December 12, 2022

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

Report on the Deliberation Results

Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Products
Non-proprietary Name	Axicabtagene ciloleucel
Brand Name	YESCARTA Intravenous Drip Infusion
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 27, 2022 (Application for partial change approval)

Results of Deliberation

In the meeting held on December 12, 2022, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The re-examination period of the product is the remainder of the re-examination period for the initial approval of the product (until January 21, 2031).

The following approval conditions must be satisfied.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. Because the number of Japanese patients participating in clinical trials is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to identify the characteristics of patients using the product and collect data on the safety and efficacy of the product as early as possible, thereby taking necessary measures to ensure the proper use of the product.

Review Report

November 24, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for partial change approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	YESCARTA Intravenous Drip Infusion
Classification	Human Cellular/Tissue-based Products 1. Human Somatic Cell-processed Products
Non-proprietary Name	Axicabtagene ciloleucel
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 27, 2022

Shape, Structure, Active Ingredients, Quantities, or Definition
The product is a regenerative medical product introduced with a transgene encoding chimeric antigen receptor that specifically recognizes CD19 antigen by using a recombinant retrovirus vector for the autologous T-cells.

Application Classification (3) Regenerative medical product with new indications

Items Warranting Special Mention
Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 8 of 2018 [*30 sai*]; PSEHB/MDED Notification No. 1001-1 dated October 1, 2018, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of Cellular and Tissue-based Products

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 large B-cell lymphoma in patients who are eligible for autologous hematopoietic stem cell transplantation (HSCT) and have received 1 line of prior therapy, 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 or performance and dosage and administration or method of use shown below, with the following approval conditions.

Indications or Performance

The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high grade B-cell lymphoma

YESCARTA should be used only in patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen. ~~meeting all of the following criteria:~~

- ~~Patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.~~
- ~~Patients who are eligible for autologous hematopoietic stem cell transplantation, have failed to respond to ≥2 lines of chemotherapy in the newly diagnosed patients and with ≥1 line of chemotherapy after relapse in the relapsed patients, or have had a relapse after autologous hematopoietic stem cell transplantation; or patients who are ineligible for autologous hematopoietic stem cell transplantation~~

(Underline denotes additions. Strikethrough denotes deletions.)

Dosage and Administration or Method of Use

Process from leukapheresis at medical institution to transportation to manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported to the manufacturing facility of YESCARTA.

Process from receipt at the medical institution to administration of YESCARTA

3. Receipt and storage of YESCARTA
   YESCARTA is received and cryopreserved in the vapor phase of liquid nitrogen (≤−150°C) until immediately before use.
4. Pretreatment before administration of YESCARTA
   The peripheral blood lymphocyte count is checked. Where necessary, the following lymphodepleting chemotherapy is conducted as pretreatment for 3 consecutive days starting 5 days before administration of YESCARTA:
   Cyclophosphamide (anhydride) 500 mg/m^2 is infused intravenously once daily for 3 days, and fludarabine phosphate 30 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.
5. Administration of YESCARTA
   The usual adult dosage is 2.0×10^6 cells/kg (body weight), as a rule, of anti-CD19 CAR T-cells (for patients weighing ≥100 kg, up to 2×10^8 cells) administered as a single intravenous dose over ≥5 minutes and <30 minutes. YESCARTA should not be re-administered.

(No change)

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. Because the number of Japanese patients participating in clinical trials is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to identify the characteristics of patients using the product and collect data on the safety and efficacy of the product as early as possible, thereby taking necessary measures to ensure the proper use of the product.

Attachment

Review Report (1)

September 16, 2022

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	YESCARTA Intravenous Drip Infusion
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Non-proprietary Name	Axicabtagene ciloleucel
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 27, 2022

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product introduced with a transgene encoding chimeric antigen receptor that specifically recognizes CD19 antigen by using a recombinant retrovirus vector for the autologous T-cells.

Proposed Indications or Performance

The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high grade B-cell lymphoma

YESCARTA should be used only in patients meeting all of the following criteria:

- Patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.
- Patients who ~~are eligible for autologous hematopoietic stem cell transplantation,~~ have failed to respond to ≥1 line ~~2 lines~~ of chemotherapy ~~in the newly diagnosed patients and with ≥1 line of chemotherapy after relapse in the relapsed patients,~~ or ~~have~~ had a relapse ~~after autologous hematopoietic stem cell transplantation; or patients who are ineligible for autologous hematopoietic stem cell transplantation~~

(Underline denotes additions. Strikethrough denotes deletions.)

Proposed Dosage and Administration or Method of Use

Process from leukapheresis at medical institution to transportation to manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported to the manufacturing facility of YESCARTA.

Process from receipt at the medical institution to administration of YESCARTA

3. Receipt and storage of YESCARTA
   YESCARTA is received and cryopreserved in the vapor phase of liquid nitrogen (≤−150°C) until immediately before use.
4. Pretreatment before administration of YESCARTA
   The peripheral blood lymphocyte count is checked. Where necessary, the following lymphodepleting chemotherapy is conducted as pretreatment for 3 consecutive days starting 5 days before administration of YESCARTA:
   Cyclophosphamide (anhydride) 500 mg/m^2 is infused intravenously once daily for 3 days, and fludarabine phosphate 30 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.
5. Administration of YESCARTA
   The usual adult dosage is 2.0×10^6 cells/kg (body weight), as a rule, of anti-CD19 CAR T-cells (for patients weighing ≥100 kg, up to 2×10^8 cells) administered as a single intravenous dose over ≥5 minutes and <30 minutes. YESCARTA should not be re-administered.

(No change)

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

YESCARTA, a regenerative medical product, is comprised of cultured autologous peripheral T-cells (cells serving as a component of the product [component cells]) that have been transduced with recombinant gammaretroviral vector containing a transgene encoding a chimeric antigen receptor (CAR) that specifically recognizes cluster of differentiation (CD)19. YESCARTA is infused intravenously into the patient to obtain a therapeutic effect based on the pharmacological action, in the same manner as drugs.

CAR protein, expressed by the transgene of YESCARTA, consists of a murine single-chain variable fragment (scFv) specifically recognizing CD19, human CD28 (a part of the extracellular domain, transmembrane domain, and a part of the intracellular domain), and human CD3ζ intracellular signaling domain (a part of the intracellular domain). When recognizing CD19-expressing cells, CAR protein drives the genetically modified T-cell to activate and proliferate themselves as well as acquire effector functions such as a cytotoxic action. Through these actions, YESCARTA is expected to be effective in killing CD19 positive B-cell tumor cells.

In Japan, YESCARTA was approved in January 2021 for treatment of patients with relapsed or refractory large B-cell lymphoma (LBCL) (diffuse large B-cell lymphoma [DLBCL], primary mediastinal large B-cell lymphoma [PMBCL], transformed follicular lymphoma [tFL], and high grade B-cell lymphoma [HGBCL]) who are eligible for autologous hematopoietic stem cell transplantation (HSCT) and have received ≥2 lines of prior therapy or patients who are ineligible for autologous HSCT and have received ≥1 line of prior therapy.

YESCARTA was designated as an orphan regenerative medical product with the intended indications or performance for treatment of "diffuse large B-cell lymphoma," "primary mediastinal (thymic) large B-cell lymphoma," "transformed follicular lymphoma," and "high grade B-cell lymphoma" on October 1, 2018 (Orphan Regenerative Medical Product Designation No. 8 of 2018 [*30 sai*]).

1.2 Development history etc.

As a clinical development project of YESCARTA for treatment of LBCL, Kite Pharma, Inc. (Kite) initiated a foreign phase III study (Study KTE-C19-107 [Study ZUMA-7]) in patients with relapsed or refractory LBCL who were eligible for autologous HSCT and had received 1 line of prior therapy in January 2018.

In the US, an application for marketing approval (application) was submitted using data from Study ZUMA-7 as the pivotal study results in September 2021, and it was approved for the following indications or performance in April 2022.

YESCARTA is indicated for the treatment of:

- Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.

- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitations of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

In Europe, an application was submitted using data from Study ZUMA-7 as the pivotal study results in November 2021 and is under review as of September 2022.

The applicant has now submitted an application for partial changes of marketing approval (partial change application) for YESCARTA based on results from Study ZUMA-7 to add an indication or performance for treatment of patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy.

2. Quality and Outline of the Review Conducted by PMDA

This application relates to the new indication, and no data relating to quality are submitted.

3. Primary Pharmacodynamics or Performance and Outline of the Review Conducted by PMDA

This application relates to the new indication, but no new data are submitted because the data relating to primary pharmacodynamics or performance had been evaluated during the review process for the initial approval.

4. Non-clinical Safety and Outline of the Review Conducted by PMDA

This application relates to the new indication, and no data relating to non-clinical safety are submitted.

5. Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted results from Study ZUMA-7 as additional data relating to biological disposition, but the results were confirmed to be similar to study results submitted for the initial approval.

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

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

Table 1. List of clinical study for efficacy and safety

Data category	Geographical location	Study ID	Phase	Study population	Number of patients enrolled	Dosing regimen	Main endpoints
Evaluation	Foreign	ZUMA-7	III	Patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy	359 (1) 180 (2) 179	(1) YESCARTA Single intravenous administration of 2×10^6 anti-CD19 CAR T-cells/kg (1×10^6 cells/kg at the minimum; for patients weighing >100 kg, up to 2×10^8 cells) (2) Standard of care 2-3 cycles of 2- to 3-week salvage chemotherapy and, if a response is achieved, HDCT with autologous HSCT	Efficacy Safety

The clinical study is summarized below. The main adverse events excluding deaths observed in the clinical study are presented in Section "8. Adverse Events Observed in Clinical Studies."

6.1 Evaluation data

6.1.1 Foreign clinical study

6.1.1.1 Foreign phase III study (CTD 5.3.5.1-1, Study ZUMA-7, ongoing since January 2018 [data cutoff on March 18, 2021])

An open-label, randomized study was conducted in patients with relapsed or refractory LBCL eligible for autologous HSCT (target sample size, 350 subjects,[1)] 175 per group) to compare YESCARTA with the standard of care in terms of the efficacy and safety at 77 study sites in 14 foreign countries. Table 2 shows the main inclusion and exclusion criteria.

