardless of PD-L1 expression status.

PMDA accepted the applicant's explanation.

7.R.4 Dosage and administration

The applicant's explanation:

The dosage and administration and the precautions concerning dosage and administration of ATZ would be specified for the present partial change application as per the table below, in response to the approval of the present partial change application pertaining to the dosage and administration¹⁵⁾ (dated September 19, 2025).

Dosage and Administration	Precautions Concerning Dosage and Administration
All indications The initial dose of Atezolizumab (Genetical Recombination) should be intravenously infused over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes. Unresectable thymic carcinoma <i>Atezolizumab in combination with carboplatin and paclitaxel</i> The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks.	All indications Recommended ATZ dosage modifications for adverse reactions (same as those for previously approved indications). Unresectable thymic carcinoma - Concomitant carboplatin and paclitaxel should be used with a full understanding of the information presented in the CLINICAL STUDIES section, especially, the dosage regimens of these concomitant anti-neoplastic drugs. - When used in combination with carboplatin and paclitaxel, the usual adult dosage is carboplatin at an AUC of 6 mg/mL/min as an intravenous infusion over ≥ 30 minutes, and paclitaxel at 200 mg/m² as intravenous infusion over 3 hours, both every 3 weeks. The dose should be reduced as necessary according to the patient's condition.

Based on the Sections "7.R.1 Efficacy," "7.R.2 Safety," and the results of the following review, PMDA concluded that the DOSAGE AND ADMINISTRATION and the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION of ATZ, CBDCA, and PTX for unresectable thymic carcinoma should be specified as shown in the table below.

¹⁵⁾ ATZ 1,680 mg Q4W was added for unresectable advanced or recurrent non-small cell lung cancer and postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer.

Dosage and Administration	Precautions Concerning Dosage and Administration
All indications The initial dose of Atezolizumab (Genetical Recombination) should be intravenously infused over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes. Unresectable thymic carcinoma <i>Atezolizumab in combination with carboplatin and paclitaxel</i> The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks.	All indications Recommended ATZ dosage modifications for adverse reactions (same as those for previously approved indications) Unresectable thymic carcinoma When used in combination with carboplatin and paclitaxel, the usual adult dosage is carboplatin at an AUC of 6 mg·min/mL equivalent as an intravenous infusion over ≥ 30 minutes, and paclitaxel at 200 mg/m² as an intravenous infusion over 3 hours, both every 3 weeks. The doses should be reduced as necessary according to the patient's condition.

7.R.4.1 Dosage and administration of ATZ

The applicant's explanation about the dosage and administration of ATZ for the present partial change application:

In view of the following outcomes, the clinical usefulness of ATZ in unresectable thymic carcinoma was demonstrated in the Marble study, in which ATZ was administered intravenously at 1,200 mg Q3W in combination with CBDCA and PTX. Accordingly, the dosage regimen of ATZ was determined based on the regimen used in the Marble study.

- The IMpower130 study conducted in chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) demonstrated the efficacy of intravenous ATZ 1,200 mg, CBDCA at an AUC of 6 mg·min/mL equivalent Q3W, and albumin-bound paclitaxel (nab-PTX) at 100 mg/m² QW (see "Review Report on Tecentriq Intravenous Infusion 1,200 mg, dated October 10, 2019").
- The Study GO29436 (IMpower150 study) conducted in chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous NSCLC demonstrated the safety of intravenous ATZ 1,200 mg, CBDCA at an AUC of 6 mg·min/mL equivalent, and PTX at 200 mg/m² Q3W (see "Review Report on Tecentriq Intravenous Infusion 1,200 mg, dated November 12, 2018").

There are no clinical study results of ATZ used in combination with anti-neoplastic drugs other than CBDCA and PTX for patients with unresectable thymic carcinoma. In this view, the DOSAGE AND ADMINISTRATION section will advise using ATZ in combination with CBDCA and PTX. At the same time, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section will seek attention to the dosage regimen of the concomitant anti-neoplastic drugs. The section will also provide the criteria for the interruption or discontinuation of ATZ for adverse drug reactions for the present partial change application, which are the same as that for the previously approved indications, in light of the criteria for the interruption or discontinuation of ATZ for adverse events in the Marble study that followed the said criteria for adverse drug reactions for the previously approved indications and demonstrated the clinical usefulness of ATZ in patients with unresectable thymic carcinoma.

