Report on the Deliberation Results

December 3, 2020

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

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	March 30, 2020 (Application for marketing approval)

Results of Deliberation

In its meeting held on December 3, 2020, the Committee on Regenerative Medical Products and Biotechnology made the following decision and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The approval is not classified as a conditional and time-limited approval. The re-examination period is 10 years.

The following approval conditions should be imposed.

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 17, 2020
Pharmaceuticals and Medical Devices Agency

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

Brand Name	YESCARTA Intravenous Drip Infusion
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Non-proprietary Name	Axicabtagene ciloleucel
Applicant	Daiichi Sankyo Company, Limited
Date of Application	March 30, 2020

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	(1-1) New regenerative medical product
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 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 as well as dosage and administration or method of use shown below, with the following 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 meeting all of the following criteria:

- Patients who have not received prior transfusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.
- Patients who are indicated for autologous hematopoietic stem cell transplantation, have failed to respond with ≥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 not indicated for autologous hematopoietic stem cell transplantation

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.

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 18, 2020

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
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	March 30, 2020

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

Relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high-grade B-cell lymphoma

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 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 following lymphodepleting chemotherapy is conducted as pretreatment for 3 consecutive days starting 5 days before administration of YESCARTA:

   Cyclophosphamide 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.

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.

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 CD3-ζ 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.

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.

Malignant lymphoma is tumor caused by malignant transformation of mature lymphocytes, a type of blood cells derived from hematopoietic stem cells. Tumor cells proliferate in lymphoid tissues such as lymph nodes and in extranodal organs, forming lesions such as masses. The symptoms, which differ depending on location of the lesion, are enlarged lymph nodes as well as systemic symptoms such as pyrexia, anorexia, and decreased body weight in most of the patients. Malignant lymphoma is largely divided histologically into Hodgkin lymphoma or non-Hodgkin lymphoma (NHL). NHLs are largely classified into B-cell NHL and T-cell NHL, but is dominated by B-cell lymphoma which expresses characteristic pan-B-cell antigen such as CD19 and CD20 on the cell surface. B-cell NHL classification is complicated, but the following tissue types are included.

Diffuse large B-cell lymphoma (DLBCL) is a type defined by diffuse growth of large tumor cells and accounts for approximately 45% of all patients with malignant lymphoma in Japan. It is classified as moderately aggressive lymphoma that progresses in a matter of months.

Primary mediastinal large B-cell lymphoma (PMBCL) is also classified as moderately aggressive lymphoma as with DLBCL, frequently occurs in adults in their 40's, and accounts for approximately 2% to 4% of patients with NHL.

Transformed follicular lymphoma (TFL) is a type of DLBCL histologically transformed from indolent follicular lymphoma (FL) and more aggressive than FL. FL is characterized by t (14;18) chromosomal

translocation and slow-growing nature, but accumulation of genetic mutation is known to cause histological transformation into DLBCL in 2% to 3% of the patients with FL annually.

High grade B-cell lymphoma (HGBCL) is a disease category introduced in the World Health Organization (WHO) classification (2016) and defined as very progressive mature B-cell lymphoma. Most cases are classified into "High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements" that includes double hit lymphoma with rearrangements of oncogenes, *MYC*(8q24) and *BCL2*(18q21) or *BCL6*(3q27), and triple hit lymphoma with rearrangements of all these oncogenes. Of DLBCL cases, approximately 4% to 8% are deemed to have rearrangements of two oncogenes (called double hit lymphoma), which are applicable to a large portion of HGBCL cases. Such double hit DLBCL is CD19 and CD20 positive and morphologically similar to DLBCL, but progresses extremely quickly in a matter of days and thus is classified as highly aggressive lymphoma.

For YESCARTA, a phase I study (Study NCI 09-C-0082) in patients with relapsed or refractory DLBCL, PMBCL, or TFL was initiated in [redacted] by National Cancer Institute (NCI) and Kite Pharma, Inc. (Kite) overseas. Then, a phase I/II study (Study KTE-C19-101 [Study ZUMA-1]) in patients with relapsed or refractory DLBCL, PMBCL, or TFL was initiated in [redacted] by Kite.

In October 2017, YESCARTA was approved based mainly on results from Study ZUMA-1 in the US for the following indications or performance: "YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of 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."

In August 2018, YESCARTA was approved based mainly on results from Study ZUMA-1 in Europe for the following indications or performance: "YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy."

In Japan, the applicant initiated a Japanese phase II study (Study KTEC19-A-J201 [Study J201]) in patients with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL in October 2018.

The applicant has now submitted the application for YESCARTA based mainly on results from Studies ZUMA-1 and J201.

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

YESCARTA is prepared from the patient's own peripheral blood mononuclear cells (PBMCs) obtained via a leukapheresis procedure. The obtained mononuclear cells are enriched for T-cells, which are then transduced with a viral vector containing a transgene encoding CAR directed against human CD19. The transduced T-cells are expanded in culture.

2.1 Viral vector

The gene transfer vector is a recombinant gammaretroviral vector with gibbon ape leukemia viral (GALV) envelope, which has murine stem cell viral (MSCV) genome as the basic structure. The anti-CD19 chimeric antigen receptor (anti-CD19 CAR) gene transferred by the viral vector includes sequences encoding the scFv region of the anti-CD19 mouse monoclonal antibody (mouse hybridoma cell line FMC63), a part of the extracellular domain, the transmembrane domain, and a part of intracellular domain of human CD28, and the signaling domain of human CD3-ζ.

The genome of the viral vector consists of sequences encoding long terminal repeat (LTR) derived from MSCV, packaging signal (Ψ) including splicing donor and splicing acceptor sites, and anti-CD19 CAR but is defective in *env* and *gag-pol* genes derived from [redacted], and thus the vector is deprived of replication competence. In the viral vector production cells, the 3 sequence segments involved in viral vector production, corresponding to the viral vector genome, [redacted]-derived *gag-pol* gene, and [redacted]-derived *env* gene, are positioned at different sites on the cell genome to minimize homologous recombination to prevent the emergence of a replication competent lentivirus.