Table 2. Main inclusion and exclusion criteria

Inclusion criteria
- Patients with histologically proven LBCL in any of the following tissue types according to the WHO classification (2016) (*Blood.* 2016;127:2375-90):
  - DLBCL*
  - tFL
  - HGBCL (with or without *MYC* and *BCL2* and/or *BCL6* rearrangement)
- Patients with refractory (PD, SD, or PR followed by PD within 12 months after the therapy; or biopsy-proven residual disease) or relapsed (relapse from complete response [CR] ≤12 months after the first-line therapy) LBCL who have received 1 line of chemotherapy including anti-CD20 monoclonal antibody and anthracycline
- Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
- Patients without history or suspicion of central nervous system (CNS) involvement by lymphoma
- Patients with intent to proceed to HDCT with autologous HSCT if a response to salvage chemotherapy is achieved

Exclusion criteria
- Patients with history of autologous or allogeneic HSCT
- Patients with prior CD19-targeted therapy, CAR T-cell therapy or genetically modified T-cell therapy
- Patients with history of Richter's transformation of CLL or PMBCL

* The following tissue types of DLBCL were deemed eligible:
Diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS); DLBCL associated with chronic inflammation; primary cutaneous DLBCL, leg type; Epstein-Barr virus positive DLBCL; and T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)

1) On the hypothesis that a hazard ratio of event-free survival (EFS), the primary endpoint, in the YESCARTA group to that in the standard-of-care group was 0.67, the number of events required to ensure approximately 90% of statistical power at a one-sided significance level of 2.5% was calculated to be 250, and the sample size of 350 (175 per group) was deemed necessary to achieve the target number of events.

In the YESCARTA group, patients intravenously received a single dose of 2×10^6 anti-CD19 CAR T-cells/kg (1×10^6 cells/kg at the minimum; for patients weighing >100 kg, up to 2×10^8 cells). In addition, patients received the following lymphodepleting chemotherapy (LD chemotherapy) as pretreatment to enhance survival and proliferation of YESCARTA in the body: Both cyclophosphamide hydrate (cyclophosphamide) 500 mg/m^2 and fludarabine phosphate (fludarabine) 30 mg/m^2 were intravenously infused once daily for 3 days. YESCARTA was used 3 days after the end of LD chemotherapy. During manufacture of YESCARTA, patients were permitted to receive corticosteroids according to their condition but required to complete the treatment 5 days before administration of YESCARTA. Of note, re-administration of YESCARTA was permitted for patients who experienced disease progression after achieving a response on Day 50 of administration of YESCARTA.

In the standard-of-care group, patients received 2 to 3 cycles of a second-line 2- to 3-week salvage chemotherapy regimen (R-ICE,[2)] R-ESHAP,[3)] R-GDP,[4)] R-DHAP,[5)] or R-DHAX[6)]) as selected by the investigator, and patients who subsequently achieved a response after 2 or 3 cycles of the chemotherapy underwent high-dose chemotherapy (HDCT) with HSCT.[7)] Patients who failed to respond to the salvage chemotherapy were allowed to receive post-treatment such as approved CAR T-cell therapy including YESCARTA outside the protocol.[8)]

The primary endpoint of this study was event-free survival ("EFS," defined as the time from randomization to the earliest date of disease progression per Lugano classification [*J Clin Oncol.* 2014;32:3059-68], commencement of new lymphoma therapy, or death from any cause as determined by central review).

A total of 359 patients enrolled in this study were randomized in a 1:1 ratio (180 in the YESCARTA group, 179 in the standard-of-care group). In the YESCARTA group, 178 patients underwent leukapheresis, excluding 2 patients (disease progression and a failure to meet the inclusion/exclusion criteria in 1 each); 172 patients received LD chemotherapy, excluding 6 patients (adverse events in 2, death in 2, disease progression in 1, and a failure to meet the inclusion/exclusion criteria in 1); and 170 patients received YESCARTA, excluding 2 patients (adverse events in 2). In the standard-of-care group, 168 patients received at least 1 salvage chemotherapy, excluding 11 patients (consent withdrawal in 8, lost to follow-up in 1, a negative disease biopsy in 1, and a false positive result on positron emission tomography [PET] leading to a finding that the disease was not refractory to chemotherapy in 1), and 80 patients (44.7%) responded as determined by the investigator. Of the responders, 69 patients underwent collection of peripheral blood hematopoietic stem cells for autologous HSCT, excluding 11 patients (disease progression in 9, adverse events in 1, and investigator's decision in 1); 64 patients

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2) Intravenous administration of rituximab 375 mg/m^2 before chemotherapy, ifosfamide 5,000 mg/m^2 24-hour continuous infusion on Day 2 with mesna, carboplatin AUC5 on Day 2 (maximum dose 800 mg), and etoposide 100 mg/m^2 on Days 1 to 3.

3) Intravenous administration of rituximab 375 mg/m^2 on Day 1, etoposide 40 mg/m^2 on Days 1 to 4, methylprednisolone 500 mg on Days 1 to 4 or Days 1 to 5, cisplatin 25 mg/m^2 on Days 1 to 4, and cytarabine 2,000 mg/m^2 on Day 5.

4) Intravenous administration of rituximab 375 mg/m^2 on Day 1 (or Day 8), gemcitabine 1,000 mg/m^2 on Days 1 and 8, dexamethasone 40 mg on Days 1 to 4, and cisplatin 75 mg/m^2 on Day 1 (or carboplatin AUC5 on Day 1).

5) Intravenous administration of rituximab 375 mg/m^2 before chemotherapy, dexamethasone 40 mg on Days 1 to 4, cisplatin 100 mg/m^2 on Day 1, and cytarabine 2,000 mg/m^2 twice daily on Day 2.

6) Intravenous administration of rituximab 375 mg/m^2 before chemotherapy, dexamethasone 40 mg on Days 1 to 4, cisplatin 100 mg/m^2 (or oxaliplatin 100 mg/m^2) 24-hour continuous infusion on Day 1, and cytarabine 2,000 mg/m^2 twice daily on Day 2.

7) Performed as per local or study site standard.

8) Of 179 patients in the standard-of-care group, 100 patients (55.8%) received approved CAR T-cell therapy including YESCARTA as new post-standard-of-care therapy for lymphoma.

received HDCT, excluding 5 patients owing to disease progression; and 62 patients underwent autologous HSCT, excluding 2 patients (disease progression in 1 and participation in other clinical trial by mistake in 1, who underwent autologous HSCT outside the concerned protocol). The efficacy analysis population included 359 randomized patients. The safety analysis population included 170 patients who received YESCARTA in the YESCARTA group and 168 patients who received standard-of-care salvage chemotherapy in the standard-of-care group.

Table 3 and Figure 1 show results on EFS, the primary endpoint, and Kaplan-Meier curve, respectively, demonstrating superiority of YESCARTA to the standard of care (one-sided *P* value <0.0001, stratified log-rank test).

Table 3. Results on EFS (centrally assessed, efficacy analysis population, data cutoff on March 18, 2021)

	YESCARTA n = 180	Standard of care n = 179
EFS event (%)	108 (60.0)	144 (80.4)
Death (%)	11 (6.1)	6 (3.4)
PD (%)	82 (45.6)	75 (41.9)
Best response of SD within 150 days after randomization (%)	4 (2.2)	0
Commencement of new lymphoma therapy (%)	9 (5.0)	63 (35.2)
Re-administration of YESCARTA (%)	2 (1.1)	0
Median [95% CI] (months)	8.3 [4.5, 15.8]	2.0 [1.6, 2.8]
Hazard ratio [95% CI]*1	0.398 [0.308, 0.514]	
One-sided *P* value*2	<0.0001	

*1 Calculated using the Cox proportional hazards model stratified by the response to the first-line therapy (primary refractory [progressive disease (PD), stable disease (SD), or partial response (PR)], relapse ≤6 months after CR to first-line therapy, or relapse >6 and ≤12 months of first-line therapy) and second-line age-adjusted international prognostic index (sAAIPI) (0 or 1, 2 or 3)

*2 One-sided significance level of 2.5%, stratified log-rank test (by the same stratification factors as those used in the Cox proportional hazards model)

