**Report on the Deliberation Results**

August 29, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Tecentriq Intravenous Infusion 840 mg,<br>Tecentriq Intravenous Infusion 1200 mg |
| **Non-proprietary Name** | Atezolizumab (Genetical Recombination) (JAN*) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | October 31, 2024 |

**Results of Deliberation**

In its meeting held on August 22, 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 4 years.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey covering all pediatric patients with relapsed or refractory extranodal NK/T-cell lymphoma, nasal type, until data from a certain number of patients arebeen accumulated.

**Japanese Accepted Name (modified INN)*

**Review Report**

August 8, 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** | (a) Tecentriq Intravenous Infusion 840 mg,<br>(b) Tecentriq Intravenous Infusion 1,200 mg |
| **Non-proprietary Name** | Atezolizumab (Genetical Recombination) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | October 31, 2024 |
| **Dosage Form/Strength** | (a) Injection: Each vial (14.0 mL) contains 840 mg of Atezolizumab (Genetical Recombination).<br>(b) Injection: Each vial (20.0 mL) contains 1,200 mg of Atezolizumab (Genetical Recombination). |
| **Application Classification** | Prescription drug, (4) Drugs with a new indication, (6) Drugs 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 has efficacy in the treatment of relapsed or refractory extranodal NK/T-cell lymphoma, nasal type, 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 conditions.

**Indications**

(a) ○ PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer
○ Unresectable alveolar soft part sarcoma
○ Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

(b) ○ 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

(Single underline denotes additions. Double-underline denotes changes made as of February 20, 2025 after submission of the present partial change application.)

**Dosage and Administration**

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

*Atezolizumab in combination with paclitaxel (albumin-bound)*

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

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 over 60 minutes 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 over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

(b) 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. 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

*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. 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 over 60 minutes 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 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. Double-underline denotes changes made as of February 20, 2025 after submission of the present partial change application.)

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey covering all pediatric patients with relapsed or refractory extranodal NK/T-cell lymphoma, nasal type, until data from a certain number of patients are accumulated.

**Attachment**

**Review Report (1)**

July 10, 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** | (a) Tecentriq Intravenous Infusion 840 mg,<br>(b) Tecentriq Intravenous Infusion 1,200 mg |
| **Non-proprietary Name** | Atezolizumab (Genetical Recombination) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | October 31, 2024 |
| **Dosage Form/Strength** | (a) Injection: Each vial (14.0 mL) contains 840 mg of Atezolizumab (Genetical Recombination).<br>(b) Injection: Each vial (20.0 mL) contains 1,200 mg of Atezolizumab (Genetical Recombination). |

**Proposed Indications**

(a) ○ PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer
○ Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

(b) ○ 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
○ Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

(Underline denotes additions.)

**Proposed Dosage and Administration**

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

*Atezolizumab in combination with paclitaxel (albumin-bound)*

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

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 over 60 minutes every 3 weeks. The usual dosage for patients aged ≥12 and <18 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.

(b) 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. 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

*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. 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.

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 over 60 minutes every 3 weeks. The usual dosage for patients aged ≥12 and <18 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.

(Underline denotes additions.)

**Table of Contents**



**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

### 1.1 Outline of the proposed product

Atezolizumab (genetical recombination) (hereinafter referred to as ATZ) is a humanized immunoglobulin (Ig) G1 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 suppressing tumor growth.

In Japan, the 1,200 mg and 840 mg preparations of ATZ have been approved for the following indications.

**1,200 mg preparation**

| Approval date | Indication of ATZ |
|---|---|
| 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 |

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

**840 mg preparation**

| Approval date | Indication of ATZ |
|---|---|
| September 2019 | PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer |
| February 2025 | Unresectable alveolar soft part sarcoma |

### 1.2 Development history, etc.

For the clinical development of ATZ for the treatment of relapsed or refractory extranodal NK/T-cell lymphoma, nasal type (ENKL), an investigator-initiated clinical study, i.e., a Japanese phase II study (NCCH1903/MK006 study [ATTACK study]), has been conducted in Japan by the National Cancer Center Hospital and other institutions since March 2020, targeting patients with ENKL.

As of May 2025, there are no countries or regions in which ATZ is approved for the indication of relapsed or refractory ENKL.

Recently, the applicant submitted a partial change application to add the indications, dosages regimen for relapsed or refractory ENKL, using the ATTACK study as the pivotal clinical study.

## 2. Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for new indications and new dosages, 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 new indications and new dosages, 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 new indications and new dosages, the non-clinical pharmacokinetic 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 new indications and new dosages, 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 new indications and new dosages, 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, in the form of the results from studies presented in Table 1.

**Table 1. Listing of efficacy and safety clinical studies**

| Data category | Geographical location | Study identifier | Phase | Study population | No. of subjects enrolled | Dosing regimen | Main endpoints |
|---|---|---|---|---|---|---|---|
| Evaluation | Japan | ATTACK | II | Patients with relapsed or refractory ENKL aged ≥12 years | 14 | ≥18 years: 1,200 mg of ATZ administered intravenously Q3W<br><18 years: 15 mg/kg* of ATZ administered intravenously Q3W | Efficacy Safety |
| | Foreign | GO29664 | I | Patients with advanced malignant tumors aged <30 years | 90 | ≥18 years: 1,200 mg of ATZ administered intravenously Q3W<br><18 years: 15 mg/kg* of ATZ administered intravenously Q3W | Safety Tolerability PK |

* Maximum 1,200 mg

The clinical studies are summarized below. Study GO29664 was already evaluated at the time of the partial change application for the additional indication and dosage regimen for unresectable alveolar soft part sarcoma (see the "Review Report on Tecentriq Intravenous Infusion 840 mg and 1,200 mg dated January 14, 2025"), its study results are omitted here. Major adverse events other than death observed in the clinical studies are described in Section "7.R.3.1 Safety profile."

## 7.1 Evaluation data

### 7.1.1 Japanese study

#### 7.1.1.1 Japanese phase II study (CTD 5.3.5.2-1, ATTACK study [ongoing since March 2, 2020 (data cutoff date, March 31, 2023)])

An open-label, uncontrolled study was conducted at 4 study sites in Japan to evaluate the efficacy and safety of ATZ in patients with relapsed or refractory ENKL[1)] aged ≥12 years (target sample size, 12-20 subjects[2)]).

For patients aged ≥18 years, ATZ was administered intravenously at 1,200 mg Q3W; for patients aged <18 years, 15 mg/kg (maximum 1,200 mg) was administered intravenously Q3W. Treatment was continued for up to 2 years unless disease progression or discontinuation criteria were met.

All 14 enrolled subjects[3)] received ATZ and were included in the safety analysis set. Of these, 13 subjects were included in the efficacy analysis set and the remaining 1 subject without measurable lesions at baseline by central review was excluded.

The primary efficacy endpoint was the response rate assessed by central review according to the Lugano criteria (*J Clin Oncol.* 2014;32:3059-68). Efficacy was evaluated using the Bayesian design proposed by Thall and Simon (*Biometrics.* 1994;50:337-49) within a Bayesian framework. The study was considered successful[4)] if the posterior probability that the true response rate exceeded the prespecified threshold response rate (5%) was ≥95%.

Table 2 shows the response rate assessed by central review according to the Lugano criteria, the primary efficacy endpoint. The posterior probability that the true response rate exceeded the prespecified threshold response rate (5%) was >99.99%.

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1) Eligible patients were those who had received ≥1 prior regimen for ENKL and had prior therapy with the combination of dexamethasone (DEX), methotrexate (MTX), ifosfamide (IFM), L-asparaginase (L-ASP), and etoposide (ETP) (SMILE), or for whom SMILE chemotherapy is not indicated. Patients meeting any of the following criteria of (1) to (8) were considered ineligible for SMILE chemotherapy: (1) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, (2) age ≥70 years, (3) required transfusion support at least once weekly due to chemotherapy received prior to enrollment, (4) peripheral blood lymphocyte count <500/mm³, (5) prior hematopoietic stem cell transplantation (HSCT), (6) at least 1 of presence of ischemic change, atrial fibrillation, or ventricular arrhythmia requiring treatment, (7) left ventricular ejection fraction <50%, or (8) intolerance to anticancer pharmacotherapy other than SMILE chemotherapy.

2) The target sample size was determined considering the feasibility of study conduct.

3) The median age [range] of the enrolled patients was 72.0 [27, 80] years, and all subjects were aged ≥18 years.

4) For the response rate assessed by central review according to the Lugano criteria (the primary endpoint), the expected response rate and threshold response rate were assumed to be 30% and 5%, respectively. A beta distribution Be (0.6, 1.4) was used as the prior distribution corresponding to an expected response rate of 30%, and beta distribution Be (10, 190) as that corresponding to a threshold response rate of 5%. When the target sample size was 12 to 20 subjects, the minimum number of responders required for the posterior probability that the true response rate would exceed the threshold response rate of 5% to reach ≥95% was calculated to be 3. A simulation assessing the operating characteristics for a target sample size of 12 to 20 subjects estimated the type I error rate and power to be 6.8% and 95.5%, respectively. The expected response rate was determined with reference to the expected response rate (25%-30%) for new agents used in Japanese phase II studies targeting relapsed or refractory mature T/NK-cell lymphomas (*Cancer Sci.* 2017;108:2061-8; *Int J Hematol.* 2017;106:655-65, etc.). The threshold response rate was specified in consideration of the fact that there is no established effective therapy for relapsed or refractory ENKL, which was the target population of the ATTACK study.