2.1.1 Generation and control of cell substrate for production of viral vector

The full-length genome of the viral vector was transferred into mouse fibroblast PG13 host cell line (ATCC CRL-10686) which stably expresses the gag and pol genes derived from moloney murine leukemia virus (MoMLV) and GALV-derived env gene. A transfected cell line that constitutively produces the viral vector and releases it into the conditioned medium was isolated. Using this cell line as the origin, the master cell bank (MCB) and working cell bank (WCB) were generated.

The MCB, WCB, and end of production cells (EPC) were subjected to characterization and purity tests in accordance with the ICH Q5A (R1), Q5B, and Q5D guidelines. Table 1 shows tests performed for adventitious agents. The results demonstrated the genetic stability throughout the manufacturing period, and neither viral nor non-viral adventitious agents were detected by any of the tests.

The MCB and WCB are stored at ≤−150°C. Neither new MCB nor WCB will be prepared.

Table 1. Tests for adventitious agents in MCB, WCB, and EPC

In vitro virus test (NIH3T3 cells, MRC-5 cells, and Vero cells)
In vivo virus test (suckling mice, adult mice, and embryonated eggs)
Mouse antibody production test
In vitro bovine virus test (BVDV, BAV5, BPV, BTV, BRSV, REO-3, PI3, and RABV)
In vitro porcine virus test (PPV, TGEV, PAV, PI3, and RABV)
In vitro human virus test (SV40, HIV-1, HIV-2, HBV, HHV-6, HHV-7, HHV-8, CMV, EBV, HTLV-1, HTLV-2, PVB19, HCV, and Ad)
Transmission electron microscopy
Extended S + L-focus assay
Extended XC plaque assay
Sterility
Mycoplasma test

2.1.2 Manufacturing process of viral vector

The manufacturing process of the viral vector consists of thawing of WCB, cell expansion culture, harvest and [redacted], filling and freezing, storage, and testing.

Critical process steps include [redacted] and [redacted].

Process validation of the manufacturing process of the viral vector has been implemented on the commercial-production and pilot scales.

2.1.3 Safety evaluation of adventitious agents in the viral vector

Table 2 shows raw materials of biological origin other than PG13 cells used in the manufacturing process of the viral vector, and all the materials other than fetal bovine serum (FBS) (a) have been confirmed to conform to the Standard for Biological Ingredients.

The FBS (a) is prepared from blood from healthy cattle born in the US, subjected to filtration to remove possible pathogens, and tested for adventitious bovine viruses, bacterial endotoxins, sterility, and mycoplasma, but there are no processes evaluated for their capacity of inactivating or removing possible virus. The FBS (a) was collected before 2013 when the US was certified as one of the countries with a negligible risk of transmission of bovine spongiform encephalopathy (BSE) by the International Epizootic Office (OIE). It has been confirmed to meet the guide for ensuring the certain safety in terms of BSE by evaluation in accordance with the "Handling of Risk Assessment in Application for Approval of Partial Change in Pharmaceutical Product or Medical Device Using Bovine-derived Raw Materials (in Japanese)" (PFSB/ELD Notification No. 0801001 and PFSB/SD Notification No. 0801001 by the Directors of Evaluation and Licensing Division and Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated August 1, 2003).

Table 2. Raw materials of biological origin other than PG13 cells

Raw material name	Animal	Material	Process
FBS (a)	Cattle	Blood	Generation of MCB
FBS (b)	Cattle	Blood	[redacted]
FBS (c)	Cattle	Blood	[redacted], [redacted], and [redacted] processes

The viral vector obtained from EPC and bulk harvest after end of expansion culture by [redacted] is subjected to tests for adventitious agents, which are included in the specifications for the viral vector, as shown in Section 2.1.6.

2.1.4 Manufacturing process development of viral vector

Main changes in manufacturing process of viral vector during the development are shown below. Table 3 shows processes of the formulations used in non-clinical and clinical studies.

- From Process A to Process B: Changes in [redacted], [redacted], [redacted], and [redacted]
- From Process B to Process C (proposed process): Change in [redacted]

In association with these changes of the manufacturing process, the pre- and post-change products were compared in terms of the quality attributes and demonstrated to be comparable.

The manufacturing process development employs the quality by design (QbD) concept.

Table 3. Manufacturing processes of viral vector applied to manufacture of formulations used in non-clinical and clinical studies

Manufacturing process	Non-clinical or clinical studies using the formulation
Process A	[redacted] studies
Process B	[redacted] studies
Process C (proposed process)	[redacted] studies, [redacted] studies

2.1.5 Characterization of viral vector

2.1.5.1 Structure and characterization

Characterization was performed, as shown in Table 4.

Table 4. Characterization items

Characterization on cell banks	Provirus DNA sequence in MCB, WCB, and EPC
Characterization on viral vector	Viral vector genome sequence, impurities (mouse [redacted] particles, host cell DNA, host cell protein, residual BSA), [redacted] copy number, [redacted] copy number, p30 protein, and relative potency with respect to [redacted] protein
Characterization on component cells of YESCARTA which is genetically modified with viral vector	IFN-γ producing capacity, cytotoxic activity, and gene insertion site analysis of viral vector in chromosome [see Section 4.2.2]

2.1.5.2 Process-related impurities

Host cell DNA, host cell protein, bovine serum albumin (BSA), and replication competent retrovirus (RCR) were identified as process-related impurities. All process-related impurities except for RCR have been demonstrated to be adequately removed by the manufacturing process. RCR is controlled by the specifications for the viral vector. No emergence of RCR has been found in batches manufactured to date.

2.1.6 Control of viral vector

The proposed specifications for the viral vector include description, identification ([redacted] method), purity ([redacted] copy number [[redacted] method]), bacterial endotoxins, mycoplasma, sterility, RCR ([redacted] in EPC and viral vector), *in vitro* virus test (human fetal lung fibroblasts [MRC-5 cells], African green monkey kidney epithelial cells [Vero cells], and TK-NIH/3T3 cells), potency (anti-CD19 CAR expression in transfected [redacted]), and biological activity (interferon-gamma [IFN-γ] producing capacity in anti-CD19 CAR expressing T-cells).