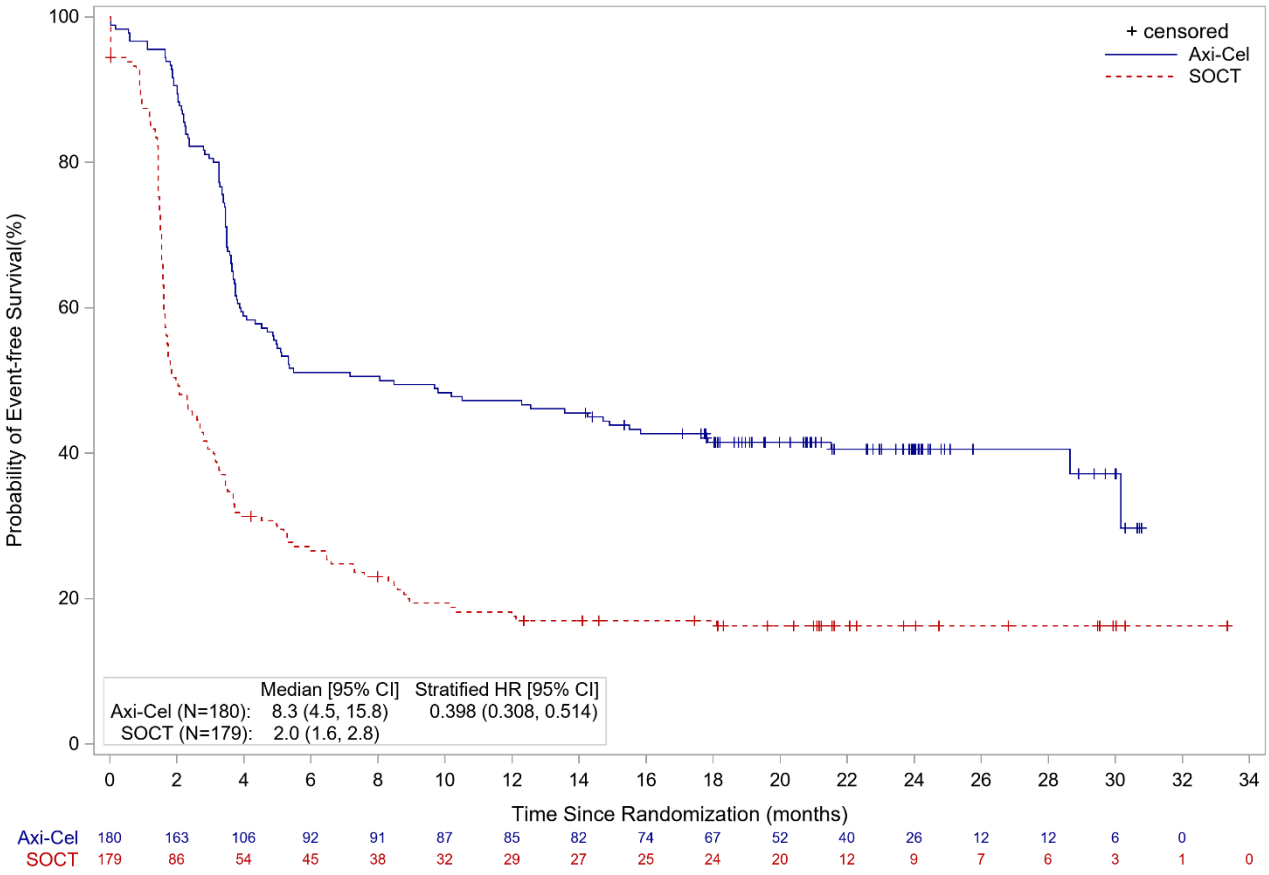

Figure 1. Kaplan-Meier curve on EFS (efficacy analysis population, data cutoff on March 18, 2021)

During the study period, death was reported in 142 patients (64 in the YESCARTA group, 78 in the standard-of-care group). Disease progression was reported in 111 patients (47 in the YESCARTA group, 64 in the standard-of-care group), and death due to adverse events[9)] was reported in 21 patients (14 in the YESCARTA group, 7 in the standard-of-care group). Outside the collection period for adverse events, death was reported in 22 patients (10 in the YESCARTA group, 12 in the standard-of-care group). Of deaths due to adverse events, disease progression (B-cell lymphoma) occurred in 7 patients in the YESCARTA group and 5 patients in the standard-of-care group, and other events occurred in 7 patients (disease caused by severe acute respiratory syndrome coronavirus 2 infection [COVID-19] in 2, and hepatitis B reactivation, lung adenocarcinoma, myocardial infarction, progressive multifocal leukoencephalopathy, and sepsis in 1 each) in the YESCARTA group and 2 patients (acute respiratory distress syndrome and cardiac arrest in 1 each) in the standard-of-care group. The death in 1 patient in the YESCARTA group (hepatitis B reactivation[10)]) was assessed as "causally related to YESCARTA,"

9) Occurrence or aggravation of adverse events through 150 days after randomization or the commencement of new lymphoma therapy, whichever occurs first, were collected. On 150 days post-randomization and thereafter, only specified serious adverse events (serious adverse events including neurological events, hematological events, infection, autoimmune disorders, and secondary malignancies) were collected. These events were collected until disease progression or 15 years after randomization in the YESCARTA group or 5 years after that in the standard-of-care group, whichever occurs first. In addition, all the subjects were followed up for 5 years to obtain survival data.

10) 6[redacted]-year old man. The patient was a hepatitis B virus carrier with viraemia and started receiving entecavir during chemotherapy prior to administration of YESCARTA. He tested positive for hepatitis B surface antigen at the screening, but no hepatitis B virus was detected. No hepatitis B virus was detected by polymerase chain reaction (PCR) on Day 331 of administration of YESCARTA, but flow cytometry of peripheral blood revealed depletion of B-cell lymphocytes, which was reported as an adverse event (Grade 4) of B-cell aplasia. On Day 399, he experienced jaundice accompanied by hypertransaminasaemia and fatigue, and hepatitis B reactivation (Grade 3) developed. Because of progression to fulminant hepatic failure, he underwent plasmapheresis as an inpatient, but his condition worsened. On Day 422, he died. According to telephone communication records on Day 168, an external nurse practitioner told the subject without consultation with the investigator that discontinuation of entecavir was possible. At his visit on Day 248, there was a record of administration of entecavir but not at his visit on Day 332, suggesting that entecavir was discontinued at a time between these visits.

and the deaths in 2 patients in the standard-of-care group were assessed as "causally related to the standard of care." Outside the collection period for adverse events, deaths occurred in 10 patients (COVID-19 in 2, stroke, *Clostridium difficile* infection/colitis ischaemic, spontaneous progression of subdural haematoma, respiratory failure of unknown etiology, euthanasia due to disease progression, lung infection, unknown etiology, and septic shock related to allogeneic HSCT in 1 each) in the YESCARTA group, and 12 patient (unknown etiology in 3, COVID-19 and sepsis in 2 each, cardio-respiratory arrest, idiopathic organising pneumonia, urosepsis, exaggerated inflammatory reaction, and septic shock in 1 each) in the standard-of-care group. None of the deaths were assessed as "causally related to YESCARTA or the standard of care."

6.R Outline of the Review Conducted by PMDA

6.R.1 Data for review

In this application, the applicant submitted the evaluation data in the form of results from a foreign phase III study (Study ZUMA-7) intended to investigate the efficacy and safety of YESCARTA in patients with relapsed or refractory LBCL who were eligible for autologous HSCT and had received 1 line of prior therapy, but no clinical study results in Japanese patients are available.

PMDA asked the applicant whether it would be possible to evaluate the efficacy and safety of YESCARTA in Japanese patients based on the results from Study ZUMA-7 to support its use.

The applicant's response:

In view of the points provided below, the efficacy and safety of YESCARTA can be evaluated in Japanese patients based on the results from Study ZUMA-7.

- Results from clinical studies (Study KTE-C19-101 [Study ZUMA-1] and Study J201) in patients with relapsed or refractory LBCL who had received ≥2 lines of prior therapy, previously submitted for application of the currently approved indication, show no clear differences in efficacy of YESCARTA between Japanese and non-Japanese patients (See Review Report on YESCARTA Intravenous Drip Infusion, dated November 17, 2020).
- LBCL, B-cell malignancy positive for the CD19 antigen, is kept positive for the CD19 antigen irrespective of treatment regimens (*Blood.* 1988;71:13-29, *Clin Cancer Res.* 2011;17:6448-58, etc.).
- In view of the points provided below, the safety of YESCARTA is considered unlikely to differ clearly between Japanese and non-Japanese patients potentially eligible for Study ZUMA-7.
  - No clear differences were observed in the safety profile of YESCARTA between a foreign phase I/II study mainly including non-Japanese patients with relapsed or refractory LBCL who had received 2 lines of prior therapy (Study ZUMA-1) and a Japanese phase II study including Japanese patients with relapsed or refractory LBCL who had received 2 lines of prior therapy (Study J201) (See Review Report on YESCARTA Intravenous Drip Infusion, dated November 17, 2020).
  - No clear differences were observed in the safety profile between the YESCARTA group in Study ZUMA-7 and Studies ZUMA-1 and J201 [see Section 6.R.3.1].
- In view of the points provided below, no clear differences are expected in biological disposition of YESCARTA between Japanese non-Japanese and patients irrespective of treatment regimens.

- C_{max} and AUC_{28d} of blood anti-CD19 CAR T-cell concentrations in Study J201 tended to be slightly lower than those in Study ZUMA-1, but the blood T-cell concentrations fell within a range of inter-individual variability of blood concentrations in the responders in Study ZUMA-1.
- A biological disposition profile of YESCARTA in Study ZUMA-7 is similar to that in Study ZUMA-1.

• The diagnosis and treatment system of LBCL do not clearly differ between Japan and foreign countries.

PMDA's view:
The above applicant's explanation is understandable to a certain extent, although no results from a study to investigate the efficacy and safety of YESCARTA in Japanese patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy are available. Clinical usefulness of YESCARTA can be evaluated in Japanese patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy based on results from Study ZUMA-7, and PMDA focused its review on this study.

6.R.2 Efficacy

As a result of the following review, PMDA concluded that YESCARTA was shown to have efficacy in patients with relapsed or refractory LBCL who were eligible for autologous HSCT and had received 1 line of prior therapy.

6.R.2.1 Inclusion of control group

The applicant's explanation about a rationale for including the control group in Study ZUMA-7:
For patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy, the Japanese and foreign clinical guidelines recommend salvage chemotherapy (R-ICE, R-ESHAP, R-GDP, R-DHAP, etc.) and, if a response is achieved, followed by HDCT with HSCT. As the control group, Study ZUMA-7 included the standard-of-care group in which the concerned recommended therapy would be performed.

PMDA accepted the applicant's explanation.

6.R.2.2 Efficacy endpoint

The applicant's explanation about a reason for specifying the centrally assessed EFS as the primary endpoint in Study ZUMA-7:
EFS was defined as the time from randomization to the earliest date of disease progression, commencement of new lymphoma therapy, or death from any cause. For patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy, the guidelines recommend salvage chemotherapy and, if a response is not achieved, followed by commencement of new lymphoma therapy instead of HDCT with autologous HSCT. The concerned commencement of new lymphoma therapy is an event corresponding to a failure of the second-line therapy. Considering it clinically meaningful to demonstrate longer EFS in the YESCARTA group than in the standard-of-care group, EFS was specified as the primary endpoint.

PMDA's view:

The applicant's explanation is largely understandable. However, progression free survival (PFS) and overall survival (OS) are also important in evaluating the therapeutic effect in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy. For the efficacy of YESCARTA, PMDA focused on results on the centrally assessed EFS, specified as the primary endpoint, but also check results on PFS and OS.

6.R.2.3 Efficacy evaluation results

The applicant's explanation about the efficacy of YESCARTA in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy:

Table 3 shows results on EFS (centrally assessed), the primary endpoint, from the main efficacy analysis (data cutoff on March 18, 2021) in Study ZUMA-7, demonstrating longer EFS in the YESCARTA group than in the standard-of-care group with a statistical significance [see Section 6.1.1.1].

Table 4 and Figure 2 show results on PFS assessed by the investigator as of data cutoff date of March 18, 2021 and Kaplan-Meier curve, respectively.