**Table 2. Best overall response and response rate**
**(central review, efficacy analysis set, data cutoff March 31, 2023)**

| Best overall response | No. of subjects (%) |
|---|---|
| | n = 13 |
| CR | 4 (30.8) |
| PR | 3 (23.1) |
| SD | 2 (15.4) |
| PD | 3 (23.1) |
| NE | 1 (7.7) |
| Response (CR + PR) | 7 |
| (Response rate [95% CI*] (%)) | (53.8 [25.1, 80.8]) |

* Clopper-Pearson method

No deaths occurred during the treatment period or within 30 days after the end of treatment.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Review strategy

PMDA determined that, among the evaluation data submitted, the pivotal study data for evaluating the efficacy and safety of ATZ was the Japanese phase II study (ATTACK study) in patients with relapsed or refractory ENKL, and decided to evaluate the results focusing on this study.

In addition, with respect to determining the dosage regimen of ATZ for pediatric patients with relapsed or refractory ENKL, PMDA decided to evaluate the data comprehensively, taking into account not only the Japanese phase II study (ATTACK study) but also the foreign phase I study (GO29664 study) and other relevant studies.

### 7.R.2 Efficacy

On the basis of the results of the following review, PMDA concluded that ATZ can be expected to provide efficacy in patients with relapsed or refractory ENKL.

#### 7.R.2.1 Efficacy endpoints and evaluation method

The applicant' explanations about (a) the efficacy endpoints and (b) the evaluation method for efficacy in the ATTACK study.

(a) Efficacy endpoints

Relapsed or refractory ENKL, the target disease in the ATTACK study, is a disease with extremely poor prognosis with no standard therapy established. Hematopoietic stem cell transplantation (HSCT) is recommended for eligible patients after achieving complete response (CR) to salvage therapy. (Practical Guidelines for Hematological Malignancies). Regardless of the eligibility for HSCT, treatment success in patients with relapsed or refractory ENKL leads to tumor reduction or disappearance, thereby improving clinical symptoms (such as nasal obstruction, discharge, and bleeding associated with nasal lesions, and ulceration or necrosis associated with extra-nasal lesions) (*Blood.* 2017;129:2437-42, etc.).

Considering it is of clinical significance to achieve treatment success in the target patients of the ATTACK study, response rate was determined as the primary efficacy endpoint.

(b) Efficacy evaluation method

Due to the extremely limited number of patients with relapsed or refractory ENKL, the target population of the ATTACK study and trends in patient enrollment that were unpredictable at the study planning stage, the ATTACK study employed a Bayesian design to define the study success criteria [see Section 7.1.1.1]. When the target sample size was 12 to 20, the minimum number of responders necessary for the posterior probability that the true response rate would exceed the prespecified threshold response rate (5%) to be ≥95% was 3 in all cases.

PMDA's view:

The applicant's explanation about the efficacy endpoint is understandable.

However, considering the minimum number of responders satisfying the success criteria in the ATTACK study, as the primary evidence of efficacy for the present partial change application, and the results of simulated operating characteristics [see Section 7.1.1.1], the evaluation method prespecified in the study has limitations in evaluating the efficacy of ATZ. Therefore, the efficacy of ATZ was evaluated comprehensively including the results of the best overall response actually obtained in the ATTACK study.

### 7.R.2.2 Results of efficacy evaluation

The applicant's explanation about the results of the efficacy evaluation:

In the ATTACK study, the number of patients who achieved a response based on the central review according to the Lugano criteria, which was defined as the primary endpoint, was 7 of 13.[5)] The posterior probability that the response rate exceeded the pre-specified threshold response rate (5%) was greater than 95%. To assess the robustness of the results with respect to the prior distribution in the Bayesian design, the posterior distribution was calculated assuming a non-informative prior distribution for the response rate, Be (1, 1). The posterior probability that the response rate exceeded the threshold response rate (5%) was then calculated and was >99.99%. Therefore, the results obtained were considered robust to the choice of the prior distribution.

Figure 1 shows the maximum percent change from baseline in the sum of the bidimensional products of target lesions in the ATTACK study. The secondary endpoint, i.e., the median duration of response according to the institutional assessment based on the Lugano criteria [95% confidence interval (CI)] (months) was not estimable [1.4, not estimable].[6)]

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5) As for the secondary endpoint, the number of patients who achieved a response according to the institutional assessment was 5 of 13 (38.5%). There were 2 patients for whom the best overall response differed between the assessment methods. The details of each assessment result and the reasons for the discrepancies are as follows.
   (a) Central review, partial response (PR)/Institutional assessment, progressive disease (PD)
   In the institutional assessment, although shrinkage of the target lesion was confirmed, the presence of a non-target lesion (right adrenal gland) was observed, leading to a judgment of PD, whereas the central review considered response to the target lesion (PR) was observed and then a non-target lesion was observed
   (b) Central review, PR/Institutional assessment, PD
   In the institutional assessment, progression of a non-target lesion (right pharynx) was observed and judged as PD, whereas the central review considered the same lesion to represent inflammatory changes.

6) In the 5 patients who achieved a response based on the institutional assessment, the median [range] observation period (months) was 24.9 [1.4, 26.8].

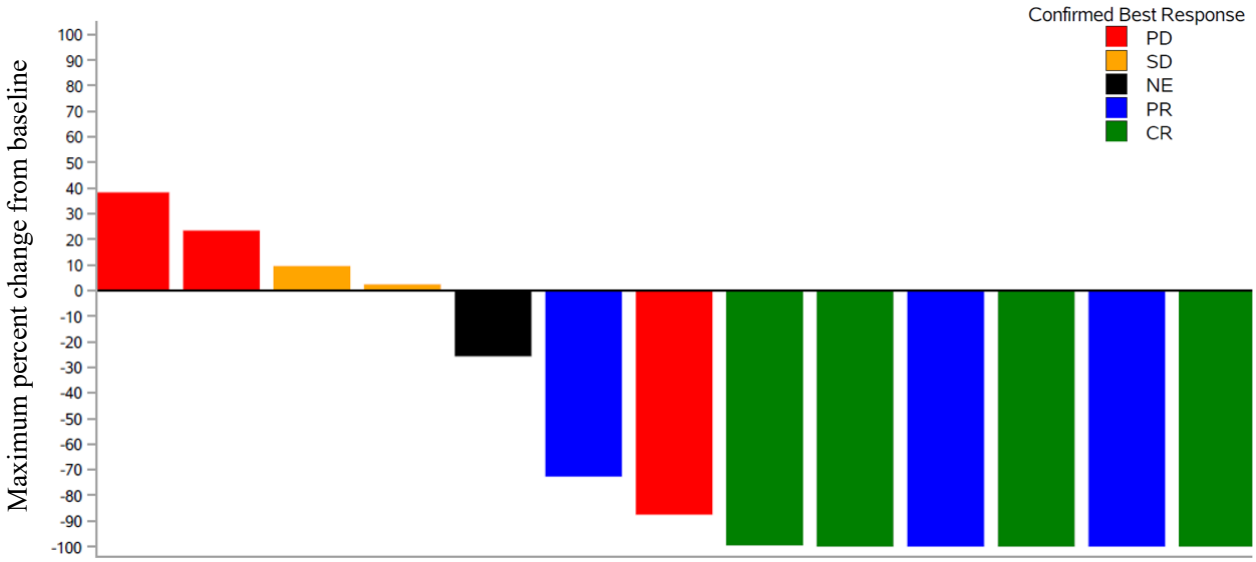


**Figure 1. Maximum percent change from baseline in the sum of the bidimensional products of target lesions (ATTACK study, Lugano criteria, central review, efficacy analysis set, data cutoff March 31, 2023)**

In the ATTACK study, a disappeared lesion in the nasal cavity, nasopharynx, pharynx, and skin[7)] was confirmed by central review in 6 of 13 patients.[8)]

PMDA's view:

Although there are limitations in evaluating the efficacy of ATZ based on the pre-specified efficacy assessment method in the ATTACK study [see Section 7.R.2.1], taking into account both the applicant's explanation as well as the response rate and CR rate observed in the ATTACK study (53.8% and 30.8%, respectively) [see Section 7.1.1.1], the efficacy of ATZ can be expected in patients with relapsed or refractory ENKL.

### 7.R.3 Safety

PMDA's view:

Based on the evaluation described below, the adverse events requiring particular attention when ATZ is administered to patients with relapsed or refractory ENKL are those that had been identified as requiring caution at the time of approval for the previously approved indications.[9)] Attention should be paid to the occurrence of these adverse events when ATZ is used.