PMDA's view:

The applicant's explanation has been generally accepted. However, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section does not need to mention a full understanding of the information about concomitant anti-neoplastic drugs provided in the CLINICAL STUDIES section as the dosage regimens of the concomitant anti-neoplastic drugs are clearly specified. [For the dosage regimens of CBDCA and PTX, see Section "7.R.4.2 Dosage and administration of CBDCA and PTX"]

7.R.4.2 Dosage and administration of CBDCA and PTX

The applicant's explanation about the dosage regimens of CBDCA and PTX to be used in combination with ATZ in unresectable thymic carcinoma:

In the Marble study, based on the Japanese clinical practice guidelines (2021 edition), etc., CBDCA was administered at an AUC of 6 mg·min/mL equivalent over ≥ 30 minutes, and PTX was administered at 200 mg/m² over 3 hours, both Q3W, which demonstrated the clinical usefulness of ATZ/CBDCA/PTX in unresectable thymic carcinoma [see Sections "7.R.1 Efficacy" and "7.R.2 Safety"]. Thus, in the ATZ/CBDCA/PTX regimen for patients with unresectable thymic carcinoma, CBDCA and PTX should be administered as per the above dosage regimen. Based on the "Handling of Marketing Applications etc. for Drugs, Medical Devices, and Regenerative Medical Products to Be Used with Other Products" (PSB/PED Notification No. 0531-1, PSB/MDED Notification No. 0531-3, and PSB/PSD Notification No. 0531-1, dated May 31, 2024), the dosage regimens of CBDCA and PTX to be concomitantly used with ATZ were specified in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of ATZ as follows. Furthermore, healthcare professionals will be provided with written materials about the dose reduction or discontinuation criteria of CBDCA and PTX for adverse events in the Marble study.

- When used in combination with CBDCA and PTX, the usual adult dosage is CBDCA at an AUC of 6 mg/mL/min as an intravenous infusion over ≥ 30 minutes, and PTX at 200 mg/m² as an intravenous infusion over 3 hours, both every 3 weeks. The doses should be reduced as necessary according to the patient's condition.

PMDA accepted the applicant's explanation and concluded that the dosage regimen of CBDCA and PTX to be used with ATZ should be specified in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, after modifying the description as follows:

- When used in combination with CBDCA and PTX, the usual adult dosage is CBDCA at an AUC of 6 mg·min/mL equivalent as an intravenous infusion over ≥ 30 minutes, and PTX at 200 mg/m² as an intravenous infusion over 3 hours, both every 3 weeks. The doses should be reduced as necessary according to the patient's condition.

7.R.5 Risk management plan (draft)

The risk management plan (RMP)¹⁶⁾ of ATZ has already been published based on the reviews and assessment for the previously approved indications.

Based on the discussions in Section "7.R.2 Safety," PMDA concluded that the draft RMP for ATZ pertaining to the present partial change application should include the safety and efficacy specifications listed in Table 8.

¹⁶⁾ RMP of Tecentriq Intravenous Infusion 840 mg, Tecentriq Intravenous Infusion 1200 mg, dated September 19, 2025

Table 8. Safety and efficacy specifications in the RMP (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Hepatic dysfunction/hepatitis/cholangitis sclerosing • Colitis/severe diarrhea • Pancreatitis • Type 1 diabetes mellitus • Endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction) • Encephalitis/meningitis/myelitis • Neuropathies (including Guillain-Barré syndrome) • Myasthenia gravis • Severe skin disorders • Renal dysfunction (tubulointerstitial nephritis, etc.) • Myositis/rhabdomyolysis • Myocarditis • Hemophagocytic syndrome • Immune thrombocytopenia • Infusion reaction • Febrile neutropenia (when combined with <u>CBDCA/PTX and CBDCA/PTX/BV</u>)	• Hemolytic anemia • Pericarditis/pericardial effusion/cardiac tamponade • Hematologic toxicity when combined with chemotherapy (neutropenia, febrile neutropenia) [excluding febrile neutropenia occurring with <u>CBDCA/PTX combination therapy and CBDCA/PTX/BV combination therapy</u>] • Infections when combined with chemotherapy • Embryo-fetal toxicity • Use in organ transplant recipients (including hematopoietic stem cell transplantation) • <u>Increased risk of severe complications associated with allogeneic hematopoietic stem cell transplantation after treatment with ATZ [hematologic malignancies]</u>	None
Efficacy specification		
<u>Efficacy in use in patients with relapsed or refractory ENKL aged >12 and <18 years</u>		

Underlines denote additions in the present partial change application

Wavy underlines denote changes or additions after the present partial change application

7.R.6. Post-marketing investigations

The applicant's explanation:

There are no newly identified safety issues for the present partial change application based on the reasons below, and at present, post-marketing surveillance aiming to evaluate the safety, etc. of ATZ is considered unnecessary immediately after approval in patients with unresectable thymic carcinoma. Safety data will be collected through routine pharmacovigilance activities.