2.1.7 Stability of viral vector

Table 5 shows a summary of major stability studies for the viral vector.

Table 5. Summary of major stability studies for the viral vector

Study	Manufacturing process	No. of batches	Storage condition	Study period	Storage form
Long-term testing	Process B	1	≤−65°C	[redacted] months	Polyolefin bag for cryopreservation
	Proposed process	7		[redacted] months*1, 2	
Accelerated testing	Proposed process	3	[redacted]°C	[redacted]	
Stress testing	Process B	1	[redacted]°C	[redacted]	
	Proposed process	2			

*1 [redacted]
*2 [redacted]

The long-term testing showed no clear changes in quality attributes throughout the study period.

The accelerated testing showed an increase in [redacted] and a change in [redacted] at [redacted]. In addition, [redacted] decreased at [redacted].

The stress testing showed a decrease in [redacted] at [redacted] in addition to the changes observed in accelerated testing.

As shown in the above, a shelf life of [redacted] months has been proposed for the viral vector when stored in a polyolefin bag for cryopreservation at [redacted].

2.2 Product

2.2.1 Description and composition of product and formulation development

The product contains component cells including anti-CD19 CAR expressing T-cells at the count (as viable cell count) dependent on the patient's body weight in each [redacted]-mL ethylene vinyl acetate (EVA) bag for cryopreservation (fluid volume, 68 mL) as specified in the dosage and administration or method of use. Excipients contained in the product include CryoStor CS10, isotonic sodium chloride solution, and human serum albumin.

2.2.2 Manufacturing process

The manufacturing process of the product includes [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], transduction, [redacted], T-cell expansion culture, [redacted], [redacted] and filling, packaging and labeling, freezing, and product testing and storage.

Critical steps include [redacted] and [redacted].

Process validation was conducted on the manufacturing process of the product on the commercial-production scale.

2.2.3 Safety evaluation of adventitious agents

2.2.3.1 Patient's peripheral blood mononuclear cells

Patient's peripheral blood mononuclear cells, which serve as a raw material of the product, conform to requirements for the collection method and documentation defined in the Human Cell and Tissue Raw Material Standards under the Standard for Biological Ingredients (MHLW Ministerial Announcement

No. 210 of 2003). Before apheresis, the patient receives an interview and a serological test (hepatitis B virus [HBV], hepatitis C virus [HCV], and human immunodeficiency virus [HIV]) at the medical institution.

2.2.3.2 Raw materials of biological origin other than patient's peripheral blood mononuclear cells

Table 6 shows raw materials of biological origin, etc. used in the manufacturing process, and all the materials have been confirmed to conform to the Standard for Biological Ingredients.

Table 6. Raw materials of biological origin, etc., other than patient's peripheral blood mononuclear cells used in the manufacturing process

Raw material name	Animal	Origin	Process
Human serum albumin (a)	Human	Blood	, , , , , and
Human serum albumin (b)	Human	Blood	, , , , , and
Human transferrin	Human	Blood	, , , , , and
Anti- antibody	Mouse	Hybridoma cells	
Human serum albumin (c)	Human	Blood	, , and

2.2.4 Manufacturing process development

Table 7 shows the main changes in the development process of the product. Largely, 2 manufacturing processes were adopted; one process was through prepared from an apheresis material, and the other one was by way of and but not through . Table 8 shows description on each process by . Manufacturing processes of the formulations used in non-clinical and clinical studies are as shown in Table 8, and the product to be marketed will be manufactured by Process CLP-2.2-5.

In association with these changes of the manufacturing process, the pre- and post-change products were compared in terms of the quality attributes and demonstrated to be comparable.

The manufacturing process development employs the QbD concept.

Table 7. Changes of manufacturing process of product

Manufacturing process	Changes, etc.
From Process CLP-1.0 to Process CLP-2.0	Changes of [redacted], [redacted] and [redacted]
From Process CLP-2.0 to Process CLP-2.1	Change of [redacted]
From Process CLP-2.1 to Process CLP-2.2-0	Changes of [redacted], [redacted], and changes of [redacted], [redacted]
From Process CLP-2.2-0 to Process CLP-2.2-1	Change of [redacted]
From Process CLP-2.2-1 to Process CLP-2.2-2	Change of [redacted], and changes of [redacted]
From Process CLP-2.2-2 to Process CLP-2.2-3	Change of [redacted]
From Process CLP-2.2-3 to Process CLP-2.2-4	Changes of [redacted], [redacted], and [redacted]
From Process CLP-2.2-4 to Process CLP-2.2-5	Changes of [redacted]

Table 8. Manufacturing processes of formulations used in non-clinical and clinical studies

Manufacturing process	Presence of [redacted]	Non-clinical or clinical studies using the formulation
Process CLP-1.0	[redacted]	[redacted] study, [redacted] study
Process CLP-2.0	[redacted]	[redacted] study, [redacted] study
Process CLP-2.1	[redacted]	—
Process CLP-2.2-0	[redacted]	[redacted] study
Process CLP-2.2-1	[redacted]	—
Process CLP-2.2-2	[redacted]	[redacted] study
Process CLP-2.2-3	[redacted]	[redacted] study, [redacted] study
Process CLP-2.2-4	[redacted]	—
Process CLP-2.2-5 (proposed process)	[redacted]	—

2.2.5 Characterization

2.2.5.1 Structure and characterization

Characterization was performed as shown in Table 9.

Table 9. Characterization of component cells

Structure and cytological properties	Transduction rate, copy number of transgene, immunophenotype ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]), T-cell subset analysis ([redacted], [redacted], [redacted], and [redacted]), risk of malignant transformation, [redacted], and gene insertion site analysis of viral vector [see Section 4.2.2]
Biological properties	CD19 binding activity, IFN-γ production in response to CD19 antigen specific stimulation, T-cell function-related cytokine analysis, and CD19 antigen specific cytotoxic activity
Purity	Non-target cells([redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]), [redacted], mouse host DNA, mouse host protein, [redacted] protein, [redacted], gentamicin, [redacted], [redacted], residual viral vector , RCR, and [redacted]

2.2.5.2 Process-related impurities

Process-related impurities include Impurity A, mouse host DNA, mouse host protein, [redacted] protein, Impurity B, gentamicin, Impurity D, Impurity E, residual viral vector, and RCR.