Although attention should be paid to the occurrence of the above adverse events during use of ATZ, provided that physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, such as monitoring of patients, management of adverse events, taking account of

7) A disappeared lesion was defined as a lesion, including non-target lesions, for which both the long and short diameters measured 0.0 cm.
8) Since patient-reported outcome evaluations had not been planned, no results were obtained regarding the assessment of tumor shrinkage and clinical symptoms.
9) Interstitial lung disease (ILD), hepatic dysfunction/hepatitis/sclerosing cholangitis, colitis/severe diarrhea, pancreatitis, type 1 diabetes mellitus, endocrine disorders (thyroid dysfunction, adrenal insufficiency, and pituitary dysfunction), encephalitis/meningitis/myelitis, neuropathy (including Guillain-Barré syndrome), myasthenia gravis, severe cutaneous disorders, renal dysfunction (including tubulointerstitial nephritis), myositis/rhabdomyolysis, myocarditis, haemophagocytic syndrome, immune thrombocytopenia, infusion reaction, haemolytic anaemia, pericarditis/pericardial effusion/cardiac tamponade (see "Review Report for Tecentriq Intravenous Infusion 840 mg and 1,200 mg dated January 14, 2025").

adverse drug reactions due to excessive immune responses, and interruption of ATZ, ATZ is tolerable in patients with relapsed or refractory ENKL.

### 7.R.3.1 Safety profile

The applicant's explanation about the safety profile of ATZ based on the safety information obtained in the ATTACK study:

The safety results in the ATTACK study are summarized in Table 3.

**Table 3. Summary of safety* (ATTACK study)**

| | Number of patients (%) |
|---|---|
| | 14 |
| All adverse events | 14 (100) |
| Adverse events for which a causal relationship to ATZ could not be ruled out | 11 (78.6) |
| Grade ≥3 adverse events | 10 (71.4) |
| Adverse events leading to death | 0 |
| Serious adverse events | 4 (28.6) |
| Adverse events leading to discontinuation of ATZ | 4 (28.6) |
| Adverse events leading to interruption of ATZ | 6 (42.9) |

* Dose reduction of ATZ was not permitted.

Table 4 shows adverse events observed in multiple patients in the ATTACK study. There were no adverse events leading to death, nor serious adverse events or adverse events leading to interruption of ATZ observed in multiple patients.

**Table 4. Adverse events observed in multiple subjects (ATTACK study)**

| PT (MedDRA/J ver.22.1) | Number of patients (%) 14 |
|---|---|
| All adverse events | |
| Pyrexia | 9 (64.3) |
| Neutrophil count decreased | 6 (42.9) |
| Anaemia | 5 (35.7) |
| White blood cell count decreased | 5 (35.7) |
| Hypoalbuminaemia | 5 (35.7) |
| AST increased | 4 (28.6) |
| Platelet count decreased | 3 (21.4) |
| Rash | 3 (21.4) |
| Immune-mediated hepatitis | 2 (14.3) |
| Contrast media allergy | 2 (14.3) |
| ALT increased | 2 (14.3) |
| Blood creatinine increased | 2 (14.3) |
| Lymphocyte count decreased | 2 (14.3) |
| Hypokalaemia | 2 (14.3) |
| Tumour pain | 2 (14.3) |
| Pruritus | 2 (14.3) |
| Grade ≥3 adverse events | |
| White blood cell count decreased | 4 (28.6) |
| Neutrophil count decreased | 3 (21.4) |
| Anaemia | 3 (21.4) |
| Pyrexia | 2 (14.3) |
| Immune-mediated hepatitis | 2 (14.3) |
| Lymphocyte count decreased | 2 (14.3) |
| Hypokalaemia | 2 (14.3) |
| Adverse events leading to discontinuation of ATZ | |
| Immune-mediated hepatitis | 2 (14.3) |

The applicant's explanation about differences in the safety profiles between the ATTACK study and the clinical studies conducted at the time of approval for the previously approved indications, in which ATZ

was administered as monotherapy to patients with advanced solid tumors ([a] foreign phase II study [NCI study],[10] [b] Japanese phase II study [ALBERT study],[11] [c] global phase III study [IMpower110 study],[12] and [d] global phase III study [OAK study])[13]:
Table 5 shows the results of the comparison of incidences of adverse event.

**Table 5. Summary of safety compared with clinical studies for previously approved indications[*1,*2]**

| | Number of patients (%) | | | | |
|---|---|---|---|---|---|
| | ATTACK study | NCI study | ALBERT study | IMpower110 study (ATZ) | OAK study (ATZ) |
| | 14 | 49 | 20 | 286 | 609 |
| All adverse events | 14 (100) | 49 (100) | 20 (100) | 258 (90.2) | 573 (94.1) |
| Grade ≥3 adverse events | 10 (71.4) | 27 (55.1) | 6 (30.0) | 97 (33.9) | 237 (38.9) |
| Adverse events leading to death | 0 | 0 | 0 | 11 (3.8) | 10 (1.6) |
| Serious adverse events | 4 (28.6) | 20 (40.8) | 3 (15.0) | 81 (28.3) | 194 (31.9) |
| Adverse events leading to discontinuation of ATZ | 4 (28.6) | 2 (4.1) | 3 (15.0) | 18 (6.3) | 46 (7.6) |
| Adverse events leading to interruption of ATZ | 6 (42.9) | 15 (30.6) | 4 (20.0) | 73 (25.5) | 151 (24.8) |

*1 Data cut-off dates were March 31, 2023 in the ATTACK study; September 1, 2021 in the NCI study; March 3, 2022 in the ALBERT study; July 7, 2016 in the IMpower110 study; and September 10, 2018 in the OAK study.
*2 In all studies, dose reduction of ATZ was not permitted.

Table 6 shows adverse events with ≥10% higher incidence in the ATTACK study compared with any of the NCI, ALBERT, IMpower110, and OAK studies. No adverse events leading to death, serious adverse events, nor adverse events leading to interruption of ATZ with ≥10% higher incidence were observed in the ATTACK study compared with these studies.

**Table 6. Adverse events with ≥10% higher incidence in the ATTACK study compared with the NCI, ALBERT, IMpower110, and OAK studies**

| PT (MedDRA/J ver. 25.1) | Number of patients (%) | | | | |
|---|---|---|---|---|---|
| | ATTACK study | NCI study | ALBERT study | IMpower110 study ATZ | OAK study ATZ |
| | 14 | 49 | 20 | 286 | 609 |
| All adverse events | | | | | |
| Pyrexia | 9 (64.3) | 12 (24.5) | 8 (40.0) | 39 (13.6) | 108 (17.7) |
| Neutrophil count decreased | 6 (42.9) | 6 (12.2) | 4 (20.0) | 0 | 2 (0.3) |
| Hypoalbuminaemia | 5 (35.7) | 2 (4.1) | 1 (5.0) | 8 (2.8) | 19 (3.1) |
| Immune-mediated hepatitis | 2 (14.3) | 0 | 0 | 0 | 0 |
| Grade ≥3 adverse events | | | | | |
| White blood cell count decreased | 4 (28.6) | 0 | 1 (5.0) | 0 | 0 |
| Neutrophil count decreased | 3 (21.4) | 0 | 0 | 0 | 1 (0.2) |
| Anaemia | 3 (21.4) | 2 (4.1) | 1 (5.0) | 5 (1.7) | 14 (2.3) |
| Hypokalaemia | 2 (14.3) | 0 | 0 | 0 | 4 (0.7) |
| Immune-mediated hepatitis | 2 (14.3) | 0 | 0 | 0 | 0 |
| Adverse events leading to discontinuation of ATZ | | | | | |
| Immune-mediated hepatitis | 2 (14.3) | 0 | 0 | 0 | 0 |

The small number of patients enrolled in the ATTACK study limited the comparison with the clinical study results for the previously approved indications. Yet, adverse events with a ≥10% higher incidence in the ATTACK study than in any of other studies were neutropenia (all grades), decreased white blood

[10] Study in patients with unresectable alveolar soft part sarcoma aged ≥2 years. The dosage regimen of ATZ was intravenous administration of 1,200 mg Q3W for patients aged ≥18 years, and 15 mg/kg (up to a maximum of 1,200 mg) Q3W for patients aged <18 years.
[11] Study in patients with unresectable alveolar soft part sarcoma aged ≥16 years. The dosage regimen of ATZ was intravenous administration of 1,200 mg Q3W for patients aged ≥18 years, and 15 mg/kg (up to a maximum of 1,200 mg) Q3W for patients aged <18 years.
[12] Study in patients with unresectable, advanced, or recurrent PD-L1-positive non-small cell lung cancer without prior chemotherapy. The dosage regimen of ATZ was intravenous administration of 1,200 mg Q3W.
[13] Study in patients with unresectable, advanced, or recurrent non-small cell lung cancer with prior chemotherapy. The dosage regimen of ATZ was intravenous administration of 1,200 mg Q3W.

cell count, decreased neutrophil count, and anemia (Grade ≥3), showing a tendency toward higher incidences of cytopenia-related adverse events. Unlike other clinical studies, the ATTACK study allowed enrollment of patients meeting specified blood cell count criteria after supportive therapy.[14)]Bone marrow infiltration by tumor cells was reported as a pathological condition of ENKL (*Int J Clin Oncol.* 2009;14:181-190). These are the possible contributing factors to the tendency. In the ATTACK study, no cytopenia (including febrile neutropenia) resulting in death[15)] or serious cytopenia (including febrile neutropenia) occurred.