- In the Marble study, the adverse events observed at an incidence above a certain percentage after the administration of ATZ/CBDCA/PTX were the known events with ATZ, CBDCA, or PTX, and were manageable by interrupting ATZ, etc. [see Section 7.R.2.1].
- The safety profile of ATZ in Japanese patients has been elucidated to a certain extent through the clinical studies for the previously approved indications, post-marketing surveillance,¹⁷⁾ and post-marketing use experiences.

PMDA accepted the applicant's explanation.

¹⁷⁾ (1) A use-results survey in patients with unresectable advanced or recurrent NSCLC with a prior chemotherapy (all-case surveillance; target sample size, 1,000 subjects): The survey has been completed with 2,640 subjects registered. (2) A post-marketing database study in chemotherapy-naïve patients with unresectable advanced or recurrent non-squamous NSCLC (febrile neutropenia in concomitant use with CBDCA/PTX/BV): The study has been completed with 301 subjects registered in the ATZ group. (3) A post-marketing database study in patients with PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer (infections in concomitant use with chemotherapy): The study has been completed with 321 subjects registered in the exposure group. (4) A post-marketing database study in patients with extensive-stage small cell lung cancer (hematologic toxicity [neutropenia, febrile neutropenia] in concomitant use with chemotherapy): Currently ongoing.

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

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

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

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

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that ATZ has efficacy in the treatment of patients with unresectable thymic carcinoma, and that ATZ has acceptable safety in view of its benefits. ATZ is clinically meaningful because it offers a new treatment option for patients with unresectable thymic carcinoma.

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

Review Report (2)

November 7, 2025

Product Submitted for Approval

Brand Name	Tecentriq Intravenous Infusion 1,200 mg
Non-proprietary Name	Atezolizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	May 14, 2025

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

In the Japanese Phase II study in chemotherapy-naïve patients with unresectable thymic carcinoma (Marble study), the response rate by central assessment according to RECIST ver.1.1, the primary endpoint, was 56.3% [95% CI, 41.2%, 70.5%].

Based on the discussion in Section “7.R.1 Efficacy” in the Review Report (1), PMDA concluded that the results of the Marble study demonstrated a certain level of efficacy of ATZ/CBDCA/PTX in chemotherapy-naïve patients with unresectable thymic carcinoma, with the following points taken into account:

- The lower limit of the 95% confidence interval for the response rate exceeded the threshold response rate, and the response rates in the Marble study are considered to be clinically meaningful, in light of the following facts:
 - The Japanese clinical practice guidelines (2024 edition) “weakly recommend” CBDCA/PTX or the combination of CBDCA and amrubicin, and reported response rates to these treatments in chemotherapy-naïve patients with unresectable thymic carcinoma were 21.7% to 42% (*J Clin Oncol.* 2011;29:2060-5; *J Thorac Oncol.* 2014;9:1805-9, etc.)
- Patients in the Marble study responded to the treatment, regardless of their histopathological subtypes of thymic carcinoma.

At the Expert Discussion, PMDA’s above conclusion was supported while the following comment was made:

- It is desirable that OS results are presented from the Marble study rather than response rates alone.

PMDA’s view:

The Marble study yielded limited OS results for being an uncontrolled study, and it is difficult to evaluate the survival benefit of ATZ/CBDCA/PTX based on the results obtained.

Although the final analysis results of the Marble study¹⁸⁾ have yet to be available, the median OS [95% CI] (months) at the time of the primary analysis (data cutoff on July 6, 2024) was not estimable [19.2, not estimable]. In the clinical studies in chemotherapy-naïve patients with unresectable thymic carcinoma, the median OS with CBDCA/PTX and with the combination of CBDCA and amrubicin was 20.0 months and 27.3 months, respectively (*J Clin Oncol.* 2011;29:2060-5; *J Thorac Oncol.* 2014;9:1805-9). The final analysis results including OS are expected to be available in the future and communicated to healthcare professionals appropriately.