The process-related impurities except for residual viral vector and RCR are unlikely to raise human safety concerns based on the estimated exposure per dose calculated from the estimated residual

impurity amount in the product, and thus control items for these process-related impurities have not been specified.

Process CLP-2.2-4 was subjected to evaluation of a process capability to remove the residual viral vector, and the amount in a most concentrated specimen after [redacted] process was demonstrated to be below the detection limit ([redacted], [redacted]/mL) and quantitation limit (infectivity assay, [redacted] CAR copies/reaction).

RCR is controlled by the specifications for the product.

2.2.6 Control of product

The proposed specifications for the product include description, identification (CAR transgene), purity (cell viability rate, copy number of transgene, RCR), bacterial endotoxins, mycoplasma, sterility, percentage of CD3-positive T-cells, percentage of anti-CD19 CAR expression (transduction rate), biological activity (IFN-γ production), and strength (number of anti-CD19 CAR-expressing T-cells).

2.2.7 Stability of product

Table 10 shows a summary of major stability studies for the product.

Table 10. Summary of major stability studies for the product

Study	No. of batches[*1]	Manufacturing process	Origin	Storage condition	Study period	Storage form	Bag volume
Long-term testing	2	CLP-2.2-0	Patients with DLBCL	≤−150°C	[redacted] months[*2]	EVA bag for cryopreservation	[redacted] mL
	1[*3]		Patients with TFL		[redacted] months		
	1		Patients with MCL		[redacted] months		
	6	CLP-2.2-2	Healthy adults		[redacted] months[*4]		[redacted] mL
	2[*5]		Patients with DLBCL		[redacted] months		[redacted] mL
	1		Patients with TFL		[redacted] months		
	1		Patients with PMBCL		[redacted] months		
	13[*6]	CLP-2.2-3	Healthy adults		[redacted] months[*7]		[redacted] mL
	4[*8]		Healthy adults		[redacted] months[*9]		[redacted] mL
	2		Patients with DLBCL		[redacted] months		
	1		Patients with TFL		[redacted] months		
	3	CLP-2.2-4	Healthy adults		12 months[*10]		
	3[*3]	CLP-2.2-5 (proposed process)	Healthy adults		[redacted] months[*11]		
Accelerated testing	6	CLP-2.2-2	Healthy adults	[redacted]°C	[redacted]		[redacted] mL
Stress testing	1	CLP-2.2-0	Healthy adults	[redacted]°C	[redacted]		
	1	CLP-2.2-2	Healthy adults				
	3		Healthy adults				
In-use stability testing	3	CLP-2.2-2	Healthy adults	20°C-25°C	3 hours		
	3	CLP-2.2-3	Healthy adults		3 hours		[redacted] mL

*1 Except for batches described in *3 and *6, all are the products manufactured at [redacted].
*2 [redacted]
*3 The product manufactured at [redacted]
*4 [redacted]
*5 The result on [redacted] was found below the specification.
*6 Of these, 7 batches were the products manufactured at [redacted].
*7 [redacted]
*8 [redacted]
*9 [redacted]
*10 [redacted]
*11 The stability testing is ongoing with 3 batches until 12 months.

The long-term and accelerated testing in [redacted]-mL bags showed no clear changes in quality attributes throughout the study period.

The long-term testing in [redacted]-mL bags showed decreases in [redacted] and [redacted] at [redacted] months. For 1 batch manufactured from the specimen of a patient with DLBCL by Process CLP-2.2-2, the result on [redacted] was found below the specification at [redacted] months. The concerned batch was manufactured from the re-apheresis specimen collected from a subject in an aggravated condition, and the decrease in [redacted] was determined to be attributable to the potentially different physiological activity of the T-cells in the re-apheresis specimen. The long-term testing is ongoing with 3 batches of YESCARTA manufactured by Process CLP-2.2-5 (proposed process).

The stress testing in [redacted]-mL bags showed decreases in [redacted] and [redacted].

In-use stability testing showed no clear changes in quality attributes throughout the study period.

As shown in the above, a shelf life of 12 months has been proposed for the product when stored in an EVA bag for cryopreservation ([redacted]-mL bag) at ≤−150°C. After thawing, the administration should be completed within 3 hours at room temperature.

2.3 QbD

QbD techniques were used to develop the product, and by the following investigations, the quality control strategy has been constructed.

- Identification of critical quality attributes (CQAs):
  The following CQAs were identified based on the information on process-related impurities and product attributes obtained through the development of YESCARTA and related knowledge, etc.
  - CQAs of viral vector
    [redacted], bacterial endotoxins, mycoplasma, sterility, RCR, and adventitious viruses
  - CQAs of product
    [redacted], mycoplasma, sterility, RCR, bacterial endotoxins, gentamicin, and Impurity A
- Process characterization:
  Process parameters were classified and characterization of each process was performed by risk assessment based on their effect on CQA.
- Establishment of control method:
  The knowledge on the process including those obtained from the above process characterization has demonstrated that the quality attributes of YESCARTA are adequately controlled by the combination of control of the process parameters, in-process control, and specifications [see Section 2.2.5.2 for the control of process-related impurities].

2.R Outline of the review conducted by PMDA

PMDA concluded that the quality of the viral vector and product is adequately controlled based on the submitted data and the following review.

2.R.1 Viral risk derived from FBS used in generation of MCB of viral vector

MCB of the viral vector was generated using FBS for which the manufacturing process had not been evaluated for their capacity of inactivating or removing possible virus. PMDA asked the applicant to explain evaluation results on a viral risk of the concerned raw material.

The applicant's response:

In view of the following points, a certain level of viral safety can be ensured for the MCB of the viral vector generated using the concerned raw material.