PMDA's view:
The adverse events observed in the ATTACK study and those showing a high incidence compared with the past clinical studies on the approved indications warrant attention. However, these are known adverse events of ATZ, and ATZ is considered tolerable in patients with relapsed or refractory ENKL when appropriate measures are taken by physicians with adequate knowledge of and experience in cancer chemotherapy, including patient monitoring, adverse event management while taking account of adverse drug reactions due to excessive immune responses, and the interruption of ATZ.

### 7.R.3.2 Complications related to allo-HSCT

The National Comprehensive Cancer Network (NCCN) Guidelines for T-Cell Lymphomas (v.2.2025) state that administration of immune checkpoint inhibitors such as anti-PD-1/PD-L1 antibodies prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT) may lead to exacerbation of transplant-related adverse reactions. PMDA requested the applicant to explain the necessity of cautionary advice on complications associated with allo-HSCT in the use of ATZ.

The applicant's response:
Adverse events related to complications associated with allo-HSCT were summarized using "Transplantation complications" in the Medical Dictionary for Regulatory Activities (MedDRA) high level term (HLT) and the preferred term (PT) corresponding to "Immune disorders and associated conditions NEC."

In the ATTACK study,[16)] there were no patients with a prior treatment with allo-HSCT or those who underwent allo-HSCT as post-treatment during the follow-up period. In the foreign post-marketing safety information (data cutoff, January 27, 2025), a serious allo-HSCT-related complication (chronic

14) The following were the inclusion criteria for hematologic parameters in the ATTACK study, based on laboratory tests within 14 days before enrollment, and patients met the following criteria:
(1) Neutrophil count ≥1,500/mm² (administration of G-CSF products permitted as supportive therapy),
(2) Platelet count ≥75,000/mm² (platelet transfusion permitted as supportive therapy), and
(3) Hemoglobin ≥8.0 g/dL (red blood cell transfusion permitted as supportive therapy).
The numbers of patients enrolled after receiving the respective supportive therapies were (1) 3 patients (all of whom developed neutropenia after administration of ATZ), (2) none (0 patients), and (3) none (0 patients).

15) Adverse events related to cytopenia (including febrile neutropenia) were summarized using PTs corresponding to the MedDRA Standardised MedDRA Queries (SMQs) "Haematopoietic cytopenias affecting more than one type of blood cell (broad)," "Haematopoietic leukopenia (narrow)," "Haematopoietic erythropenia (narrow)," and "Haematopoietic thrombocytopenia (narrow)," as well as the MedDRA PTs "Anaemia," "Haemoglobin decreased," and "Haematocrit decreased."

16) In the ATTACK study, absence of a prior treatment with allo-HSCT within the past 6 months was an inclusion criterion.

graft-versus-host disease [GVHD]) was reported in 1 patient[17] who underwent allo-HSCT following the administration of ATZ, and a causal relationship to ATZ could not be ruled out.

To date, there is no published literature available suggesting an association between ATZ administration and the risk of allo-HSCT-related complications.

Based on the above, the possibility cannot be ruled out that the administration of ATZ may increase the risk of allo-HSCT-related complications. However, in light of no findings suggestive of a relationship between ATZ and allo-HSCT-related complications and of the previously offered cautions against possible immune-associated events overall as allo-HSCT-related complications in use of ATZ for the approved indications, cautionary advice is unnecessary at present for patients with prior treatment with allo-HSCT or those scheduled to undergo allo-HSCT. The collection of information will continue on the association between ATZ administration pre/post-allo-HSCT and the risk of serious complications such as GVHD [see Section 7.R.6].

PMDA's view:
PMDA accepted the applicant's explanation. However, healthcare professionals should be properly updated with new findings on complications associated with allo-HSCT following ATZ treatment in a timely manner.

### 7.R.4 Clinical positioning and indications

The indication for ATZ in the present partial change application was defined as "relapsed or refractory extranodal NK/T-cell lymphoma, nasal type." There were no cautionary statements relevant to this indication.

Based on the Sections "7.R.2 Efficacy" and "7.R.3 Safety," as well as the results of the following review, PMDA concluded that the PRECAUTIONS CONCERNING INDICATION section should offer the following advice, and that the Indication for ATZ in the present partial change application should be "relapsed or refractory extranodal NK/T-cell lymphoma, nasal type, as proposed by the applicant.

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

[17] A 5[redacted]-year-old man with diffuse large B-cell lymphoma received the combination of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisolone/prednisone/methylprednisolone (R-CHOP), the combination of rituximab (genetical recombination) (RIT), methylprednisolone (mPSL), ETP, cytarabine, and cisplatin (CDDP) (R-ESHAP), and allo-HSCT. After administration of glofitamab (unapproved in Japan) and ATZ (not indicated in Japan), allo-HSCT was performed with thiotepa, busulfan, and fludarabine phosphate, followed by post-transplant cyclophosphamide hydrate (CY), mycophenolate mofetil, and tacrolimus for GVHD prophylaxis. Subsequently, chronic GVHD of the gastrointestinal tract and lungs developed, and the patient died on Day 257 post-allo-HSCT due to GVHD (serious; causal relationship to ATZ could not be ruled out) (*Bone Marrow Transplant.* 2023;58:1282-5).

### 7.R.4.1 Clinical positioning of ATZ

In major Japanese and foreign clinical practice guidelines,[18] as well as representative textbooks of hematology and clinical oncology,[19] no description of ATZ for the treatment of relapsed or refractory ENKL has been identified.

The applicant's explanation about the clinical positioning of ATZ for relapsed or refractory ENKL:
Patients with localized disease outside the nasal area, patients with nasal-area disease extending beyond the cervical lymph nodes (initial advanced stage), and patients with localized nasal-area disease who experience initial relapse or are refractory to treatment have a poor prognosis (*Ann Oncol.* 2017;28:2199-205). For such patients, SMILE chemotherapy (the combination of dexamethasone [DEX], methotrexate [MTX], ifosfamide [IFM], L-asparaginase [L-ASP], and etoposide [ETP]) is recommended as salvage chemotherapy (NCCN Guidelines for T-Cell Lymphomas, v.2.2025[20]; Practical Guidelines for Hematologic Malignancies). However, there is no established standard treatment for patients with ENKL relapsed after SMILE chemotherapy, those who are refractory to or ineligible for SMILE chemotherapy (Practical Guidelines for Hematologic Malignancies).

Accordingly, with its clinical usefulness demonstrated in the ATTACK study in patients with relapsed or refractory ENKL who had prior SMILE chemotherapy or are ineligible for SMILE chemotherapy [see Sections 7.R.2 and 7.R.3], ATZ is considered a new therapeutic option for these populations.

Although salvage chemotherapies[21] other than SMILE chemotherapy are listed as treatment options for patients with relapsed or refractory ENKL who had prior SMILE chemotherapy or are ineligible for the therapy (Practical Guidelines for Hematologic Malignancies), currently there are no regimens supported by results from prospective clinical studies. Therefore, ATZ is expected to serve as a first-line option for these patients.

PMDA's view:
PMDA generally accepted the applicant's explanation regarding the clinical positioning of ATZ. However, the current lack of clinical study results comparing the efficacy and safety of ATZ with conventional treatments precludes the conclusion that ATZ will serve as a first-line therapy for patients with relapsed or refractory ENKL who had prior SMILE chemotherapy or those ineligible for SMILE chemotherapy. To select appropriate treatment, whether to choose ATZ or a conventional option should be determined by physicians with adequate knowledge of and experience in cancer chemotherapy, taking account of action mechanisms and efficacy/safety profiles of drug products as well as the clinical condition and prior treatment of individual patients.

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18) Practical Guidelines for Hematologic Malignancies; A Practical Guideline for Pediatric Leukemia and Lymphoma (Japanese Society of Pediatric Hematology/Oncology, 2016 edition); NCCN Guidelines for T-Cell Lymphomas (v.2.2025); European Society for Medical Oncology (ESMO) Guidelines (published online February 20, 2013); and National Cancer Institute Physician Data Query (NCI-PDQ) Peripheral T-Cell Non-Hodgkin Lymphoma Treatment (version of February 3, 2025).

19) Textbook of Hematology, fourth revised edition (Japanese Society of Hematology, 2023); Clinical oncology update-essentials for medical oncologists, seventh revised edition (Japanese Society of Medical Oncology, 2024); Williams Hematology, 10th Edition (McGraw Hill Medical, 2021, USA); Wintrobe's Clinical Hematology, 15th Edition (Wolters Kluwer, 2023, USA); Principles & Practice of Oncology, 12th Edition (Wolters Kluwer, 2023, Netherlands); and Pizzo and Poplack's Pediatric Oncology, 8th Edition (Wolters Kluwer, 2020, USA).