Table 4. Results on PFS
(assessed by the investigator, efficacy analysis population, data cutoff on March 18, 2021)

	YESCARTA n = 180	Standard of care n = 179
Death or aggravation (%)	96 (53.3)	103 (57.5)
Median [95% CI] (months)	14.7 [5.4, NE]	3.7 [2.9, 5.3]
Hazard ratio [95% CI]*	0.490 [0.368, 0.652]	

* Calculated using the Cox proportional hazards model stratified by the response level to the first-line therapy (refractory level to the first-line therapy [PD, SD, or PR], relapse within 6 months after CR achieved by the first-line therapy, or relapse at >6 and ≤12 months after completion of the first-line therapy) and sAAIPI (0 or 1, 2 or 3)

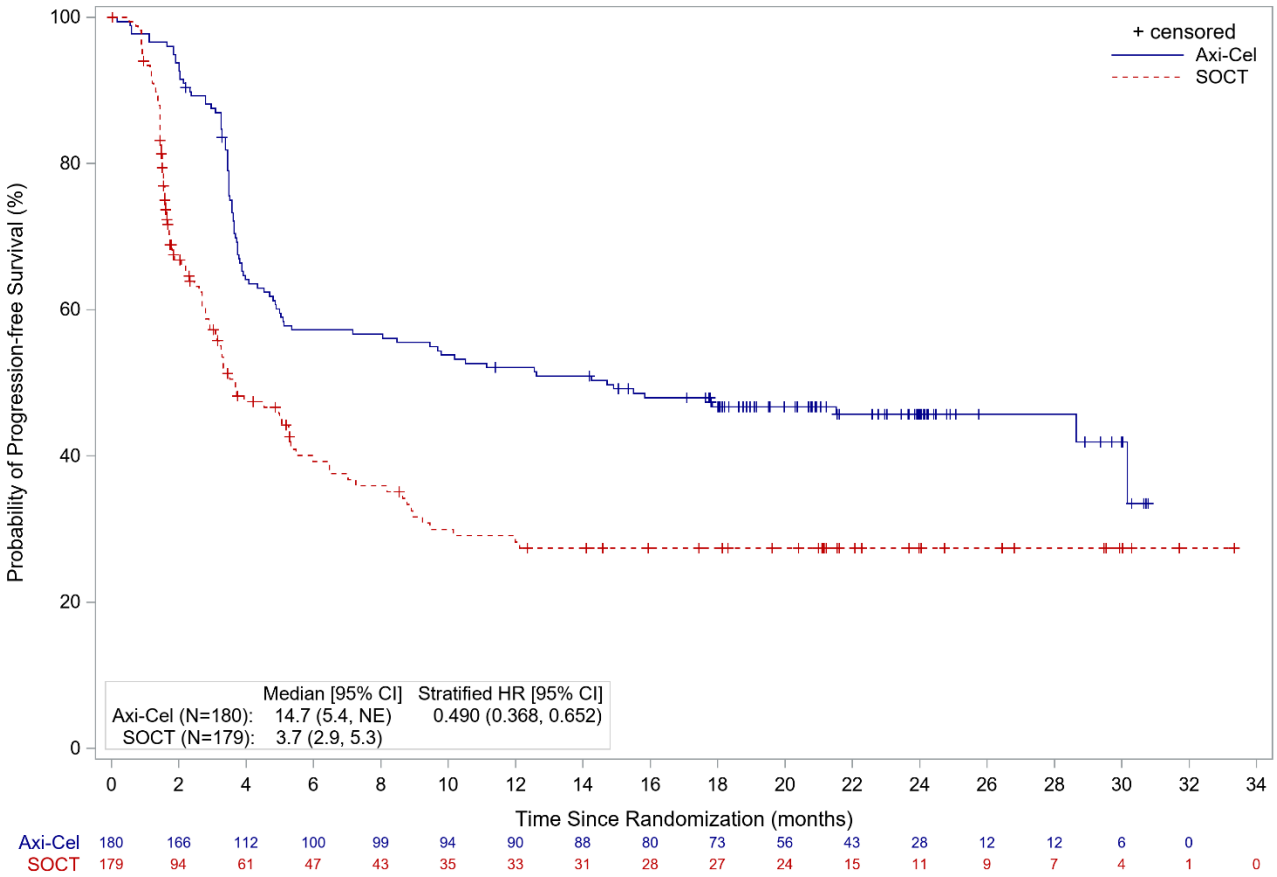

Figure 2. Kaplan-Meier curve on PFS (efficacy analysis population, data cutoff on March 18, 2021)

Table 5 and Figure 3 show results on OS as of data cutoff date of March 18, 2021 and Kaplan-Meier curve, respectively.

Table 5. Results on OS (efficacy analysis population, data cutoff on March 18, 2021)

	YESCARTA n = 180	Standard of care n = 179
Death (%)	72 (40.0)	81 (45.3)
Median [95% CI] (months)	NE [28.3, NE]	35.1 [18.5, NE]
Hazard ratio [95% CI]*	0.730 [0.530, 1.007]	

* Calculated using the Cox proportional hazards model stratified by the response level to the first-line therapy (refractory level to the first-line therapy [PD, SD, or PR], relapse within 6 months after CR achieved by the first-line therapy, or relapse at >6 and ≤12 months after completion of the first-line therapy) and sAAIPI (0 or 1, 2 or 3)

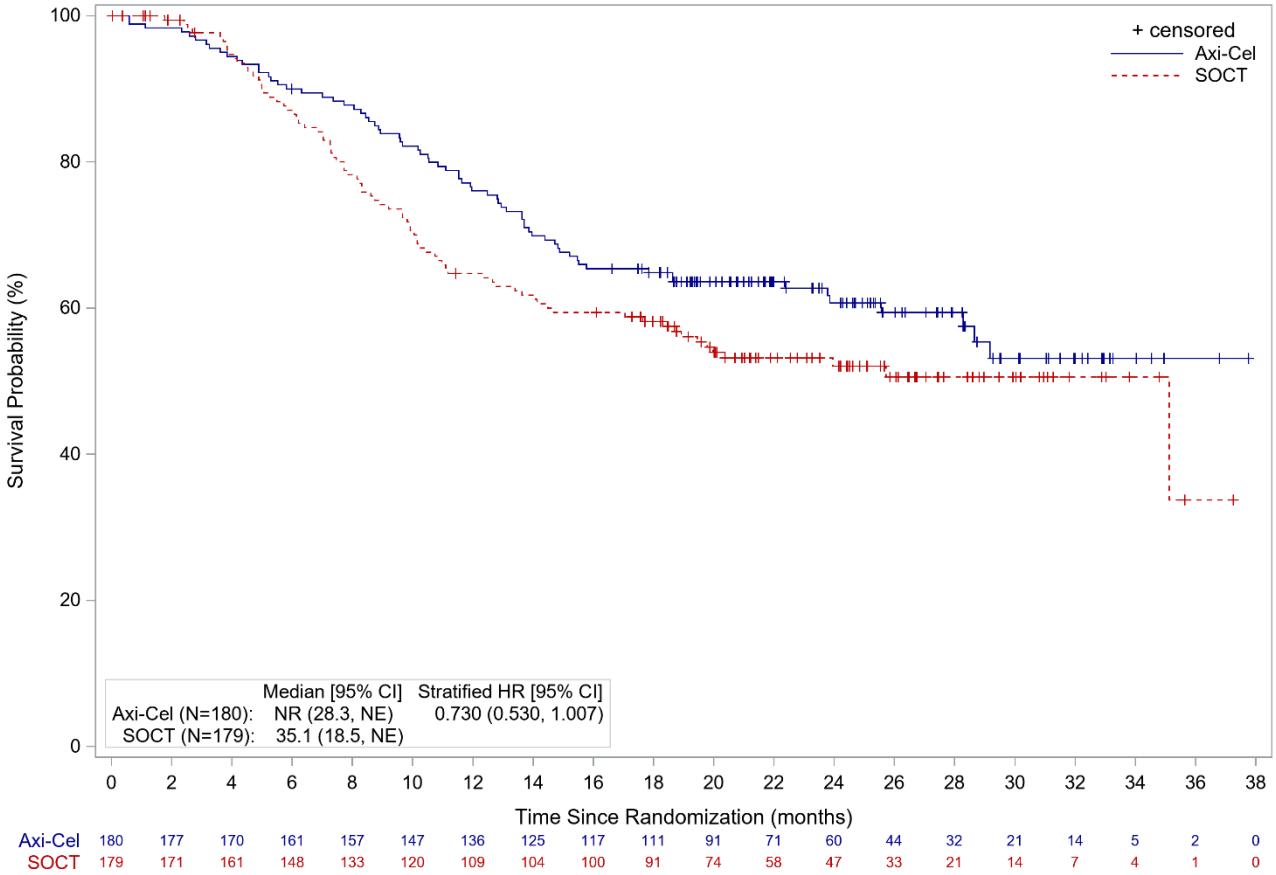

Figure 3. Kaplan-Meier curve on OS (efficacy analysis population, data cutoff on March 18, 2021)

Table 6 shows results on the efficacy by tissue type.[11)]

[11)] The standard-of-care group included 1 patient each of whom received a centrally assessed diagnosis of transformed chronic lymphocytic leukemia (CLL), ALK-positive LBCL, or ALK-positive large B-cell lymphoma.