- The test for bovine viruses was performed on filtered FBS in accordance with Title 9 of the Code of Federal Regulations (9 CFR), and the presence of bovine viruses was denied.
- In indicator cells highly susceptible to bovine viruses (bovine turbinate cells [BT-cells] and Vero cells), the test for bovine viruses was performed on the MCB generated using the concerned raw

material and showed that no bovine viruses (bovine viral diarrhea virus [BVDV], bovine adenovirus [BAV]5, bovine parvovirus [BPV], bluetongue virus [BTV], bovine respiratory syncytial virus [BRSV], reo virus [REO]-3, parainfluenza-3 [PI3], and rabies virus [RABV]) were detected.

In light of the applicant's explanation, PMDA considered that the viral risk attributable to the concerned raw material could not be completely ruled out but was extremely low and thus concluded that the concerned risk is acceptable.

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

The applicant submitted the results from *in vitro* and *in vivo* studies as data relating to primary pharmacodynamics or performance of YESCARTA.

3.1 *In vitro* studies (CTD 4.2.1.1-1, 4.2.1.1-2, 4.2.1.1-3, and 4.2.1.1-4)

The following studies were conducted: *In vitro* studies using anti-human CD19 CAR T-cells prepared from PBMCs of patients with melanoma (Table 11), quality-related characterization of YESCARTA manufactured in Study NCI 09-C-0082 in patients with NHL (Table 12), and *in vitro* studies using anti-mouse CD19 CAR T-cells (Table 13).

Table 11. Summary of *in vitro* studies using anti-human CD19 CAR T-cells[*1] prepared from PBMCs of patients with melanoma

Item	Outline	Attached document (CTD No.)
IFN-γ production in anti-human CD19 CAR T-cells from patients with melanoma	In co-culture with CD19 positive target cells or CD19 negative target cells as shown below, amounts of IFN-γ produced in anti-human CD19 CAR T-cells (1×10^5 cells) from 2 patients with melanoma were measured by ELISA. The amount of IFN-γ produced was increased only in the co-culture with CD19 positive target cells. CD19 positive target cells • Chronic myeloid leukaemia cells bv173 • Acute lymphocytic leukaemia cells SupB15 • CLL cells (primary cultured cells from patients) CD19 negative target cells • Breast cancer cells MDA231 • Lung cancer cells A549 • T-cell leukaemia cells CCRF-CEM	4.2.1.1-1[*2]
Cytotoxic activity of anti-human CD19 CAR T-cells from patients with melanoma	Anti-human CD19 CAR T-cells (5×10^6 cells/mL) from 3 patients with melanoma were co-cultured with CFSE-fluorescence-labeled CD19 positive target cells and CMTMR-fluorescence-labeled CD19 negative target cells as shown below, and the ratio of viable CD19 positive target cells to CD19 negative target cells was determined by flow cytometry for evaluation of the cytotoxic activity. Anti-human CD19 CAR T-cells were cytotoxic on CD19 positive target cells, and the cytotoxic activity was increased with the increasing number of anti-human CD19 CAR T-cells. CD19 positive target cells • CLL cells (primary cultured cells from patients, 5×10^4 cells) CD19 negative target cells • T-cell leukaemia cells CCRF-CEM (5×10^4 cells)	

*1 PBMCs of patients with melanoma collected at NCI were transduced with the same anti-human CD19 CAR gene as that in YESCARTA, and the concerned CAR T-cells were manufactured by Process CLP-1.0.
*2 Submitted as the reference data (*J Immunother.* 2009;32:689-702).

Table 12. Summary of *in vitro* studies using YESCARTA[*1] prepared from PBMCs of patients with NHL

Item	Outline	Attached document (CTD No.)
Subset analysis of YESCARTA from patients with NHL	YESCARTA from 15 patients with NHL were analyzed for CD3, CD4, CD8, CCR7, and CD45RA expression on the surface by flow cytometry, and the analysis revealed that YESCARTA consisted of $CD3^+CD4^+$ T-cells and $CD3^+CD8^+$ T-cells. The analysis on CCR7/CD45RA expression revealed that YESCARTA mainly consisted of central memory T-cells ($CD3^+CD19CAR^+CD45RA^-CCR7^+$) and effector memory T-cells ($CD3^+CD19CAR^+CD45RA^-CCR7^-$).	4.2.1.1-2
Production of bioactive substances in YESCARTA from patients with NHL	YESCARTA from 15 patients with NHL were co-cultured with CD19 positive target cells or CD19 negative target cells as shown below, and amounts of cytokines, chemokines, and effector molecules[*2] produced were measured by Luminex Assay. YESCARTA produced bioactive substances such as IFN-γ in a CD19-dependent manner. CD19 positive target cells • Human CD19-expressing human leukaemia cells CD19-K562 CD19 negative target cells • Human NGFR-expressing human leukaemia cells NGFR-K562	4.2.1.1-3

*1 Manufactured by Process CLP-2.0
*2 CD137, granulocyte macrophage-colony stimulating factor (GM-CSF), granzyme A, granzyme B, IFN-γ, interleukin (IL)-2, IL-4, IL-5, IL-6, IL-10, IL-13, macrophage inflammatory protein (MIP)-1α, MIP-1β, perforin, soluble FAS (receptor) (sFAS), soluble FAS ligand (sFASL), and tumor necrosis factor (TNF)-α

Table 13. Summary of *in vitro* study using anti-mouse CD19 CAR T-cells[*1] prepared from mouse spleen T-cells

Item	Outline	Attached document (CTD No.)
IFN-γ production in anti-mouse CD19 CAR T-cells	In co-culture with mouse CD19 positive target cells or mouse CD19 negative target cells as shown below, amounts of IFN-γ produced in anti-mouse CD19 CAR T-cells (2.5×10^4 cells) were measured by ELISA. The amount of IFN-γ produced in anti-mouse CD19 CAR T-cells was increased only in the co-culture with mouse CD19 positive target cells. CD19 positive target cells • Mouse B-cell lymphoma cells 38c13 • Mouse CD19-expressing human leukaemia cells CD19-K562 • Mouse spleen cells CD19 negative target cells • Mouse skeletal muscle cells Sol8 • Mouse fibroblasts CCL12 • Human NGFR-expressing human leukaemia cells NGFR-K562	4.2.1.1-4[*2]

*1 Prepared by transfecting mouse spleen cells with anti-mouse CD19 CAR gene encoding scFv of rat anti-mouse CD19 antibody, mouse CD28, and modified CD3ζ
*2 Submitted as the reference data (*Blood.* 2010;116:3875-86).