20) Recommended as Category 2A (a uniform consensus of the NCCN that the intervention is appropriate based on relatively low-level evidence).

21) GDP therapy (gemcitabine hydrochloride [GEM], DEX, and CDDP), DeVIC therapy (DEX, ETP, IFM, and CBDCA), ICE therapy (IFM, CBDCA, and ETP), and L-ASP monotherapy.

### 7.R.4.2 Patient population and indications for ATZ

The applicant's explanation about the patient population and indications for ATZ from the following 2 perspectives: (1) prior treatment of patients for whom administration of ATZ is recommended, and (2) PD-L1 expression status:

(1) Prior treatment

The ATTACK study enrolled patients with relapsed or refractory ENKL who had prior SMILE chemotherapy or those who are ineligible for SMILE chemotherapy. Since the study demonstrated the clinical usefulness of ATZ [see Sections 7.R.2 and 7.R.3], treatment with ATZ is considered recommendable for these patient populations.

Furthermore, considering the following point, administration of ATZ may also be acceptable for patients with relapsed or refractory ENKL who are eligible for but naïve to SMILE chemotherapy.

- In the ATTACK study, a certain proportion of patients who were SMILE chemotherapy-naïve, because of their ineligibility judged, responded to ATZ.[22)]

(2) PD-L1 expression status

The ATTACK study enrolled patients regardless of PD-L1 expression. Among patients for whom PD-L1 testing was feasible, exploratory analyses of efficacy and safety were conducted by the PD-L1 expression subgroup.[23)] The efficacy analysis showed the response rates [95% CI] of 80.0% [28.4%, 99.5%] (4 of 5 patients) in PD-L1-positive patients and 33.3% [4.3%, 77.7%] (2 of 6 patients) in PD-L1-negative patients. The safety analysis revealed that the incidence of adverse events was 100% (5 of 5 patients) in PD-L1-positive patients and 100% (6 of 6 patients) in PD-L1-negative patients.[24)]

Considering the following findings, it is unnecessary to restrict the patient population of ATZ based on PD-L1 expression:

- A certain proportion of PD-L1-negative patients responded.
- No clear differences in the safety profile of ATZ were observed between PD-L1-positive and PD-L1-negative patients.

PMDA's view:

PMDA generally accepted the applicant's explanation regarding the prior treatment of patients for whom the use of ATZ is recommended. Since no clinical study data evaluating the efficacy and safety of ATZ are available for patients with relapsed or refractory ENKL eligible for SMILE chemotherapy, the package insert should note in the CLINICAL STUDIES section that the participants of the ATTACK study were patients with prior SMILE chemotherapy or those who were ineligible for SMILE chemotherapy. In addition, the PRECAUTIONS CONCERNING INDICATION section should caution

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22) Among the 6 patients in the ATTACK study who were assessed to be not indicated for SMILE chemotherapy, the best overall responses by central review were CR in 3 patients, stable disease (SD) in 1 patient, and PD in 2 patients.

23) PD-L1 positivity was determined using Cell Signaling Technology SP142 and Spring Bioscience E1J2J antibodies. Tumor cells were considered PD-L1-positive when their staining intensity was equal to or greater than that of PD-L1-expressing intratumoral macrophages serving as internal controls.

24) No serious adverse events occurred in PD-L1-positive patients, whereas serious adverse events were observed in 50.0% (3 of 6) of PD-L1-negative patients, consisting of arthritis, skin infection, and immune-mediated hepatitis (1 patient each). A causal relationship to ATZ could not be ruled out for arthritis and immune-mediated hepatitis, but both resolved after interruption or discontinuation of ATZ. The incidence of Grade ≥3 adverse events was 80.0% (4 of 5 patients) in PD-L1-positive patients and 100% (6 of 6 patients) in PD-L1-negative patients.

that healthcare professionals should select eligible patients based on a full understanding of the prior treatment of patients enrolled in the clinical study described in the CLINICAL STUDIES section.

PMDA also accepted the applicant's explanation about eligibility decision made for the use of ATZ regardless of PD-L1 expression status. Yet, any new efficacy information or other findings based on PD-L1 expression status should be properly communicated to healthcare professionals.

PMDA concluded that the following cautionary note should be provided in the PRECAUTIONS CONCERNING INDICATION section and that the indication should be "relapsed or refractory extranodal NK/T-cell lymphoma, nasal type," as proposed by the applicant.

**Precautions Concerning Indications**

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

### 7.R.5 Dosage and administration

For relapsed or refractory ENKL, the proposed dosage and administration, as well as precautions concerning dosage and administration of ATZ, were established as follows:

**Dosage and Administration**

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 patients aged ≥12 and <18 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.

**Precautions Concerning Dosage and Administration**

All indications

- Recommended ATZ dosage modification following an adverse reaction (identical to those for previously approved indications).

Relapsed or refractory ENKL

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

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following considerations, PMDA has concluded that the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION for ATZ in relapsed or refractory ENKL should be described as follows.

**Dosage and Administration**

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 ≥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 over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

**Precautions Concerning Dosage and Administration**

All indications

- Recommended ATZ dosage modifications for adverse reactions (identical to those for previously approved indications).

Relapsed or refractory ENKL

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

### 7.R.5.1 Dosage and administration of ATZ

The applicant's explanation about the dosage regimen of ATZ:

In the ATTACK study, the dosage regimen of ATZ was intravenous administration of 1,200 mg Q3W for subjects aged ≥18 years, and intravenous administration of 15 mg/kg (up to a maximum of 1,200 mg) Q3W for subjects aged ≥12[25)] and <18 years, taking into account the following considerations:

- For patients aged ≥18 years, at the time of the ATTACK study design, the efficacy and safety of intravenous administration of ATZ 1,200 mg Q3W had already been confirmed in multiple tumor types (see the "Review Report on Tecentriq Intravenous Infusion 1,200 mg, dated October 23, 2017"). Therefore, a dosage of 1,200 mg Q3W was selected.

- For patients aged ≥12 and <18 years, the GO29664 study, which was ongoing at the time of the ATTACK study design, showed no clear differences in pharmacokinetics (PK) and safety profiles between adults and pediatric patients (see the "Review Report on Tecentriq Intravenous Infusion 840 mg and 1,200 mg, dated January 14, 2025"). In addition, no notable differences in PK and safety profiles between Japanese and foreign populations were observed in clinical studies of ATZ in adults (see the "Review Report on Tecentriq Intravenous Infusion 1,200 mg, dated October 23, 2017"). Accordingly, the dosage for patients aged <18 years was 15 mg/kg (up to a maximum of 1,200 mg) Q3W, consistent with that in the GO29664 study.

Under the above conditions, the ATTACK study demonstrated the clinical usefulness of ATZ [see Sections 7.R.2 and 7.R.3].

Although no patients aged ≥12 and <18 years were enrolled in the ATTACK study, and no post-marketing or published data are available regarding ATZ 15 mg/kg dosing in patients with ENKL aged

[25)] Tumor cells in ENKL, an Epstein-Barr virus (EBV)-associated malignancy, are EBV-positive regardless of age. PD-L1 expression is upregulated through Latent membrane protein 1 (LMP1) encoded by EBV (*Leukemia.* 2019;33:1687-99; *J Hematol Oncol.* 2016;9:109), and the median age at onset of ENKL is 52 years [14, 89] (*Ann Oncol.* 2010;21:1032-40). Based on the above and other findings, patients aged ≥12 years, who were considered evaluable together with adults, were included as eligible subjects in the ATTACK study.

<18 years, the applicant considers it acceptable to specify the dosage for patients with relapsed or refractory ENKL aged ≥12 and <18 years at 15 mg/kg Q3W, based on the following rationale:

- In addition to the mechanism of action of ATZ, the following findings suggest that efficacy can be expected in pediatric patients with relapsed or refractory ENKL aged ≥12 years, similar to adults:
  - Tumor cells in ENKL, an Epstein-Barr virus (EBV)-associated malignancy, are EBV-positive regardless of age, and PD-L1 expression is upregulated through Latent membrane protein 1 (LMP1) encoded by EBV (*Leukemia.* 2019;33:1687-99; *J Hematol Oncol.* 2016;9:109).
  - There are no clear differences in diagnostic or therapeutic approaches for relapsed or refractory ENKL between pediatric and adult patients (*Br J Haematol.* 2019;185:1086-98).

- Simulation of exposure to ATZ ($C_{min}$, $C_{max}$, and AUC) by age group using a population pharmacokinetics (PPK) model indicated that exposure after ATZ 15 mg/kg Q3W dosing in patients aged ≥12 and <18 years tended to be slightly lower than that after ATZ 1,200 mg Q3W dosing in patients aged ≥18 years (see "Review Report on Tecentriq Intravenous Infusion 840 mg and 1,200 mg, dated January 14, 2025"). However, the geometric mean values were within the range observed in 7 clinical studies of adult patients with other cancer types,[26] suggesting no clinically meaningful difference in exposure between the 2 age groups (i.e., ATZ 15 mg/kg Q3W dosing in patients aged ≥12 and <18 years and ATZ 1,200 mg Q3W dosing in patients aged ≥18 years).