1.2 Safety

PMDA’s view:

Based on the results of the review in Section “7.R.2 Safety” in the Review Report (1), the adverse events of special attention during the administration of ATZ/CBDCA/PTX to chemotherapy-naïve patients with unresectable thymic carcinoma are those identified as such at the time of approval for the previously approved indications.

Although these adverse events warrant attention during the administration of ATZ/CBDCA/PTX, the treatment is tolerable when appropriate measures such as patient monitoring, adverse event management, interruption of ATZ, etc. are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

The conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

Based on the results of the review in Section “7.R.3 Clinical positioning and indication” of the Review Report (1), PMDA concluded that the INDICATION and the PRECAUTIONS CONCERNING INDICATION

sections should be described as per the table below for ATZ for unresectable thymic carcinoma.

Indication	Precautions Concerning Indication
Unresectable thymic carcinoma	• The efficacy and safety of ATZ as pre-operative adjuvant therapy have not been established.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

¹⁸⁾ Scheduled 2 years after the start of treatment of the last enrolled patient or the date of completion of study drug administration in all patients, whichever came first.

Accordingly, PMDA instructed the applicant to finalize the descriptions in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections as above. The applicant agreed.

1.4 Dosage and administration

After the discussion in Section “7.R.4 Dosage and administration” in the Review Report (1), PMDA concluded that the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections should be specified as follows:

Dosage and Administration	Precautions Concerning Dosage and Administration
All indications The initial dose of Atezolizumab (Genetical Recombination) should be intravenously infused over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes. Unresectable thymic carcinoma <i>Atezolizumab in combination with carboplatin and paclitaxel</i> The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks.	All indications - Recommended ATZ dosage modifications for adverse reactions (same as those for previously approved indications) Unresectable thymic carcinoma - When used in combination with carboplatin and paclitaxel, the usual adult dosage is carboplatin at an AUC of 6 mg·min/mL equivalent as an intravenous infusion over ≥30 minutes, and paclitaxel at 200 mg/m² as an intravenous infusion over 3 hours, both every 3 weeks. The doses should be reduced as necessary according to the patient’s condition.

The conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to finalize the descriptions in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections as above. The applicant agreed.

1.5 Risk management plan (draft) and post-marketing investigations

PMDA’s view:

Based on the review in Section “7.R.5 Risk management plan (draft)” in the Review Report (1), the RMP (draft) for ATZ pertaining to the present partial change application should include the safety and efficacy specifications shown in Table 9.

Table 9. Safety and efficacy specifications in the RMP (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Hepatic dysfunction/hepatitis/cholangitis sclerosing • Colitis/severe diarrhea • Pancreatitis • Type 1 diabetes mellitus • Endocrinopathies (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction) • Encephalitis/meningitis/myelitis • Neuropathies (including Guillain-Barré syndrome) • Myasthenia gravis • Severe skin disorders • Renal dysfunction (tubulointerstitial nephritis, etc.) • Myositis/rhabdomyolysis • Myocarditis • Hemophagocytic syndrome • <u>Immune thrombocytopenia</u> • Infusion reaction • Febrile neutropenia (<u>when combined with CBDCA/PTX and CBDCA/PTX/BV</u>)	• Hemolytic anemia • Pericarditis/pericardial effusion/cardiac tamponade • Hematologic toxicity when combined with chemotherapy (neutropenia, febrile neutropenia) [excluding febrile neutropenia occurring with <u>CBDCA/PTX combination therapy and CBDCA/PTX/BV combination therapy</u>] • Infections when combined with chemotherapy • Embryo-fetal toxicity • Use in organ transplant recipients (including hematopoietic stem cell transplantation) • <u>Increased risk of severe complications associated with allogeneic hematopoietic stem cell transplantation after treatment with ATZ [hematologic malignancies]</u>	None
Efficacy specification		
<u>Efficacy in clinical use in patients with relapsed or refractory ENKL aged >12 and <18 years</u>		

Underlines denote additions in the present partial change application.

Wavy underlines denote changes or additions after the present partial change application.

Based on the review in Section “7.R.6 Post-marketing investigations” in the Review Report (1), at present, post-marketing surveillance is considered unnecessary immediately after approval to evaluate the safety of ATZ in patients with unresectable thymic carcinoma, as routine pharmacovigilance activities will serve to collect safety data.

The conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above discussions, PMDA concluded that the applicant should conduct the additional risk minimization activities shown in Table 10 for the RMP (draft).

Table 10. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Post-marketing database survey [hematologic toxicity (neutropenia, febrile neutropenia) associated with chemotherapy] targeting patients with small cell lung cancer [on combination therapy with CBDCA/ETP]	• <u>Drug use-results survey (all-case surveillance) in patients with relapsed or refractory ENKL aged >12 and <18 years</u>	• <u>Develop information materials for healthcare professionals</u> • Develop information materials for patients

Underlines denote activities planned for the indication added in the present partial change application.

Wavy underlines denote activities added after the present partial change application.

2. Overall Evaluation

PMDA’s conclusion:

As a result of the above review, the product may be approved for the following indications and dosage and administration, with the approval condition written below, premising on proper post-marketing

communication including cautioning via in the package insert and providing proper use-related information and on adherence to proper product use under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions fully prepared for emergencies. The product has been designated as an orphan drug for the intended indication of “unresectable thymic carcinoma,” and thus the re-examination period for the newly added indication should be 10 years.

Indications (Underline denotes additions. Double underline denotes changes made as of September 19, 2025 after submission of the present partial change application.)

- Unresectable advanced or recurrent non-small cell lung cancer
- Postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer
- Extensive-stage small cell lung cancer
- Unresectable hepatocellular carcinoma
- Unresectable alveolar soft part sarcoma
- Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type
- Unresectable thymic carcinoma

Dosage and Administration (Underline denotes addition. Double underline denotes changes made as of September 19, 2025 after submission of the present partial change application.)

The initial dose of Atezolizumab (Genetical Recombination) should be intravenously infused over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable advanced or recurrent non-small cell lung cancer

Chemotherapy-naïve unresectable advanced or recurrent non-squamous non-small cell lung cancer

Atezolizumab in combination with other anti-neoplastic drugs

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks. Thereafter, when administered as monotherapy, Atezolizumab (Genetical Recombination) is administered at a dose of 1,200 mg every 3 weeks or 1,680 mg every 4 weeks as an intravenous infusion. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Chemotherapy-naïve PD-L1-positive unresectable advanced or recurrent non-small cell lung cancer

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks or 1,680 mg every 4 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks or 1,680 mg every 4 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks or 1,680 mg every 4 weeks for up to 12 months. ~~If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.~~

Extensive-stage small cell lung cancer

Atezolizumab in combination with carboplatin and etoposide

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks for 4 doses. Thereafter, Atezolizumab (Genetical Recombination) is administered at a dose of 1,200 mg every 3 weeks or 1,680 mg every 4 weeks as an intravenous infusion. ~~If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.~~

Unresectable hepatocellular carcinoma

Atezolizumab in combination with bevacizumab (genetical recombination)

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks. ~~If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.~~

Unresectable alveolar soft part sarcoma

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks. The usual dosage for children aged ≥ 2 years is 15 mg/kg (body weight) of Atezolizumab (Genetical Recombination) (up to a maximum of 1,200 mg) administered as an intravenous infusion ~~over 60 minutes~~ every 3 weeks. ~~If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.~~

Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks. The usual dosage for children aged ≥ 12 years is 15 mg/kg (body weight) of Atezolizumab (Genetical Recombination) (up to a maximum of 1,200 mg) administered as an intravenous infusion every 3 weeks.

Unresectable thymic carcinoma

Atezolizumab in combination with carboplatin and paclitaxel

The usual adult dosage is 1,200 mg of Atezolizumab (Genetical Recombination) administered as an intravenous infusion every 3 weeks.

Approval Condition

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

Warnings (No change)

1. ATZ should be administered only to patients eligible for ATZ therapy, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patient or their families should be fully informed of its efficacy and risks, and their consent should be obtained.
2. As cases of interstitial lung disease, including fatal cases, have been reported, patients should be closely monitored, e.g. detection of initial symptoms (dyspnoea, cough, pyrexia, etc.) and chest X-ray. If abnormalities are observed, ATZ should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

Contraindication (No change)

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

Precautions Concerning Indications (Underline denotes additions. Double underline denotes changes made as of September 19, 2025 after submission of the present partial change application.)