3.2 *In vivo* studies

Table 14 shows *in vivo* studies in mouse lymphoma model to which anti-mouse CD19 CAR T-cells prepared from mouse spleen T-cells were administered.

Table 14. Summary of *in vivo* studies

Item	Outline	Attached document (CTD No.)
Characterization of anti-mouse CD19 CAR T-cells in mouse lymphoma model[*1]	To mouse lymphoma model 1 day after the establishment, anti-mouse CD19 CAR T-cells[*3] (6×10^6 cells) were intravenously administered, and on Day 8, T-cells collected from the spleen were analyzed by flow cytometry to determine the numbers of CAR-expressing CD8 positive T-cells and CD4 positive T-cells in the spleen. In the spleen on Day 8, CAR-expressing CD8 positive T-cells and CAR-expressing CD4 positive T-cells were detected.	4.2.1.1-4[*5]
Impact of anti-mouse CD19 CAR T-cells on normal B-cells in mouse lymphoma model[*1]	To mouse lymphoma model 1 day after the establishment, anti-mouse CD19 CAR T-cells[*3] (6×10^6 cells) or negative control CAR T-cells[*4] were intravenously administered, and on Day 8, cells collected from the spleen were analyzed by flow cytometry to determine the number of normal B-cells (B220 positive κ light chain positive) in the spleen. Normal B-cells were not found in mouse lymphoma model treated with anti-mouse CD19 CAR T-cells but were found in mice treated with negative control CAR T-cells. Separately from the above, in mouse lymphoma model treated with anti-mouse CD19 CAR T-cells, normal B-cells were not found in the spleen on Day 63, 143, or 209.	
Anti-lymphoma effects of anti-mouse CD19 CAR T-cells in mouse lymphoma model[*1] (administration just after tumor implantation)	The anti-lymphoma effect of anti-mouse CD19 CAR T-cells[*3] on mouse lymphoma model was evaluated based on survival of mice treated as shown below (n = 5/group). • Intravenous administration of anti-mouse CD19 CAR T-cells (6×10^6 cells) and then IL-2 immediately and on the next day • Intravenous administration of negative control CAR T-cells[*4] (6×10^6 cells) and then IL-2 immediately and on the next day • Intravenous administration of IL-2 on 2 consecutive days • Untreated All of the mice treated with anti-mouse CD19 CAR T-cells survived until Day 140, while all of the mice treated with negative control CAR T-cells and untreated mice died on or before Day 20. Using the same mouse lymphoma model as the above, impacts of lymphocyte depletion by total body irradiation and IL-2 administration on the anti-lymphoma effect were evaluated based on survival of the mice (n = 5/group, n = 4 only in the untreated group). • On the day after administration of lymphoma cells, anti-mouse CD19 CAR T-cells (6×10^6 cells) were intravenously administered to total body irradiated mice followed by intravenous administration of IL-2 just after the cell administration and on the next day. • On the day after administration of lymphoma cells, anti-mouse CD19 CAR T-cells (6×10^6 cells) were intravenously administered to non-irradiated mice followed by intravenous administration of IL-2 just after the cell administration and on the next day. • On the day after administration of lymphoma cells, anti-mouse CD19 CAR T-cells (6×10^6 cells) were intravenously administered to total body irradiated mice. • Untreated All of the mice which had received anti-mouse CD19 CAR T-cells after lymphocyte depletion by total body irradiation survived until Day 100 irrespective of IL-2 administration. All of the mice which had received anti-mouse CD19 CAR T-cells without total body irradiation, on the other hand, died on or before Day 30.	
Anti-lymphoma effect of anti-mouse CD19 CAR T-cells in subcutaneous mouse lymphoma model[*2] (administration after lymphoma engraftment)	The anti-lymphoma effect of anti-mouse CD19 CAR T-cells[*3] on engrafted lymphoma subcutaneous mass was evaluated based on survival of mouse subcutaneous lymphoma model treated as shown below (n = 5/group). • Intravenous administration of anti-mouse CD19 CAR T-cells (6×10^6 cells) and then IL-2 immediately and on the next 2 consecutive days • Intravenous administration of anti-mouse CD19 CAR T-cells (6×10^6 cells) and then phosphate-buffered saline immediately and on the next 2 consecutive days (without IL-2 administration) • Intravenous administration of negative control CAR T-cells[*4] (6×10^6 cells) and then IL-2 immediately and on the next 2 consecutive days • Intravenous administration of IL-2 on 3 consecutive days • Untreated In mice treated with anti-mouse CD19 CAR T-cells, the engrafted lymphoma mass disappeared irrespective of the IL-2 administration, and the mice survived until Day 50, but in mice not treated with anti-mouse CD19 CAR T-cells, the lymphoma mass grew with metastases to the spleen and lymph nodes.	

*1 Established by subjecting immunocompetent C3H/HeN-MTV-negative (C3H) mice to total body irradiation at 5 Gy for lymphocyte depletion and intraperitoneal administration of mouse B-cells lymphoma cells 38c13 (10^5 cells) of the same strain within one day.

*2 Established by subjecting immunocompetent C3H/HeN-MTV-negative (C3H) mice to total body irradiation at 5 Gy for lymphocyte depletion and subcutaneous implantation of mouse B-cells lymphoma cells 38c13 (0.5×10^6 cells) of the same strain within one day.

*3 Prepared by transfecting mouse spleen cells with anti-mouse CD19 CAR gene encoding scFv of rat anti-mouse CD19 antibody, mouse CD28, and modified CD3ζ.