- Given the following considerations, administration of 15 mg/kg Q3W is tolerable in patients with relapsed or refractory ENKL aged ≥12 and <18 years, provided that physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, such as monitoring of patients, management of adverse events, taking account of adverse drug reactions due to excessive immune responses, and interruption of ATZ.
  - In the GO29664 study, no clear differences in the safety profile were observed between patients aged ≥18 years who received intravenously ATZ 1,200 mg Q3W and those aged ≥12 and <18 years who received intravenously ATZ 15 mg/kg Q3W (maximum 1,200 mg), and tolerability was confirmed in patients aged ≥12 and <18 years (see "Review Report on Tecentriq Intravenous Infusion 840 mg and 1,200 mg, dated January 14, 2025").

In the ATTACK study, the treatment period with ATZ was 2 years based on the feasibility of evaluation on clinical usefulness, in view of extremely poor prognosis of patients with relapsed or refractory ENKL, with a median survival time of less than 1 year (*Ann Oncol.* 2017;28:2199-205). However, considering

[26] Studies YO40245 (IMbrave150 study) (hepatocellular carcinoma), WO29637 (IMmotion151 study) (renal cell carcinoma), GO29527 (IMpower010 study), GO29431 (IMpower110 study), GO29436 (IMpower150 study), and the OAK study (all NSCLC), as well as Study GO29294 (IMvigor211 study) (urothelial carcinoma).

the following, the upper limit of treatment duration needs not be specified in the DOSAGE AND ADMINISTRATION of ATZ:

- Although no patients in the ATTACK study received ATZ beyond 2 years,[27)] safety profile data from a study on >2-year treatment for a different cancer type[28)] suggest no clear safety concerns associated with long-term treatment.
- Safety profiles from the clinical studies in patients with non-ENKL cancer aged <18 years treated with ATZ beyond 2 years and post-marketing safety data[29)] indicate no specific safety concerns associated with ATZ administered for >2 years to patients with relapsed or refractory ENKL aged ≥12 and <18 years.

Accordingly, the following dosage regimen of ATZ were proposed: 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 patients aged ≥12 and <18 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.

At present, no clinical study results have been obtained regarding the efficacy and safety of ATZ when administered in combination with other anti-neoplastic drugs in patients with relapsed or refractory ENKL. Therefore, the use of ATZ in combination with other anti-neoplastic drugs is not recommended, and appropriate caution should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

In addition, the ATTACK study applied the same criteria for interruption and discontinuation of ATZ upon the occurrence of adverse drug reactions as those approved for other indications. Given that clinical usefulness was demonstrated under the aforementioned conditions, for the present partial change application, the criteria for interruption or discontinuation in the event of adverse drug reactions in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, including in pediatric patients aged ≥12 years, should remain identical to those for existing approved indications.

PMDA's view:
PMDA accepted the applicant's explanation regarding the dosage regimen for patients aged ≥18 years, the concomitant use with other anti-neoplastic drugs, and the guidelines for interruption or discontinuation of ATZ.

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27) In the ATTACK study, the median [range] number of dosing cycles of ATZ was 4 [1, 35] (1 cycle consisted of 21 days).

28) In the foreign phase III/IV study (Study MO39171), which evaluated the long-term efficacy and safety of ATZ 1,200 mg Q3W in patients with unresectable, advanced, or recurrent non-small cell lung cancer, serious adverse events observed with a ≥2% higher incidence and in multiple patients among those treated for ≥2 years compared with those treated for <2 years were COVID-19 (corona virus infectious disease emerged in 2019) and anaphylactic shock (both: ≥2 years, 2 of 56 patients [3.6%]; <2 years, 0 of 559 patients). A causal relationship to ATZ was ruled out for both events (data cut-off date, June 26, 2021).

29) Among 3 patients treated with ATZ for ≥2 years in the NCI study and Study GO29664, 1 patient experienced a serious adverse event (dyspnea, Grade 4), for which a causal relationship to ATZ was ruled out. In other clinical studies and post-marketing safety data (data cut-off date, March 31, 2025), adverse events were reported in 118 pediatric patients; however, no adverse events were reported in those treated for ≥2 years.

In principle, the dosage regimen for patients aged ≥12 and <18 years should be established based on the results of clinical studies on the efficacy and safety of the 15 mg/kg Q3W dose of ATZ in pediatric patients with relapsed or refractory ENKL aged ≥12 years. Nevertheless, the applicant's explanation is acceptable to a certain extent. Furthermore, relapsed or refractory ENKL is a life-threatening disease with poor prognosis and rapid, irreversible progression that occurs in children extremely rarely. Despite the uncertainty with efficacy and safety remaining unknown in this population, it is acceptable to establish a dosage regimen for patients with relapsed or refractory ENKL aged ≥12 and <18 years, in light of expected disadvantages created for patients by consuming considerable time in a clinical study for approval.

Nevertheless, there is no experience with ATZ 15 mg/kg Q3W administered in patients with relapsed or refractory ENKL aged ≥12 and <18 years in and outside Japan. Exposure to ATZ 15 mg/kg Q3W of patients aged <18 years tends to be lower than that to ATZ 1,200 mg Q3W of patients aged ≥18 years (see "Review Report on Tecentriq Intravenous Infusion 840 mg and 1,200 mg, dated January 14, 2025"). Therefore, efficacy information of ATZ 15 mg/kg Q3W in pediatric patients with relapsed or refractory ENKL aged ≥12 years should be collected in the post-marketing setting.

For the reason above, the applicant should conduct a post-marketing surveillance to confirm the efficacy of ATZ 15 mg/kg Q3W administered in pediatric patients, and appropriately update healthcare professionals with new information available, including published literature.

Out of consideration for the description of the dosage regimen of other anti-neoplastic drugs, the dosage regimen in the ATTACK study should be provided in the CLINICAL STUDIES section of the package insert, and the description of "patients aged ≥12 and <18 years" in the proposed dosage and administration should be modified to "pediatric patients aged ≥12 years."

Based on the above, PMDA concluded that the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section should include the following statements and the dosage regimen of ATZ should be modified as described below.

**Dosage and Administration**

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 ≥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 over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

**Precautions Concerning Dosage and Administration**

All indications

- Recommended ATZ dosage modifications for adverse reactions (identical to those for previously approved indications).

Relapsed or refractory ENKL

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

### 7.R.6 Risk management plan (draft)

ATZ already has a published risk management plan (RMP)[30] based on the review and assessment for previously approved indications.

Based on the discussions described in Sections "7.R.3 Safety" and "7.R.5.1 Dosage and administration of ATZ," PMDA concluded that, in the draft RMP for the present partial change application, the following should be added to specifications:
For safety specification, increased risk of severe complications associated with allo-HSCT following administration of ATZ (hematologic malignancies)
For efficacy specifications, efficacy in clinical use in patients with relapsed or refractory ENKL aged ≥12 and <18 years.

PMDA concluded that the RMP for ATZ should include the safety and efficacy specifications shown in Table 7.

**Table 7. Safety and efficacy specifications in the RMP (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • ILD<br>• Hepatic dysfunction/hepatitis/cholangitis sclerosing<br>• Colitis/Severe diarrhea<br>• Pancreatitis<br>• Type 1 diabetes mellitus<br>• Endocrine disorders (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction)<br>• Encephalitis/Meningitis/Myelitis<br>• Neuropathies (including Guillain-Barre syndrome)<br>• Myasthenia gravis<br>• Severe skin disorders<br>• Renal dysfunction (tubulointerstitial nephritis, etc.)<br>• Myositis/Rhabdomyolysis<br>• Myocarditis<br>• Haemophagocytic syndrome<br>• Immune thrombocytopenia<br>• Infusion reaction<br>• Febrile neutropenia (in co-administration with CBDCA, PTX, and/or BV) | • Hemolytic anemia<br>• Pericarditis/pericardial effusion/cardiac tamponade<br>• Hematologic toxicity (neutropenia and febrile neutropenia) when used in combination with chemotherapy [excluding febrile neutropenia when used in combination with CBDCA, PTX, and BV]<br>• Infections when used in combination with chemotherapy<br>• Embryo-fetal toxicity<br>• Use in patients with a history of organ transplantation (including a history of HSCT)<br>• <u>Increased risk of developing severe complications associated with allo-HSCT after administration of ATZ [hematologic malignancies]</u> | None |
| Efficacy specifications | | |
| • <u>Efficacy in clinical use in patients with relapsed or refractory ENKL aged ≥12 and <18 years</u> | | |

Underlined part: Items added in the present partial change application

[30] RMP for Tecentriq Intravenous Infusion 840 mg and 1,200 mg (submitted on June 10, 2025)

### 7.R.7 Post-marketing investigations

The applicant's explanation about a post-marketing investigation plan:

A post-marketing surveillance study is planned to evaluate the efficacy of ATZ in patients with relapsed or refractory ENKL aged ≥12 and <18 years in clinical use.