Table 6. Results on efficacy by tissue type*1
(centrally assessed, efficacy analysis population, data cutoff on March 18, 2021)

	DLBCL NOS		tFL		HGBCL	
	YESCARTA n = 110	Standard of care n = 116	YESCARTA n = 19	Standard of care n = 27	YESCARTA n = 43	Standard of care n = 27
EFS event (%)	68 (61.8)	97 (83.6)	10 (52.6)	24 (88.9)	23 (53.4)	18 (66.7)
Median [95% CI] (months)	5.4 [3.9, 14.9]	1.8 [1.6, 2.7]	28.6 [3.6, NE]	2.7 [1.6, 7.3]	21.5 [3.7, NE]	2.1 [1.5, 6.6]
CR	70	34	16	10	30	9
Percentage of CR (%) [95% CI*2] (%)	63.6 [53.9, 72.6]	29.3 [21.2, 38.5]	84.2 [60.4, 96.6]	37.0 [19.4, 57.6]	69.8 [53.9, 82.8]	33.3 [16.5, 54.0]
Response (CR or PR)	92	57	17	15	36	12
Percentage of overall response (%) [95% CI*2] (%)	83.6 [75.4, 90.0]	49.1 [39.7, 58.6]	89.5 [66.9, 98.7]	55.6 [35.3, 74.5]	83.7 [69.3, 93.2]	44.4 [25.5, 64.7]

	THRLBCL		Epstein-Barr virus positive DLBCL		Primary cutaneous DLBCL, leg type	
	YESCARTA n = 5	Standard of care n = 6	YESCARTA n = 2	Standard of care n = 0	YESCARTA n = 1	Standard of care n = 0
EFS event (%)	4 (80.0)	2 (33.3)	2 (100)	—	1 (100)	—
Median [95% CI] (months)	3.7 [3.0, NE]	NE [5.0, NE]	3.6 [2.3, NE]	—	3.3	—
CR	1	5	0	—	0	—
Percentage of CR (%) [95% CI*2] (%)	20.0 [0.5, 71.6]	83.3 [35.9, 99.6]	0 [0.0, 84.2]	—	0 [0.0, 97.5]	—
Response (CR or PR)	3	5	1	—	1	—
Percentage of overall response (%) [95% CI*2] (%)	60.0 [14.7, 94.7]	83.3 [35.9, 99.6]	50.0 [1.3, 98.7]	—	100 [2.5, 100]	—

*1 Tissue type determined by the investigator
*2 Clopper-Pearson method

PMDA's view:

The applicant's explanation above is understandable. In view of the points provided below, results from Study ZUMA-7 demonstrated the efficacy of YESCARTA in patients with relapsed or refractory LBCL who were eligible for autologous HSCT and had received 1 line of prior therapy.

- The centrally assessed EFS, the primary endpoint in Study ZUMA-7, was longer in the YESCARTA group than in the standard-of-care group with a statistical significance.
- Results on PFS in Study ZUMA-7 showed a similar trend to that for EFS.
- In Study ZUMA-7, OS in the YESCARTA group did not tend to be shorter than that in the standard-of-care group.

6.R.3 Safety [for adverse events, see Section "8. Adverse Events Observed in Clinical Studies"]

As a result of the following review, PMDA has concluded that adverse events requiring special attention when using YESCARTA in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy are similar to events[12)] that were determined to require attention when the initial indications were approved; and thus as done for the approved indications, attention should be paid to these adverse events when YESCARTA is used for the proposed indication.

12) Cytokine release syndrome (CRS), haemophagocytic lymphohistiocytosis, neurologic toxicity, infection, myelosuppression, hypersensitivity, hypogammaglobulinaemia, and tumor lysis syndrome (TLS) (Review Report on YESCARTA Intravenous Drip Infusion, dated November 17, 2020)

PMDA has concluded that YESCARTA is tolerable in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy if appropriate measures on adverse events such as monitoring and controlling are taken by physicians with sufficient knowledge and experience in treatment of LBCL at a medical institution with adequate equipment capable of taking actions on the above adverse events.

6.R.3.1 Safety profile of YESCARTA

The applicant's explanation about the safety of YESCARTA in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy:

Table 7 shows the summary of safety profiles in Study ZUMA-7 (data cutoff on March 18, 2021) and in foreign Study ZUMA-1[13)] and Japanese Study J201,[14)] which included patients with relapsed or refractory LBCL applicable to the approved indications.

Table 7. Summary of safety (Studies ZUMA-7, ZUMA-1, and J201,*1 safety analysis population)

	n (%)			
	Study ZUMA-7		Study ZUMA-1	Study J201
	YESCARTA n = 170	Standard of care n = 168	YESCARTA n = 108	YESCARTA n = 16
All adverse event	170 (100)	168 (100)	108 (100)	16 (100)
Grade ≥3 adverse events	155 (91.2)	140 (83.3)	104 (96.3)	16 (100)
Serious adverse events	85 (50.0)	77 (45.8)	58 (53.7)	13 (81.3)
Adverse events leading to death	14 (8.2)	7 (4.2)	9 (8.3)	0
CRS*2	157 (92.4)	—	100 (92.6)	13 (81.3)
Grade ≥3 CRS	11 (6.5)	—	12 (11.1)	1 (6.3)
Adverse events related to nervous system*3	138 (81.2)	104 (61.9)	95 (88.0)	6 (37.5)
Grade ≥3 adverse events related to nervous system	44 (25.9)	16 (9.5)	37 (34.3)	0
Nervous system events*4	102 (60.0)	33 (19.6)	71 (65.7)	0
Grade ≥3 nervous system events	36 (21.2)	1 (0.6)	34 (31.5)	0
Cytopenia*5	136 (80.0)	135 (80.4)	98 (90.7)	16 (100)
Grade ≥3 cytopenia	128 (75.3)	126 (75.0)	89 (82.4)	16 (100)
Infection*6	70 (41.2)	51 (30.4)	43 (39.8)	12 (75.0)
Grade ≥3 infection	24 (14.1)	19 (11.3)	29 (26.9)	2 (12.5)

*1 Studies ZUMA-7 and ZUMA-1, data cutoff on March 18, 2021; Study J201, data cutoff on October 23, 2019. In Study ZUMA-1, adverse events were collected from the beginning of leukapheresis and serious adverse events from the time of obtaining informed consent. The collection period of adverse events and serious adverse events was extended to 3 months after administration of YESCARTA, and then only the specified serious adverse events (the same as ones specified in Study ZUMA-7) were collected until 24 months after the administration or disease progression, whichever occurs first.

*2 Cytokine release syndrome (CRS)-related events were entered in case report forms (CRFs) and were included in the tabulation. When CRS occurred, adverse event terms such as "Pyrexia" and "Hypotension," which led to identification of CRS, were entered as report terms in CRFs instead of "CRS." In addition, a note was entered, stating that the event terms such as "Pyrexia" and "Hypotension" linked to CRS.

*3 Adverse events coded as "Nervous system disorders" or "Psychiatric disorders" in System Organ Class (SOC) of Medical Dictionary for Regulatory Activities Japanese version (MedDRA)

*4 Events applicable to preferred terms (PTs) listed in Table 8

*5 Events coded as MedDRA standardised MedDRA queries (SMQ) "Haematopoietic thrombocytopenia" (narrow), MedDRA PTs "Neutropenia," "Febrile neutropenia," and "Neutrophil count decreased" as well as MedDRA SMQ "Haematopoietic erythropenia" (broad)

*6 Events coded as MedDRA high level group terms (HLGTs) "Bacterial infection," "Chlamydial infection," "Viral infection," "Infections - pathogen unspecified," SMQ "Opportunistic infections" (narrow), or SMQ "COVID-19" (narrow)

13) Foreign open-label, uncontrolled phase I/II study conducted to investigate the efficacy and safety of YESCARTA in patients with relapsed or refractory LBCL. In this study, patients intravenously received a single dose of 2×10^6 anti-CD19 CAR T-cells/kg (1×10^6 cells/kg at the minimum; for patients weighing >100 kg, up to 2×10^8 cells) (Review Report on YESCARTA Intravenous Drip Infusion, dated November 17, 2020).

14) Japanese open-label, uncontrolled phase II study conducted to investigate the efficacy and safety of YESCARTA in patients with relapsed or refractory LBCL. In this study, patients intravenously received a single dose of 2×10^6 anti-CD19 CAR T-cells/kg (1×10^6 cells/kg at the minimum; for patients weighing >100 kg, up to 2×10^8 cells) (Review Report on YESCARTA Intravenous Drip Infusion, dated November 17, 2020).

Table 8. List of events applicable to neurologic toxicity for tabulation*

Aberrant motor behaviour, acalculia, hypertonia, acquired epileptic aphasia, hypoaesthesia, action tremor, acute flaccid myelitis, ageusia, hypogeusia, hypokinesia, hypotonia, idioglossia, aggression, idiopathic generalised epilepsy, agitation, incoherent, agnosia, intention tremor, agraphia, intermediate syndrome, akathisia, language disorder, akinaesthesia, lethargy, akinesia, leukoencephalopathy, alexia, locked-in syndrome, allodynia, loss of consciousness, altered state of consciousness, lower motor neurone lesion, amnesia, amnestic disorder, memory impairment, anaesthesia, mental impairment, anterograde amnesia, mental status changes, apallic syndrome, micrographia, aphasia, mixed anxiety and depressive disorder, aphonia, mixed delusion, apraxia, monoparesis, aprosody, monoplegia, asterixis, Morvan syndrome, ataxia, motor dysfunction, athetosis, motor neurone disease, atonic seizures, movement disorder, auditory perseveration, muscle contractions involuntary, aura, muscle spasticity, autoimmune encephalopathy, muscle tone disorder, myelitis, myelitis transverse, autonomic failure syndrome, myoclonic epilepsy, autonomic nervous system imbalance, myoclonus, autonomic neuropathy, myotonia, autonomic seizure, nervous system disorders, balance disorder, nervous system injury, neuralgia, bradykinesia, neurological decompensation, bradyphrenia, neurological symptom, brain compression, neuromuscular blockade, brain herniation, neuromuscular pain, brain oedema, neuromuscular toxicity, brain stem syndrome, neuromyopathy, cardiac autonomic neuropathy, central nervous system lymphoma, neuromyotonia, cerebellar ataxia, neurotoxicity, noninfectious myelitis, cerebellar syndrome, nystagmus, cerebral ataxia, optic disc pigmentation, cerebral congestion, oromandibular dystonia, cerebral disorder, orthostatic intolerance, cerebral oedema management, cerebral venous sinus thrombosis, paraesthesia, cervicogenic vertigo, paralysis, paraneoplastic myelopathy, change in seizure presentation, ciliary ganglionitis, paraparesis, paratonia, clonic convulsion, paresis, paroxysmal extreme pain disorder, clonus, partial seizures, clumsiness, cognitive disorder, partial seizures with secondary generalisation, coma, peripheral nerve palsy, confusional state, peripheral nerve paresis, consciousness fluctuating, peripheral paralysis, convulsions local, petit mal epilepsy, coordination abnormal, cytotoxic oedema, decreased gait velocity, phonasthenia, pituitary apoplexy, delirium, posterior reversible encephalopathy syndrome, delusion, postictal state, dementia, preictal state, propulsive gait, depressed level of consciousness, prosopagnosia, disorientation, psychomotor disadaptation syndrome, disturbance in attention, psychomotor hyperactivity, dysaesthesia, pyramidal tract syndrome, dysarthria, reduced facial expression, dyscalculia, dysdiadochokinesis, reflexes abnormal, dysgraphia, resting tremor, dyskinesia, restlessness, dyslalia, retrograde amnesia, dystonia, right hemisphere deficit syndrome, dystonic tremor, sedation, encephalopathy, seizure, epilepsy, epilepsy with myoclonic-atonic seizures, seizure cluster, epileptic aura, seizure like phenomena, seizure prophylaxis, essential tremor, sensorimotor disorder, extraischaemic cerebral haematoma, faciobrachial dystonic seizure, sensory disturbance, fine motor delay, sensory loss, fine motor skill dysfunction, simple partial seizures, simultanagnosia, focal dyscognitive seizures, Foville syndrome, sleep deficit, frontal lobe epilepsy, slow speech, fumbling, somnolence, gait apraxia, speech disorder, gait spastic, generalised onset non-motor seizure, spinal cord oedema, spinal stroke, status epilepticus, generalised tonic-clonic seizure, genital dysaesthesia, stupor, supranuclear palsy, taste disorder, hallucination, temporal lobe epilepsy, hallucination auditory, tonic clonic movements, hallucination gustatory, tonic convulsion, hallucination olfactory, tonic posturing, hallucination synaesthetic, toxic encephalopathy, hallucination tactile, toxic leukoencephalopathy, hallucination visual, transient epileptic amnesia, transient global amnesia, hallucinations mixed, tremor, head discomfort, hemiataxia, hemidysaesthesia, unresponsive to stimuli, hemihyperaesthesia, vasogenic cerebral oedema, vertebrobasilar stroke, hemiplegia, vertigo CNS origin, hyperaesthesia, vestibulocerebellar syndrome, hypergeusia, visual perseveration, hyperkinesia, visuospatial deficit, hyperpathia, hyperresponsive to stimuli, hypersomnia, immune effector cell-associated neurotoxicity syndrome, immune-mediated encephalitis, immune-mediated encephalopathy, intramyelinic oedema, papilloedema