*4 Prepared by transfecting mouse spleen cells with a gene encoding scFv of SP6 antibody specifically recognizing hapten 2, 4, 6-trinitrobenzenesulfonic acid, mouse CD28, and modified CD3ζ.

*5 Submitted as the reference data (*Blood.* 2010;116:3875-86).

3.R Outline of the review conducted by PMDA

The applicant's explanation about the effect of YESCARTA:

The *in vitro* studies showed that anti-human CD19 CAR T-cells produced IFN-γ and presented cytotoxic activity in a CD19-dependent manner. The *in vivo* studies showed that anti-mouse CD19 CAR T-cells presented the anti-tumor effect against lymphoma and prolonged the survival, when intravenously administered as a single dose to mice which had undergone total body irradiation for lymphocyte depletion and intraperitoneally or subcutaneously received mouse B-cells lymphoma cells of the same strain. No anti-tumor effect was observed in mice which had not undergone total body irradiation for lymphocyte depletion. The interleukin (IL)-2 administration after the administration of anti-mouse CD19 CAR T-cells had no impact on the anti-tumor effect of anti-mouse CD19 CAR T-cells.

The above non-clinical pharmacology studies indicate that YESCARTA recognizes B-cell malignant lymphoma cells and presents the cytotoxic activity in a CD19-dependent manner. Lymphocytes must be depleted to ensure the biological effect of YESCARTA.

PMDA accepted the applicant's explanation.

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

The applicant submitted the following data relating to non-clinical safety: The results from a pharmacology study of anti-mouse CD19 CAR T-cells in mouse lymphoma model, *in vitro* proliferation test of YESCARTA, gene insertion site analysis of the gamma retroviral vector, and safety evaluation of impurities and excipients.

4.1 Evaluation of general toxicity

No *in vivo* toxicity studies of YESCARTA have been conducted since it was considered difficult to evaluate the safety of YESCARTA in experimental animals appropriately for the following reasons: YESCARTA is CAR T-cells manufactured from human T-cells and thus would cause graft versus host disease when administered to animals; and YESCARTA does not bind to CD19 in experimental animals. To evaluate the general toxicity, a non-clinical pharmacology study using a surrogate of YESCARTA was conducted, although it had limitations in the safety evaluation.

4.1.1 Study where anti-mouse CD19 CAR T-cells were administered to mouse lymphoma model (CTD 4.2.1.1-4)

Anti-mouse CD19 CAR T-cells were prepared as a surrogate of YESCARTA in toxicity evaluation. General toxicity of YESCARTA was evaluated in a study where 6×10^6 anti-mouse CD19 CAR T-cells were intravenously administered to mouse lymphoma model as a single dose [see Section 3.2]. Administration of anti-mouse CD19 CAR T-cells resulted in disappearance of normal B-cells, but there were no other findings suggesting clear toxicity.

4.2 Evaluation of potential tumorigenesis and malignant transformation

In order to evaluate tumorigenicity of YESCARTA, an *in vitro* proliferation study was performed. A gene insertion site analysis of the gamma retroviral vector was performed to evaluate a risk of

malignant transformation of the T-cells in association with integration of the gamma retroviral vector into the chromosome.

4.2.1 *In vitro* proliferation study of YESCARTA (CTD 3.2.S.3.1-1)

The *in vitro* proliferation study where YESCARTA was cultured in [redacted] (Table 15) showed no uncontrolled cell growth, and a risk of tumorigenicity was not suggested.

Table 15. *In vitro* proliferation study of YESCARTA

Study	Test cells	Culture period (days)	Result	Attached document (CTD No.)
In vitro proliferation study of YESCARTA	YESCARTA of T-cells from healthy adult donor	[redacted]	The viable cell density was below the detection limit ([redacted]%).	3.2.S.3.1-1

4.2.2 Gene insertion site analysis of gamma retroviral vector (CTD 2.3.S)

By the analysis using [redacted], the gene insertion site and distribution were identified (Table 16). The results showed that the insertion tended to occur in the vicinity of transcription start sites and in [redacted] as with other retroviral vectors, but the gene insertion sites varied highly in [redacted] and [redacted].

The applicant's explanation about a risk of T-cell malignant transformation associated with the vector gene insertion:

Because the analysis results showed that the gene insertion sites varied, the viral vector is considered unlikely to be preferentially inserted in the vicinity of oncogenes, although the concerned analysis cannot characterize the gene insertion sites completely. To control a risk of insertion mutation, the copy number of transgene per cell of YESCARTA is defined in the product specifications [see Section 2.2.6].

Table 16. Gene insertion site analysis of gamma retroviral vector

Test system and study method	Results	Attached document (CTD No.)
Genome DNA extracted from YESCARTA (transduction [redacted]) from healthy adult donors (n = [redacted]) was subjected to [redacted] to identify genome coordinates and gene insertion sites and also subjected to [redacted] to identify [redacted] and [redacted] of retrovirus [redacted].	• The gene insertion was suggested to occur in the vicinity of transcription start sites, preferentially in [redacted] in particular. • Of all the gene insertion sites, [redacted]% involved exons. • The gene insertion sites varied in [redacted] and [redacted]. • None of the gene insertion sites suggested [redacted].	2.3.S

4.3 Safety evaluation of impurities

Process-related impurities potentially present in the final product include host cell DNA, host cell protein, Impurity B, viral vector protein ([redacted] protein), Impurity E, Impurity A, gentamicin, and Impurity D. The applicant conducted the safety evaluation of these impurities at actual residual amounts based on clinical use experience and physiologically active concentrations, and determined that these impurities would not put humans at a safety risk.

4.4 Safety evaluation of excipients

Excipients of YESCARTA include CryoStor CS10, isotonic sodium chloride solution, and human serum albumin. The applicant conducted the safety evaluation of these excipients based on clinical use experience, and determined that these would not raise any safety concern. The applicant, however, explained that YESCARTA should be administered over ≥5 minutes to prevent a rapid increase of blood concentration of potassium, which is contained in CryoStor CS10.