- Efficacy specifications: The efficacy in patients with relapsed or refractory ENKL aged ≥12 and <18 years in clinical use was established as the evaluation objective.
- Planned sample size: Because the number of patients with relapsed or refractory ENKL aged ≥12 and <18 years is extremely limited,[31)] the planned sample size will not be prespecified. Instead, all patients with relapsed or refractory ENKL aged ≥12 and <18 years who receive ATZ during the 2 years and 3 months following the approval of the present partial change application will be enrolled, to include as many patients as possible.
- Observation period: Considering that the median PFS in the ATTACK study was 2.4 months and that the evaluation timing before disease progression includes the best response assessment, the observation period was 3 months.

PMDA's view:

As discussed in Section 7.R.5.1 "Dosage and administration of ATZ," there is no experience with 15 mg/kg Q3W administration of ATZ in patients with relapsed or refractory ENKL aged ≥12 and <18 years, either in Japan or abroad. Therefore, the applicant should conduct post-marketing surveillance to evaluate the efficacy of ATZ in patients with relapsed or refractory ENKL aged ≥12 and <18 years, collect information promptly and without bias, and provide healthcare professionals with efficacy-related information as soon as it becomes available.

PMDA also concluded that the applicant's planned implementation details for the above surveillance are acceptable. However, if the number of registered patients is insufficient and it becomes difficult to evaluate the efficacy of ATZ, measures such as extending the registration period and continuing the surveillance should be considered.

### 7.R.8 Development for pediatric patients with relapsed or refractory ENKL aged <12 years

PMDA requested the applicant to explain their plan on the development of ATZ for pediatric patients with relapsed or refractory ENKL aged <12 years.

The applicant's response:

Treatment options for relapsed or refractory ENKL are limited regardless of patient age, and there is a potential need for the development of ATZ for pediatric patients with relapsed or refractory ENKL aged <12 years. However, there is currently no development plan targeting these patients for the following reasons:

- Although there are no reports of the number of patients with ENKL aged <12 years in Japan, the number of those aged <20 years is extremely low.[31)] Moreover, EBV, which is implicated in the pathogenesis of ENKL, often causes asymptomatic infection in early childhood and may lead to

31) The number of ENKL cases registered as hematologic diseases or pediatric cancers in patients aged <20 years, as reported to the Japanese Society of Pediatric Hematology/Oncology, were 1 case in 2018, 4 cases in 2019, 2 cases in 2020, 1 case in 2021, 0 cases in 2022, and 1 case in 2023 (https://www.jspho.org/disease_record.html, last accessed on June 18, 2025).

disease onset during adolescence or later (*J Jpn Soc Int Med.* 2015;104:1878-84). Thus, the product development for this population is considered difficult.

PMDA's view:
The need for clinical development of ATZ for children with relapsed or refractory ENKL aged <12 years and its feasibility should be closely investigated in clinical settings in Japan, warranting appropriate actions.

## 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 relapsed or refractory ENKL, and that ATZ has acceptable safety in view of its benefits. ATZ is clinically meaningful because it offers a treatment option for patents with relapsed or refractory ENKL. Efficacy, dosage and administration, and post-marketing investigation items need to be further discussed.

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

**Review Report (2)**

August 7, 2025

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | (a) Tecentriq Intravenous Infusion 840 mg,<br>(b) Tecentriq Intravenous Infusion 1,200 mg |
| **Non-proprietary Name** | Atezolizumab (Genetical Recombination) |
| **Applicant** | Chugai Pharmaceutical Co., Ltd. |
| **Date of Application** | October 31, 2024 |

**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 view:

Based on the review in Section "7.R.2 Efficacy" in the Review Report (1), the ATTACK study, recognized as the primary evidence for the efficacy of ATZ in the present partial change application, showed limitations in evaluating the efficacy of ATZ based on the predetermined evaluation methods, in view of the minimum number of responders satisfying the Bayesian-based success criteria (a posterior probability of ≥95% exceeding the prespecified threshold response rate of 5%) and the outcomes of simulated operating characteristics. However, the centrally-assessed response rate and CR rate based on the Lugano criteria were 53.8% and 30.8%, respectively, indicating promising efficacy of ATZ against relapsed or refractory ENKL.

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

### 1.2 Safety

PMDA's view:

Based on the review in Section "7.R.3 Safety" in the Review Report (1), the use of ATZ in patients with relapsed or refractory ENKL require particular attention to the same adverse events as those identified during the review on the previously approved indications.

Although ATZ needs to be used with caution against these events, the product is tolerable in patients with relapsed or refractory ENKL when physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, i.e., patient monitoring, adverse event management while taking account of adverse drug reactions due to excessive immune responses, and the interruption, etc. of ATZ.

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

### 1.3 Clinical positioning and indications

Based on the review described in Section "7.R.4 Clinical positioning and indications" in the Review Report (1), PMDA concluded that the indication should be "relapsed or refractory extranodal NK/T-cell lymphoma, nasal type" as proposed, with the following advice offered in the PRECAUTIONS CONCERNING INDICATION section.

**Precautions Concerning Indications**

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

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

Based on the above, PMDA instructed the applicant to modify the descriptions of the Indications and the PRECAUTIONS CONCERNING INDICATION sections. The applicant agreed.

### 1.4 Dosage and administration

Based on the review in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA concluded that the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections should be described as follows:

**Dosage and Administration**

The 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 ≥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 over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

**Precautions Concerning Dosage and Administration**

All indications

- Recommended ATZ dosage modifications after adverse reactions (no change from those for previously approved indications)

Relapsed or refractory ENKL

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

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

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

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

PMDA's view:

Based on the review in Section "7.R.6 Risk management plan (draft)" in the Review Report (1), the RMP (draft) for ATZ in the present partial change application should include the safety and efficacy specifications listed in Table 8.

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

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • ILD<br>• Hepatic dysfunction/hepatitis/sclerosing cholangitis<br>• Colitis/Severe diarrhea<br>• Pancreatitis<br>• Type 1 diabetes mellitus<br>• Endocrine disorders (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction)<br>• Encephalitis/Meningitis/Myelitis<br>• Neuropathies (including Guillain-Barré syndrome)<br>• Myasthenia gravis<br>• Severe skin disorders<br>• Renal dysfunction (e.g., tubulointerstitial nephritis)<br>• Myositis/Rhabdomyolysis<br>• Myocarditis<br>• Hemophagocytic syndrome<br>• Immune thrombocytopenia<br>• Infusion reaction<br>• Febrile neutropenia (when used in combination with CBDCA, PTX, or BV) | • Hemolytic anemia<br>• Pericarditis, pericardial effusion, cardiac tamponade<br>• Hematologic toxicity when combined with chemotherapy (neutropenia, febrile neutropenia) [excluding febrile neutropenia occurring with CBDCA, PTX, and BV combination therapy]<br>• Infections associated with combination chemotherapy<br>• Embryo-fetal toxicity<br>• Use in organ transplant recipients (including HSCT)<br>• <u>Increased risk of severe complications associated with allo-HSCT 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.

Based on the review described in Section "7.R.7 Post-marketing investigations" in the Review Report (1), post-marketing surveillance study should be conducted to evaluate the efficacy of ATZ in clinical use in patients with relapsed or refractory ENKL aged ≥12 and <18 years.

The applicant's study plan is acceptable. However, if inadequacy in the number of enrolled patients, etc. hinders efficacy evaluation, the extension of enrollment period, etc. should be considered to ensure the implementation of the surveillance.

In the Expert Discussion, the expert advisors supported the above conclusions and made the following comment:

- It is recommended that the surveillance also collect information on the execution of allo-HSCT after treatment with ATZ and the occurrence of post-allo-HSCT complications.

PMDA instructed the applicant to take appropriate actions accordingly. The applicant agreed.

In view of the discussion above, PMDA has also concluded that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Tables 9 and 10 for the RMP (draft).

**Table 9. 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 [hematotoxicity (neutropenia, febrile neutropenia) associated with chemotherapy] targeting patients with small cell lung cancer (on combination therapy with CBDCA and ETP) | Specified drug use-results survey (all-case surveillance) in patients with relapsed or refractory ENKL aged ≥12 and <18 years | • Information provision to healthcare professionals (proper use guidelines)<br>• Information provision to patients (patient handbook) |

Underlined items indicate activities planned for the newly added indication.

**Table 10. Outline of use-results survey (draft)**

| | |
|---|---|
| Objective | To evaluate the efficacy of ATZ in patients with relapsed or refractory ENKL aged ≥12 and <18 years in clinical use |
| Survey method | All-case surveillance |
| Population | Patients with relapsed or refractory ENKL aged ≥12 and <18 years treated with ATZ |
| Observation Period | The first 3 months of the administration of ATZ; or until the time of discontinuation for patients who discontinue ATZ |
| Planned sample size | All patients with ENKL aged ≥12 and <18 years who are treated with ATZ within 2 years and 3 months after approval of the present partial change application |
| Main survey items | Efficacy specification: efficacy in clinical use<br>Other main survey items: patient characteristics (age, sex, medical history, comorbidities, etc.), prior treatment, treatment status with ATZ, adverse events, and organ transplant (including HSCT). |

### 1.6 Development for pediatric patients with relapsed or refractory ENKL aged <12 years

PMDA's view:

Based on the review in Section 7.R.8 "Development for pediatric patients with relapsed or refractory ENKL aged <12 years" in the Review Report (1), the necessity and feasibility of clinical development of ATZ should be carefully assessed for the relevant patient population in healthcare settings in Japan to take appropriate actions.