* MedDRA ver.23.1 for Studies ZUMA-7 and ZUMA-1 and MedDRA ver.21.0 for Study J201

Adverse events with a ≥10% higher incidence in the YESCARTA group than in the standard-of-care group in Study ZUMA-7 were pyrexia (158 patients [92.9%] in the YESCARTA group, 43 patients [25.6%] in the standard-of-care group), neutropenia (75 [44.1%], 29 [17.3%]), hypotension (75 [44.1%], 25 [14.9%]), headache (70 [41.2%], 43 [25.6%]), chills (47 [27.6%], 14 [8.3%]), sinus tachycardia (58 [34.1%], 17 [10.1%]), tremor (44 [25.9%], 1 [0.6%]), hypoxia (37 [21.8%], 13 [7.7%]), confusional state (40 [23.5%], 4 [2.4%]), cough (42 [24.7%], 18 [10.7%]), encephalopathy (29 [17.1%], 2 [1.2%]), aphasia (36 [21.2%], 0 [0%]), somnolence (19 [11.2%], 2 [1.2%]), and hypogammaglobulinaemia (19 [11.2%], 1 [0.6%]).

Grade ≥3 adverse events with a ≥10% higher incidence in the YESCARTA group than in the standard-of-care group were neutropenia (73 patients [42.9%] in the YESCARTA group, 28 patients [16.7%] in the standard-of-care group) and encephalopathy (20 [11.8%], 0 [0%]).

Serious adverse events with a ≥5% higher incidence in the YESCARTA group than in the standard-of-care group were pyrexia (27 patients [15.9%] in the YESCARTA group, 8 patients [4.8%] in the

standard-of-care group), encephalopathy (17 [10.0%], 1 [0.6%]), hypotension (15 [8.8%], 3 [1.8%]), and aphasia (9 [5.3%], 0 [0%]).

For differences in the safety profile of YESCARTA between patients with relapsed or refractory LBCL who were eligible for autologous HSCT and had received 1 line of prior therapy and patients of the approved indications, an adverse event with a ≥10% higher incidence in the YESCARTA group in Study ZUMA-7 than in Study ZUMA-1 was sinus tachycardia (58 patients [34.1%] in Study ZUMA-7, 21 patients [19.4%] in Study ZUMA-1). There were no Grade ≥3 adverse events with a ≥10% higher incidence in the YESCARTA group in Study ZUMA-7 than in Study ZUMA-1. Serious adverse events with a ≥5% higher incidence in the YESCARTA group in Study ZUMA-7 than in Study ZUMA-1 were pyrexia (27 patients [15.9%], 6 patients [5.6%]) and hypotension (15 [8.8%], 3 [2.8%]).

PMDA's view:
Attention should be paid to the Grade ≥3 adverse events and serious adverse events of which the incidence was higher in the YESCARTA group than in the standard-of-care group in Study ZUMA-7. Although no clear differences in the safety profile were observed between the YESCARTA group in Study ZUMA-7 and Studies ZUMA-1 and J201, which included patients with relapsed or refractory LBCL of the approved indications, serious adverse events such as CRS frequently occurred after administration of YESCARTA. When YESCARTA is used, the patient should be very carefully monitored, and if an adverse event occurs, multimodal measures should be taken according to its nature.

The above adverse events, on the other hand, are all known to occur in patients treated with YESCARTA. In view of this, YESCARTA is tolerable in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy if appropriate measures on adverse events such as monitoring and controlling are taken by physicians with sufficient knowledge and experience in treatment of LBCL at a medical institution with adequate equipment capable of taking actions on the adverse events.

6.R.4 Clinical positioning, indications, or performance

At the application of YESCARTA, the "Indications or Performance" was proposed as described below.

Indications or Performance (Underline denotes additions to the approved content. Strikethrough denotes deletions from the approved content.)
The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high grade B-cell lymphoma

YESCARTA should be used only in patients meeting all of the following criteria:

- Patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.
- Patients who ~~are eligible for autologous hematopoietic stem cell transplantation,~~ have failed to respond to ≥1 line ~~2 lines~~ of chemotherapy ~~in the newly diagnosed patients and with ≥1 line of chemotherapy after relapse in the relapsed patients,~~ or ~~have~~ had a relapse ~~after autologous~~

~~hematopoietic stem cell transplantation; or patients who are ineligible for autologous hematopoietic stem cell transplantation~~

In addition, the "Precautions Concerning Indications or Performance" section included the following statements:

- Appropriate patients must be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of YESCARTA, concerning tissue type, prior treatment, etc. of patients enrolled in the clinical studies.

PMDA's view:

On the basis of the reviews in Sections "6.R.2 Efficacy," "6.R.3 Safety," and the review provided below, the "Indications or Performance" of YESCARTA should be specified as follows. The "Precautions Concerning Indications or Performance" section should be specified as proposed.

Indications or Performance (Underline denotes additions to the proposed partial change application. Strikethrough denotes deletions from the proposed partial change application.)

The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high grade B-cell lymphoma

YESCARTA should be used only in patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen. ~~meeting all of the following criteria:~~

- ~~Patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.~~
- ~~Patients who failed to respond to ≥1 line of chemotherapy or had a relapse~~

6.R.4.1 Clinical positioning and target population of YESCARTA

Of the Japanese and foreign clinical guidelines, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas (NCCN guidelines) include a description about use of YESCARTA in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy.

Clinical guidelines

- NCCN guidelines (v.5.2022): YESCARTA is recommended for patients with LBCL who are refractory to the first-line therapy or have a relapse within 12 months after the first-line therapy (Category 1[15)]).

The applicant's explanation about the clinical positioning and "Indications or Performance" of YESCARTA in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy:

For patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy, the Japanese and foreign clinical guidelines recommend salvage chemotherapy

[15)] The recommendation is based on high-level evidence, and there is uniform NCCN consensus that the intervention is appropriate.

and, if a response is achieved, followed by HDCT with HSCT. In clinical studies where the concerned recommended therapy was conducted (*J Clin Oncol.* 2010;28:4184-90, *J Clin Oncol.* 2014;32:3490-6, etc.), only approximately 20% of the patients achieved a complete response (CR), and patients who started the recommended therapy but failed to complete HDCT with autologous HSCT had a poor prognosis. A new treatment method is therefore needed. In the above situation, Study ZUMA-7 demonstrated the efficacy and safety of YESCARTA in patients with relapsed or refractory LBCL who were eligible for autologous HSCT and had received 1 line of prior therapy [see Sections 6.R.2 and 6.R.3], and thus YESCARTA will be a new treatment option for the concerned patient population. In view of the approved content, the "Indications or Performance" is specified to clarify the target patient population of YESCARTA, who are required to have received ≥1 line of prior therapy.

The proposed "Indications or Performance" included PMBCL as an eligible tissue type, while Study ZUMA-7 excluded PMBCL. PMDA asked the applicant whether YESCARTA would be recommended for patients with relapsed or refractory PMBCL who were eligible for autologous HSCT and had received 1 line of prior therapy.

The applicant's response:
For PMBCL, radiotherapy conducted after the first-line therapy is deemed as an EFS event, potentially underestimating EFS in the standard-of-care group, and thus Study ZUMA-7 excluded this tissue type. The applicant, however, considers it possible to recommend YESCARTA for patients with relapsed or refractory PMBCL who are eligible for autologous HSCT and have received 1 line of prior therapy in view of the results from clinical studies in patients with relapsed or refractory LBCL of the approved indications, which demonstrated the efficacy of YESCARTA in patients with PMBCL (See "Review Report on YESCARTA Intravenous Drip Infusion, dated November 17, 2020").

Because Study ZUMA-7 did not include patients who had relapsed from CR >12 months after the primary (first-line) treatment, PMDA asked the applicant whether YESCARTA would be recommended for the concerned patients.