Unresectable advanced or recurrent non-small cell lung cancer

1. The efficacy and safety of ATZ in chemotherapy-naïve PD-L1-negative patients with squamous cell carcinoma have not been established.
2. ATZ monotherapy for chemotherapy-naïve unresectable, advanced, or recurrent non-small cell lung cancer should be provided to PD-L1-positive patients tested by a pathologist or testing facility with adequate experience and a full understanding of PD-L1 expression rates in tumor cells and tumor-infiltrating immune cells presented in the CLINICAL STUDIES section. The approved *in vitro* diagnostic products or medical devices should be used for such testing.
3. Eligible patients must be selected by physicians with a full understanding of the information provided in the CLINICAL STUDIES section concerning prior treatments and the presence or absence of *EGFR* gene mutations or *ALK* fusion genes, etc. of patients enrolled in the clinical studies, and of the efficacy and safety of ATZ.

Postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer:

4. ATZ should be used in PD-L1 positive patients tested by a pathologist or testing facility with adequate experience and a full understanding of PD-L1 expression rates in tumor cells presented in the CLINICAL STUDIES section. The approved *in vitro* diagnostic products or medical devices should be used for such testing.
5. Eligible patients must be selected by physicians with a full understanding of the information provided in the CLINICAL STUDIES section concerning prior therapies and disease stage, etc. of patients enrolled in the clinical study, and of the efficacy and safety of ATZ. Because the survival benefit of ATZ is suggested to vary with the tumor cell PD-L1 expression rate (TC), eligible patients should be selected by physicians with a full understanding of the efficacy and safety of ATZ.

Extensive-stage small cell lung cancer

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

Unresectable hepatocellular carcinoma

7. The efficacy and safety of ATZ have not been established in patients with hepatocellular carcinoma eligible for local therapies (e.g., percutaneous ethanol injection therapy, radiofrequency ablation therapy, microwave coagulation therapy, transcatheter arterial embolization/chemoembolization, or radiotherapy).
8. Eligible patients must be selected by physicians with a full understanding of the information provided in the CLINICAL STUDIES section concerning the severity of hepatic impairment in patients enrolled in the clinical study, and of the efficacy and safety of ATZ.

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

9. The efficacy and safety of ATZ as pre/post-operative pharmacotherapy have not been established.
10. ATZ should be used in PD-L1-positive patients tested by a pathologists or testing facility with adequate experience in determining the percentage of tumor-infiltrating immune cells expressing PD-L1. The approved *in vitro* diagnostic products or medical devices should be used for such testing.

Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

11. Eligible patients must be selected by physicians with a full understanding of the description in the CLINICAL STUDIES section concerning prior therapies, etc. of patients enrolled in the clinical study, and of the efficacy and safety of ATZ.

Unresectable thymic carcinoma

12. The efficacy and safety of ATZ as pre-operative adjuvant therapy have not been established.

Precautions Concerning Dosage and Administration (Underline denotes additions. Double underline denotes changes made as of September 19, 2025 after submission of the present partial change application.)

All indications:

1. 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 modification
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 (excl. unresectable hepatocellular carcinoma)	Grade 2 (AST or ALT $>3 \times$ ULN and $\leq 5 \times$ ULN, or total bilirubin $>1.5 \times$ ULN and $\leq 3 \times$ ULN) persisting 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 $>5 \times$ ULN, or total bilirubin $>3 \times$ ULN)	Permanently discontinue.

Adverse reaction	Severity of adverse reaction	Dosage modification
Hepatic dysfunction (unresectable hepatocellular carcinoma)	- Patients whose baseline AST or ALT is within the reference range: AST or ALT $>3 \times \text{ULN}$ and $\leq 10 \times \text{ULN}$. - Patients whose baseline AST or ALT is $>1 \times \text{ULN}$ and $\leq 3 \times \text{ULN}$: AST or ALT $>5 \times \text{ULN}$ and $\leq 10 \times \text{ULN}$. - Patients whose baseline AST or ALT is $>3 \times \text{ULN}$ and $\leq 5 \times \text{ULN}$: AST or ALT $>8 \times \text{ULN}$ and $\leq 10 \times \text{ULN}$.	Withhold dose until resolution to Grade ≤ 1 . Permanently discontinue if resolution to Grade ≤ 1 does not occur within 12 weeks.
	AST or ALT $>10 \times \text{ULN}$ or total bilirubin $>3 \times \text{ULN}$.	Permanently discontinue.
Colitis/Diarrhea	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	- Amylase or lipase $>2 \times \text{ULN}$ - 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	Fasting blood glucose level $>250 \text{ mg/dL}$	Withhold dose until stabilization of blood glucose levels.
	- Symptomatic hypothyroidism - Symptomatic hyperthyroidism, or asymptomatic hyperthyroidism with thyroid-stimulating hormone $<0.1 \text{ mU/L}$	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-Barré 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	Serum creatinine $>1.5 \times$ and $\leq 3 \times \text{ULN}$ or baseline	Withhold dose until resolution to Grade ≤ 1 . Permanently discontinue if resolution to Grade ≤ 1 does not occur within 12 weeks.
	Serum creatinine $>3 \times \text{ULN}$ or baseline	Permanently discontinue.
Myositis	Grade 2 or 3	Withhold dose until resolution to Grade ≤ 1 . Permanently discontinue if resolution to Grade ≤ 1 does not occur within 12 weeks.
	Grade 3 recurrent or Grade 4 myositis	Permanently discontinue.
Myocarditis	Grade ≥ 2	Permanently discontinue.
Haemophagocytic syndrome	All Grades	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.