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

PMDA instructed the applicant to address the matter appropriately, and the applicant agreed to follow the instruction.

## 2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indications and dosage and administration shown below, with the following conditions, premising on proper post-marketing communication including cautioning via 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 adequately prepared for emergencies. The present application pertains to drug with new indications and new dosages, for which the re-examination period is 4 years.

**Indications** (Underline denotes additions. Double-underline denotes changes made as of February 20, 2025, after submission of the present partial change application.)

(a) ○ PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer
○ Unresectable alveolar soft part sarcoma
○ Relapsed or refractory extranodal NK/T-cell lymphoma, nasal type

(b) ○ 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

(Underline denotes additions. Double-underline denotes changes made as of February 20, 2025, after submission of the present partial change application.)

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

*Atezolizumab in combination with paclitaxel (albumin-bound)*

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

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 over 60 minutes 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 over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

(b) 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. 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

*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. 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 over 60 minutes 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 over 60 minutes every 3 weeks. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey covering all pediatric patients with relapsed or refractory extranodal NK/T-cell lymphoma, nasal type, until data from a certain number of patients are accumulated.

**Warnings** (No change)

1. ATZ should be administered only to patients eligible for ATZ therapy, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.
2. As cases of interstitial lung disease, including fatal cases, have been reported, patients should be closely monitored, e.g. detection of initial symptoms (dyspnea, 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.)

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-possitive 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 reagents or medical devices should be used for such testing.
3. Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning prior therapies and the presence or

absence of *EGFR* gene mutations or *ALK* fusion genes, etc. of patients enrolled in 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-possitive 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 reagents or medical devices should be used for such testing.
5. Eligible patients must be selected by physicians with a full understanding of the information presented 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 presented in the CLINICAL STUDIES section concerning the definition of extensive-stage disease for patients enrolled in the clinical study, etc., and of the efficacy and safety of ATZ.

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-possitive patients tested by a pathologist or testing facility with adequate experience in determining the percentage of tumor-infiltrating immune cells expressing PD-L1. The approved *in vitro* diagnostic reagents or medical devices should be used for such testing.

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

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

**Precautions Concerning Dosage and Administration** (Single underline denotes new additions. Double underline denotes additions made as of February 20, 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 modifications |
|---|---|---|
| Respiratory disorders such as interstitial lung disease | Grade 2 | Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks. |
| | Grade ≥3, or recurrent respiratory disorder | Permanently discontinue. |
| Hepatic dysfunction (excl. unresectable hepatocellular carcinoma) | Grade 2 (AST or ALT >3× ULN and <5 × ULN or total bilirubin >1.5 × ULN and <3 × ULN) persists for >5 days | Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks. |
| | Grade ≥3 (AST or ALT >5 × ULN or total bilirubin >3 × ULN) | Permanently discontinue. |
| Hepatic dysfunction (unresectable hepatocellular carcinoma) | • Patients whose baseline AST or ALT is within the reference range: AST or ALT >3 × ULN and ≤10 × ULN.<br>• Patients whose baseline AST or ALT is >1 × ULN and ≤3 × ULN: AST or ALT >5 × ULN and ≤10 × ULN.<br>• Patients whose baseline AST or ALT is >3 × ULN and ≤5 × ULN: AST or ALT >8 × ULN and ≤10 × 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 × ULN or total bilirubin >3 × 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 | • ~~Grade ≥3 amylase or lipase levels increased~~ Amylase or lipase >2 × ULN<br>• Grade 2 or 3 pancreatitis | Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks. |
| | Grade 4 or recurrent pancreatitis | Permanently discontinue. |
| Endocrinopathies | ~~Grade ≥3 hyperglycemia~~ Fasting blood glucose level >250 mg/dL | Withhold dose until stabilization of blood glucose levels. |
| | • Symptomatic hypothyroidism<br>• Symptomatic hyperthyroidism, or asymptomatic hyperthyroidism with thyroid stimulating hormone <0.1 mU/L | Withhold dose until resolution. |
| | Grade ≥2 adrenal insufficiency | Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks. |
| | • Grade 2 or 3 hypophysitis<br>• 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<br>• Grade 4 or recurrent hypopituitarism | Permanently discontinue. |
| Encephalitis, Meningitis | All Grades | Permanently discontinue. |
| Neuropathies | Grade 2 | Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks. |
| | Grade ≥3 | Permanently discontinue. |
| | Any grade of Guillain-Barre syndrome | Permanently discontinue. |
| Myasthenia gravis | All Grades | Permanently discontinue. |
| Skin disorders | Grade 3 | Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks. |
| | Grade 4 | Permanently discontinue. |
| Nephritis | ~~Grade 2:~~ Serum creatinine >1.5 × and <3 × ULN or baseline | Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks. |
| | ~~Grade ≥3:~~ Serum creatinine >3× ULN or baseline | Permanently discontinue. |

| Adverse reaction | Severity of adverse reaction | Dosage modifications |
|---|---|---|
| Myositis | Grade 2 or 3 | Withhold dose until resolution to Grade ≤1.<br>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. |
| Hemophagocytic syndrome | All Grades | Permanently discontinue. |
| Ophthalmopathies | Grade 2 | Withhold dose until resolution to Grade ≤1.<br>Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks. |
| | Grade ≥3 | Permanently discontinue |
| Infusion reaction | Grade 1 | Reduce the infusion rate by 50%. Monitor for 30 minutes after symptoms have improved, and if the event does not recur, the infusion rate may be increased back to baseline. |
| | Grade 2 | Interrupt infusion, and resume infusion at a 50% reduction in rate after 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

2. 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

3. 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

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

Extensive-stage small cell lung cancer

5. 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.

**List of Abbreviations**

| | |
|---|---|
| ALBERT study | Study NCCH1907/MK008 |
| allo-HSCT | allogeneic hematopoietic stem cell transplantation |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATZ | atezolizumab (genetical recombination) |
| ATTACK study | Study NCCH1903/MK006 |
| ATZ/CBDCA/PTX/BV | the combination of ATZ, CBDCA, PTX, and BV |
| BV | bevacizumab (genetical recombination) |
| CBDCA | carboplatin |
| CDDP | cisplatin |
| CI | confidence interval |
| COVID-19 | corona virus infectious disease emerged in 2019 |
| CR | complete response |
| CY | cyclophosphamide hydrate |
| DEX | dexamethasone |
| EBV | Epstein-Barr virus |
| ECOG | Eastern Cooperative Oncology Group |
| ENKL | extranodal NK/T-cell lymphoma, nasal type |
| ESMO | European Society for Medical Oncology |
| ETP | etoposide |
| GEM | gemcitabine hydrochloride |
| GVHD | graft-versus-host disease |
| HER2 | Human epidermal growth factor receptor 2 |
| HLT | high level term |
| HSCT | hematopoietic stem cell transplantation |
| IFM | ifosfamide |
| Ig | immunoglobulin |
| ILD | interstitial lung disease |
| IMbrave150 study | Study YO40245 |
| IMmotion151 study | Study WO29637 |
| IMpower010 study | Study GO29527 |
| IMpower110 study | Study GO29431 |
| IMpower150 study | Study GO29436 |
| IMvigor211 study | Study GO29294 |
| L-ASP | L-asparaginase |
| LMP1 | Latent membrane protein 1 |
| MedDRA | Medical Dictionary for Regulatory Activities ICH |
| MedDRA/J | Medical Dictionary for Regulatory Activities Japanese version |
| mPSL | methylprednisolone |
| MTX | methotrexate |
| NCCN | National Comprehensive Cancer Network |
| NCI study | Study ML39345 |
| NCI-PDQ | National Cancer Institute Physician Data Query |
| NE | not evaluable |
| OAK study | Study GO28915 |
| Partial change application | Application for Partial Change of Marketing Approval |
| PD | progressive disease |
| PD-1 | programmed cell death-1 |
| PD-L1 | programmed cell death-ligand 1 |
| PK | pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |

| | |
|---|---|
| PPK | population pharmacokinetics |
| PR | partial response |
| PS | performance status |
| Practical Guidelines for Hematologic Malignancies | JSH Practical Guidelines for Hematological Malignancies, 2024, Version 3.1, edited by the Japanese Society of Hematology |
| PSL | prednisolone/prednisone/methylprednisolone |
| PT | preferred term |
| PTX | paclitaxel |
| Q3W | quaque 3 weeks |
| R-CHOP | cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisolone/prednisone/methylprednisolone |
| R-ESHAP | the combination of RIT, mPSL, ETP, cytarabine, and CDDP |
| RIT | rituximab (genetical recombination) |
| RMP | Risk Management Plan |
| SD | stable disease |
| SMILE | the combination of DEX, MTX, IFM, L-ASP, and ETP |
| SMQ | Standardised MedDRA Queries |
| SOC | system organ class |