The applicant's response:
Patients who were refractory to the first-line therapy or had relapsed from CR ≤12 months after first-line treatment had a poorer prognosis than patients who had relapsed later (*J Clin Oncol.* 2010;28:4184-90). In view of this report, Study ZUMA-7 included patients who were refractory to the first-line therapy or had relapsed from CR ≤12 months. YESCARTA therefore has not been used in patients who are eligible for autologous HSCT and have relapsed from CR >12 months after the first-line therapy. Taking account of the mechanism of action of YESCARTA, etc., however, YESCARTA is recommended as one of the treatment options for patients who are eligible for autologous HSCT and have relapsed from CR >12 months after the first-line therapy.

PMDA's view:
Although the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections should be specified based on results from Study ZUMA-7, the applicant's explanation about PMBCL is understandable. On the other hand, clinical positioning of YESCARTA for patients who are

eligible for autologous HSCT and had relapsed from CR ≤12 months after the first-line therapy is unclear because there are no clinical study results on the compared use of YESCARTA and conventional therapy in the concerned patient population. Therefore, the target patient population of Study ZUMA-7, being patients who had relapsed from CR ≤12 months after the first-line therapy, is important information when selecting YESCARTA for patients who had relapsed after the first-line therapy. In conclusion, the "Clinical Studies" section in the package insert should state that the patients included in Study ZUMA-7 had relapsed ≤12 months from CR to the first-line therapy in addition to tissue types and prior therapies of the patients included in each study; and the "Precautions Concerning Indications or Performance" section should instruct physicians to select appropriate patients with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of YESCARTA. Of note, the "Indications or Performance" section defines the intended patients as those with "relapsed or refractory LBCL," and it is obvious that the intended patients for YESCARTA have ≥1 line of prior therapy. Thus, the following statement is unnecessary and should be deleted: "Patients who failed to respond to ≥1 line of chemotherapy or had a relapse."

6.R.5 Dosage and administration or method of use

The proposed "Dosage and Administration or Method of Use" of YESCARTA in this application is the same as the approved content.

The applicant's explanation about a rationale for specifying the "Dosage and Administration or Method of Use" of YESCARTA:

Study ZUMA-7 was conducted using the approved "Dosage and Administration or Method of Use," and the efficacy and safety of YESCARTA were demonstrated. For patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have 1 line of prior therapy, the applicant also specified the same "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" as those for the approved indications.

PMDA's view:

The applicant's explanation is understandable. In view of its review in Sections "6.R.2 Efficacy" and "6.R.3 Safety," the "Dosage and Administration or Method of Use" of YESCARTA for patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have 1 line of prior therapy might be the same as the approved content.

7. Risk Analysis and Outline of the Review Conducted by PMDA

The applicant's explanation:

For reasons provided below, the currently ongoing post-marketing database survey[16)] which covers all the patients treated with YESCARTA for the approved indications will additionally cover patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have 1 line of prior therapy.

16) Safety specification
CRS, haemophagocytic lymphohistiocytosis, nervous system event, infection, hypogammaglobulinaemia, cytopenia, TLS, hypersensitivity, secondary malignant tumor, use in pregnant and breast feeding women, onset or aggravation of autoimmune disease, and long-term safety

- The safety profile of YESCARTA in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have 1 line of prior therapy in Study ZUMA-7 is comparable to that in patients for the approved indications [see Section 6.R.3.1].
- In view of the Japanese guidelines stating that patients aged up to approximately 70 years are subjected to autologous HSCT, patients who had received 1 line of prior therapy and were <70 years when treated with YESCARTA are extracted from the patient population in the post-marketing database survey. Using data on the efficacy (best response, relapse or progression, survival, etc.) in an extracted patient population, the efficacy of YESCARTA in Japanese patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy in clinical settings can be evaluated.

PMDA's view:
Post-marketing information about the efficacy and safety of YESCARTA is important and should be collected for Japanese patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy because YESCARTA has not been used in such patients. The applicant, therefore, should collect information about the efficacy and safety in all patients who have received YESCARTA in post-marketing settings and provide the obtained information about the efficacy and safety to healthcare professionals without delay.

Measures to collect post-marketing information will be finalized, taking account of comments on the efficacy and safety evaluation of YESCARTA raised in the Expert Discussion.

8. Adverse Events Observed in Clinical Studies

Data on deaths reported in clinical studies submitted as the safety evaluation data are presented in Section "6.1 Evaluation data." Main adverse events other than death are shown below.

8.1 Foreign phase III study (Study ZUMA-7)

Adverse events occurred in all patients in the YESCARTA group and standard-of-care group, and events for which a causal relationship to YESCARTA or the standard of care could not be ruled out occurred in 163 of 170 patients (95.9%) in the YESCARTA group and 160 of 168 patients (95.2%) in the standard-of-care group. Table 9 shows adverse events with an incidence of ≥10% in either group.

Table 9. Adverse events with an incidence of ≥10% in either group (Study ZUMA-7)

SOC PT (MedDRA ver.23.1)	n (%)			
	YESCARTA n = 170		Standard of care n = 168	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	170 (100)	155 (91.2)	168 (100)	140 (83.3)
Blood and lymphatic system disorders				
Neutropenia	75 (44.1)	73 (42.9)	29 (17.3)	28 (16.7)
Anaemia	71 (41.8)	51 (30.0)	91 (54.2)	65 (38.7)
Thrombocytopenia	22 (12.9)	14 (8.2)	41 (24.4)	37 (22.0)
Febrile neutropenia	4 (2.4)	4 (2.4)	46 (27.4)	46 (27.4)
Gastrointestinal disorders				
Diarrhoea	71 (41.8)	4 (2.4)	66 (39.3)	7 (4.2)
Nausea	69 (40.6)	3 (1.8)	116 (69.0)	9 (5.4)
Constipation	34 (20.0)	0	58 (34.5)	0
Vomiting	33 (19.4)	0	55 (32.7)	1 (0.6)
Abdominal pain	24 (14.1)	5 (2.9)	25 (14.9)	2 (1.2)
Stomatitis	5 (2.9)	0	29 (17.3)	3 (1.8)
General disorders and administration site conditions				
Pyrexia	158 (92.9)	15 (8.8)	43 (25.6)	1 (0.6)
Fatigue	71 (41.8)	11 (6.5)	87 (51.8)	4 (2.4)
Chills	47 (27.6)	1 (0.6)	14 (8.3)	0
Oedema peripheral	20 (11.8)	0	28 (16.7)	1 (0.6)
Malaise	17 (10.0)	0	9 (5.4)	0
Immune system disorders				
Hypogammaglobulinaemia	19 (11.2)	0	1 (0.6)	0
Investigations				
White blood cell count decreased	46 (27.1)	43 (25.3)	37 (22.0)	31 (18.5)
Neutrophil count decreased	52 (30.6)	49 (28.8)	47 (28.0)	47 (28.0)
Platelet count decreased	30 (17.6)	12 (7.1)	64 (38.1)	60 (35.7)
Lymphocyte count decreased	31 (18.2)	29 (17.1)	21 (12.5)	18 (10.7)
Alanine aminotransferase increased	31 (18.2)	1 (0.6)	16 (9.5)	3 (1.8)
Aspartate aminotransferase increased	24 (14.1)	1 (0.6)	15 (8.9)	1 (0.6)
Musculoskeletal and connective tissue disorders				
Back pain	16 (9.4)	0	25 (14.9)	4 (2.4)
Arthralgia	19 (11.2)	1 (0.6)	14 (8.3)	1 (0.6)
Muscular weakness	19 (11.2)	6 (3.5)	10 (6.0)	0
Nervous system disorders				
Headache	70 (41.2)	5 (2.9)	43 (25.6)	2 (1.2)
Tremor	44 (25.9)	2 (1.2)	1 (0.6)	0
Encephalopathy	29 (17.1)	20 (11.8)	2 (1.2)	0
Dizziness	36 (21.2)	2 (1.2)	21 (12.5)	1 (0.6)
Aphasia	36 (21.2)	12 (7.1)	0	0
Somnolence	19 (11.2)	5 (2.9)	2 (1.2)	0
Psychiatric disorders				
Confusional state	40 (23.5)	9 (5.3)	4 (2.4)	0
Insomnia	21 (12.4)	0	26 (15.5)	1 (0.6)
Respiratory, thoracic and mediastinal disorders				
Cough	42 (24.7)	1 (0.6)	18 (10.7)	0
Hypoxia	37 (21.8)	16 (9.4)	13 (7.7)	7 (4.2)
Dyspnoea	14 (8.2)	5 (2.9)	20 (11.9)	2 (1.2)
Hiccups	5 (2.9)	0	21 (12.5)	1 (0.6)
Metabolism and nutrition disorders				
Decreased appetite	42 (24.7)	7 (4.1)	42 (25.0)	6 (3.6)
Hyperglycaemia	27 (15.9)	7 (4.1)	17 (10.1)	5 (3.0)
Hypokalaemia	44 (25.9)	10 (5.9)	49 (29.2)	11 (6.5)
Hypophosphataemia	45 (26.5)	31 (18.2)	29 (17.3)	21 (12.5)
Hypocalcaemia	27 (15.9)	1 (0.6)	17 (10.1)	3 (1.8)
Hypoalbuminaemia	22 (12.9)	1 (0.6)	12 (7.1)	0
Hyponatraemia	21 (12.4)	10 (5.9)	8 (4.8)	4 (2.4)
Hypomagnesaemia	20 (11.8)	1 (0.6)	34 (20.2)	4 (2.4)
Cardiac disorders				
Sinus tachycardia	58 (34.1)	3 (1.8)	17 (10.1)	1 (0.6)
Vascular disorders				
Hypotension	75 (44.1)	19 (11.2)	25 (14.9)	5 (3.0)
Renal and urinary disorders				
Acute kidney injury	13 (7.6)	3 (1.8)	21 (12.5)	4 (2.4)

Serious adverse events occurred in 85 of 170 patients (50.0%) in the YESCARTA group and 77 of 168 patients (45.8%) in the standard-of-care group.