Adverse reaction	Severity of adverse reaction	Dosage modification
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 improvement in symptoms.
	Grade ≥ 3	Discontinue infusion immediately.

Severity grade based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Chemotherapy-naïve unresectable, advanced or recurrent non-squamous non-small cell lung cancer

- Other anti-neoplastic drugs for use with ATZ should be selected based on a full understanding of the information presented in the CLINICAL STUDIES section.

Chemotherapy-naïve PD-L1-positive, unresectable, advanced or recurrent non-small cell lung cancer

- In patients with squamous cell carcinoma, the efficacy and safety of ATZ used in combination with other anti-neoplastic drugs have not been established.

Unresectable advanced or recurrent non-small cell lung cancer previously treated with chemotherapy; postoperative adjuvant treatment for PD-L1-positive non-small cell lung cancer; unresectable alveolar soft part sarcoma; relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

- The efficacy and safety of ATZ used in combination with other anti-neoplastic drugs have not been established.

Extensive-stage small cell lung cancer

- Concomitant carboplatin and etoposide should be used with a full understanding of the information presented in the CLINICAL STUDIES section, especially, the dosage regimens of these concomitant anti-neoplastic drugs.

Unresectable thymic carcinoma

- When used in combination with carboplatin and paclitaxel, the usual adult dosage is carboplatin at an AUC of 6 mg·min/mL equivalent as an intravenous infusion over ≥ 30 minutes, and paclitaxel at 200 mg/m² as an intravenous infusion over 3 hours, both every 3 weeks. The doses should be reduced as necessary according to the patient's condition.

List of Abbreviations

ALT	alanine aminotransferase
Amrubicin	amrubicin hydrochloride
AST	aspartate aminotransferase
ATZ	atezolizumab (genetical recombination)
ATZ/CBDCA/PTX	the combination of ATZ, CBDCA, and PTX
ATZ/CBDCA/PTX/BV	the combination of ATZ, CBDCA, PTX, and BV
AUC	area under the concentration-time curve
BV	bevacizumab (genetical recombination)
CBDCA	carboplatin
CBDCA/PTX	the combination of CBDCA and PTX
CBDCA/PTX/BV	the combination of CBDCA, PTX, and BV
CI	confidence interval
CR	complete response
CTD	common technical document
ENKL	extranodal NK/T-cell lymphoma, nasal type
ETP	etoposide
G-CSF	granulocyte colony stimulating factor
IC	the proportion of tumor-infiltrating immune cells expressing PD-L1 in tumor tissue
ILD	interstitial lung disease
IMpower150 study	Study GO29436
Japanese clinical practice guidelines	Guidelines for Diagnosis and Treatment of Lung Cancer/Malignant Pleural Mesothelioma/Thymic Tumors (edited by the Japan Lung Cancer Society)
Marble study	Study JTD2101
MedDRA	Medical Dictionary for Regulatory Activities
nab-PTX	albumin-bound paclitaxel
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Thymomas and Thymic Carcinomas
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NCI-PDQ	National Cancer Institute Physician Data Query
NOS	not otherwise specified
NSCLC	non-small cell lung cancer
OS	overall survival
Partial change application	Partial change application for marketing approval
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
Pembrolizumab	pembrolizumab (genetical recombination)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
PTX	paclitaxel
Q3W	quaque 3 weeks
Q4W	quaque 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	risk management plan
SD	stable disease
TC	the proportion of tumor cells expressing PD-L1 in all tumor cells