Serious adverse events reported by ≥2% of patients in the YESCARTA group were pyrexia in 27 patients (15.9%), encephalopathy in 17 patients (10.0%), hypotension in 15 patients (8.8%), aphasia in 9 patients (5.3%), pneumonia in 8 patients (4.7%), B-cell lymphoma in 7 patients (4.1%), confusional state in 6 patients (3.5%), somnolence and tremor in 5 patients (2.9%) each, febrile neutropenia, atrial fibrillation, headache, and neutropenia in 4 patients (2.4%) each. A causal relationship to YESCARTA could not be ruled out for pyrexia in 24 patients, encephalopathy in 17 patients, hypotension in 15 patients, aphasia in 9 patients, confusional state, somnolence, and tremor in 5 patients each, pneumonia and atrial fibrillation in 4 patients each, headache and neutropenia in 3 patients each, and febrile neutropenia in 1 patient.

Serious adverse events reported by ≥2% of patients in the standard-of-care group were febrile neutropenia in 22 patients (13.1%), pyrexia and acute kidney injury in 8 patients (4.8%) each, B-cell lymphoma and platelet count decreased in 5 patients (3.0%) each, and pneumonia and sepsis in 4 patients (2.4%) each. A causal relationship to the standard of care could not be ruled out for febrile neutropenia in 19 patients, acute kidney injury in 6 patients, platelet count decreased in 5 patients, pyrexia in 4 patients, sepsis in 3 patients, and pneumonia in 2 patients.

9. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

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

The assessment is currently ongoing, and the results and conclusion reached by PMDA are presented in the Review Report (2).

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

The assessment is currently ongoing, and the results and conclusion reached by PMDA are presented in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that YESCARTA has a certain level of efficacy in the treatment of relapsed or refractory LBCL in patients who are eligible for autologous HSCT and have received 1 line of prior therapy, and that YESCARTA has acceptable safety in view of its benefits. PMDA therefore considers that making YESCARTA available in clinical practice is meaningful because it offers a new treatment option for patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy.

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

Review Report (2)

November 22, 2022

Product Submitted for Approval

Brand Name	YESCARTA Intravenous Drip Infusion
Non-proprietary Name	Axicabtagene ciloleucel
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 27, 2022

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

As a result of the review in Section "6.R.2 Efficacy" of the Review Report (1), PMDA has concluded that the centrally assessed EFS, the primary endpoint, is longer in the YESCARTA group than in the standard-of-care group with a statistical significance in Study ZUMA-7 in patients with relapsed or refractory LBCL who were eligible for autologous HSCT and had received 1 line of prior therapy, and therefore that YESCARTA is shown to have efficacy in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy.

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

1.2 Safety

As a result of the review in Section "6.R.3 Safety" of the Review report (1), PMDA has concluded that adverse events requiring special attention when using YESCARTA in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy are similar to events[17)] that were determined to require attention when the initial indications were approved; and thus as done for the approved indications, attention should be paid to these adverse events when YESCARTA is used for the proposed indication.

[17)] CRS, haemophagocytic lymphohistiocytosis, neurologic toxicity, infection, myelosuppression, hypersensitivity, hypogammaglobulinaemia, and TLS (Review Report on YESCARTA Intravenous Drip Infusion, dated November 17, 2020)

PMDA has concluded that YESCARTA is tolerable if appropriate measures on adverse events such as monitoring and controlling are taken by physicians with sufficient knowledge and experience in treatment of LBCL at a medical institution with adequate equipment capable of taking actions on the above adverse events.

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

1.3 Clinical positioning, indications, or performance

As a result of the review in Section "6.R.4 Clinical positioning, indications, or performance" of the Review Report (1), PMDA has concluded that the "Clinical Studies" section in the package insert should include that the patients in Study ZUMA-7 had relapsed from CR ≤12 months after the completion of first-line therapy, in addition to tissue types and prior therapies of the study patients; and the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections should be specified as provided below and in the applicable sections of the Review Report (1).

Indications or Performance

The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high grade B-cell lymphoma

YESCARTA should be used only in patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.

Precautions Concerning Indications or Performance

- Appropriate patients must be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of YESCARTA, concerning tissue type, prior treatment, etc. of patients enrolled in the clinical studies.

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

PMDA requested the applicant to specify the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections as described above. The applicant appropriately responded to request, and PMDA accepted.

1.4 Dosage and administration or method of use

As a result of the review in Section "6.R.5 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" of YESCARTA may be the same as the approved content.

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

1.5 Post-marketing surveillance plan (draft)

At the time of application, the applicant proposed a plan of post-marketing surveillance presented in Table 10 for the reason that the safety profile of YESCARTA in patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have 1 line of prior therapy is comparable to that in patients for the approved indications. The surveillance is planned to cover all patients treated with YESCARTA, by expanding the target patients of the post-marketing database survey previously planned at the time of the initial approval to patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have ≥1 line of prior therapy.

PMDA's view:

PMDA considers it possible to collect data on the safety and efficacy of YESCARTA in patients with relapsed or refractory LBCL by setting the planned sample size of 300, which will include patients treated with YESCARTA for the approved indications and patients for the indication added in this application. In addition, as reviewed in Section "7. Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), information about the efficacy and safety of YESCARTA is important and should be collected for Japanese patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy because YESCARTA has not been used in such patients. Regarding this point, an analysis in an extracted population of patients treated for the added indication is planned [see Section 7 of the Review Report (1)]. On the basis of the above plans, the proposed plan of post-marketing surveillance is acceptable. In addition to this, the information collected through this surveillance should be provided to healthcare professionals without delay.

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

PMDA instructed the applicant to provide the post-marketing information about the efficacy and safety of YESCARTA in Japanese patients with relapsed or refractory LBCL who are eligible for autologous HSCT and have received 1 line of prior therapy to healthcare professionals when results from use in such patients accumulate to a certain extent.

The applicant explained their plan in the post-marketing database survey to evaluate the efficacy and safety using interim tabulation data every year starting 3 years after the initial approval and provide the concerned evaluation results to healthcare professionals every year. PMDA accepted their plan.

Table 10. Outline of post-marketing surveillance

Objective	To evaluate the safety and efficacy of YESCARTA in clinical use
Survey method	All-case surveillance The applicant will obtain the data on the target population from the data accumulated in the registry database (FormsNet) owned by the Center for International Blood and Marrow Transplant Research (CIBMTR) via the Japanese Data Center for Hematopoietic Cell Transplantation.
Population	Patients with relapsed or refractory LBCL
Observation period	Up to 8 years
Planned sample size	300 patients
Main survey items	**Safety** CRS, nervous system event, infection, hypogammaglobulinaemia, cytopenia, TLS, secondary malignant tumor, haemophagocytic lymphohistiocytosis, hypersensitivity, use in pregnant and breast feeding women, onset or aggravation of autoimmune disease, and long-term safety **Efficacy** Best response, PFS, and OS

2. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

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

The new regenerative medical product 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.

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

The new regenerative medical product application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication or performance and dosage and administration or method of use as shown below, with the following conditions. However, a cautionary statement must be given in the package insert, and information on proper use of the product must be disseminated appropriately in the post-marketing settings. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until January 21, 2031).

Indications or Performance

The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high grade B-cell lymphoma

YESCARTA should be used only in patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen. ~~meeting all of the following criteria:~~

- ~~Patients who have not received prior infusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.~~
- ~~Patients who failed to respond to ≥1 line of chemotherapy or had a relapse~~

(Underline denotes additions. Strikethrough denotes deletions.)

Dosage and Administration or Method of Use

Process from leukapheresis at medical institution to transportation to manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported to the manufacturing facility of YESCARTA.

Process from receipt at the medical institution to administration of YESCARTA

3. Receipt and storage of YESCARTA
   YESCARTA is received and cryopreserved in the vapor phase of liquid nitrogen (≤−150°C) until immediately before use.
4. Pretreatment before administration of YESCARTA
   The peripheral blood lymphocyte count is checked. Where necessary, the following lymphodepleting chemotherapy is conducted as pretreatment for 3 consecutive days starting 5 days before administration of YESCARTA:
   Cyclophosphamide (anhydride) 500 mg/m^2 is infused intravenously once daily for 3 days, and fludarabine phosphate 30 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.
5. Administration of YESCARTA
   The usual adult dosage is 2.0×10^6 cells/kg (body weight), as a rule, of anti-CD19 CAR T-cells (for patients weighing ≥100 kg, up to 2×10^8 cells) administered as a single intravenous dose over ≥5 minutes and <30 minutes. YESCARTA should not be re-administered.

(No change)

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. Because the number of Japanese patients participating in clinical trials is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to identify the characteristics of patients using the product and collect data on the safety and efficacy of the product as early as possible, thereby taking necessary measures to ensure the proper use of the product.

Appendix

List of Abbreviations

Application	application for marketing approval
AUC	area under the curve
CAR	chimeric antigen receptor
CD	cluster of differentiation
CI	confidence interval
CLL	chronic lymphocytic leukemia
COVID-19	disease caused by severe acute respiratory syndrome coronavirus 2 infection (Coronavirus disease)
CR	complete response
CRS	cytokine release syndrome
Cyclophosphamide	Cyclophosphamide Hydrate
DLBCL	diffuse large B-cell lymphoma
DLBCL NOS	diffuse large B-cell lymphoma, Not otherwise specified
ECOG	Eastern Cooperative Oncology Group
EFS	event free survival
Fludarabine	Fludarabine Phosphate
HDCT	high dose chemotherapy
HGBCL	high grade B-cell lymphoma
HLGT	high level group terms
HSCT	hematopoietic stem cell transplant
IPI	international prognostic index
Kite	Kite Pharma, Inc.
LBCL	large B-cell lymphoma
LD chemotherapy	lymphodepleting chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
NCCN	National Comprehensive Cancer Network
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas
NE	not evaluable
OS	overall survival
Partial change application	application for partial changes of marketing approval
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emissiom tomography
PFS	progression free survival
PMBCL	primary mediastinal large B-cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PS	performance status
PT	preferred term
sAAIPI	second-line age-adjusted IPI
scFv	single-chain variable fragment
SD	stable disease
SMQ	standardised MedDRA queries
SOC	system organ class
Study ZUMA-1	Study KTE-C19-101

Study ZUMA-7	Study KTE-C19-107
tFL	transformed follicular lymphoma
THRLBCL	T-cell/histiocyte-rich large B-cell lymphoma
TLS	tumor lysis syndrome
WHO	World Health Organization
YESCARTA	YESCARTA Intravenous Drip Infusion