4.R Outline of the review conducted by PMDA

PMDA has concluded that YESCARTA raises no particular concerns about the non-clinical safety based on the data submitted and the following review.

4.R.1 Potential effect of YESCARTA on normal tissues

Because there are no studies conducted to investigate a binding potential of YESCARTA to normal tissues, PMDA asked the applicant to explain a potential effect of YESCARTA on human normal tissues.

The applicant's response:

Because CD19 is expressed only on B-cell lineage but not on hematopoietic stem cells or most of plasma cells (*Immunol Res*. 2005;31:119-31), YESCARTA is considered unlikely to bind to unintended cells other than CD19-expressing cells ("off-target binding"). The adverse events reported frequently or as severe adverse events in clinical studies (cytokine release syndrome [CRS], nervous system event, cytopenia, infection, and hypogammaglobulinaemia) are considered attributable to binding of YESCARTA to CD19 positive cells. Although it cannot be ruled out that the other adverse events are attributable to the off-target binding, no clinically significant events have been reported, and these events are considered manageable.

PMDA's view:

Although the information about the effect of YESCARTA on normal tissues obtained from non-clinical safety investigations is limited, YESCARTA may be used in clinical settings from a viewpoint of the safety, based on the review in Section 6.R.3 and clinical use experience with tisagenlecleucel that has the same scFv derived from anti-CD19 mouse monoclonal antibody (mouse hybridoma cell line, FMC63) as that of YESCARTA.

4.R.2 Reproductive and developmental toxicity

PMDA asked the applicant to explain the effect of YESCARTA on fetuses in treated pregnant women and their newborns.

The applicant's response:

CD19-knockout mice were characterized by a deficiency in B-cells, incomplete splenic germinal center formation, decreased immunoglobulin (Ig)M level, and impaired response to T-cell-dependent antigen, but were found fertile without any physical abnormalities (The Jaxson Laboratory Mouse Strain Datasheet-006785). When a pregnant woman receives YESCARTA or a patient treated with

YESCARTA becomes pregnant, therefore, the decreased CD19-positive B cells in pregnant women are considered unlikely to affect pregnancy maintenance and embryo-fetal development.

On the other hand, a state of maternal microchimerism allowing maternal cells to enter fetal blood and tissues may be created during pregnancy (*Int J Dev Biol.* 2010;54:531-43), and maternal $CD3^+$, $CD19^+$, $CD34^+$, and $CD45^+$ cells were found in the fetal liver, lungs, heart, thymus, spleen, adrenal gland, kidneys, pancreas, brain, and gonad (*Am J Obstet Gynecol.* 2008;198:325. e1-e6). Therefore, the following possibility cannot be ruled out: When a pregnant woman receives YESCARTA or a patient treated with YESCARTA becomes pregnant, YESCARTA may cross the placenta and have an unintended effect on the fetuses or newborns such as decreased B-cells. In light of toxicity of cyclophosphamide hydrate (cyclophosphamide) and fludarabine phosphate (fludarabine) used in lymphodepleting chemotherapy prior to administration of YESCARTA, the applicant plans to include in the package insert a caution statement to the effect that woman of childbearing potential should practice contraception for a certain period during and after administration of YESCARTA. The search for pregnant cases in the applicant's safety database (data cut-off on April 17, 2020) detected 2 cases. One case was reported from a female who was found pregnant about 2 years and 10 months after administration of YESCARTA and delivered a newborn without any abnormalities. The other case was reported from a male patient treated with YESCARTA whose partner became pregnant, but the outcome of the pregnancy remains unknown. These cases raise no safety concerns.

PMDA accepted the applicant's explanation. At present, however, information about reproductive and developmental toxicity of YESCARTA is very limited, and thus when administration of YESCARTA to a pregnant woman is found after the market launch, information about the effects on the fetus and newborns should be collected.

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

Biological disposition of YESCARTA was investigated based on information obtained from a single intravenous dose pharmacology study in mouse lymphoma model, Study ZUMA-1, and Study J201.

5.1 Non-clinical biological disposition (CTD 4.2.1.1-4)

Biological disposition and residual period of YESCARTA were investigated based on the results from a single intravenous dose pharmacology study in mouse lymphoma model [see Section 3.2].

To mouse lymphoma model, 6×10^6 mouse T-cells transduced with anti-mouse CD19 CAR gene (equivalent to 3.9×10^6 CAR-expressing T-cells based on the transduction rate of 65%) were intravenously administered, and the number of CAR-expressing T-cells in the spleen was determined by flow cytometry. CAR-expressing T-cells were detected in the spleen on Day 8 but not on Day 63. The survival of anti-mouse CD19 CAR T-cells in organs other than the spleen has not been evaluated.

5.2 Clinical biological disposition

5.2.1 Study ZUMA-1 (CTD 5.3.5.2-1)

Change over time of concentrations of anti-CD19 CAR T-cells in blood were investigated in 108 patients (7 in the phase I part, 101 in the phase II part) in Study ZUMA-1 (Figure 1). In Study

ZUMA-1, patients with relapsed or refractory DLBCL, PMBCL, or TFL intravenously received YESCARTA at 2.0 × 10^6 cells/kg (for patients weighing >100 kg, fixed dose of 2.0 × 10^8 cells/body) as a single dose. Blood specimens were collected 5 days before administration of YESCARTA and on Days 7, 14, and 28 as well as at Months 3, 6, 9, 12, 15, 18, and 24, and concentrations of anti-CD19 CAR T-cells in the blood specimens were determined by quantitative polymerase chain reaction (qPCR).

The concentration of anti-CD19 CAR T-cells in blood increased immediately after administration of YESCARTA and reached the maximum on Day 8 (median) in both phase I and phase II parts. Then, the concentration decreased slowly to 0 to 1.6 cells/μL in the phase I part and 0 to 28.4 cells/μL in the phase II part at Month 3 (Figure 1). In the phase I part, the median C_{max} of anti-CD19 CAR T-cells in blood was 58.5 cells/μL, and the median area under concentration of anti-CD19 CAR T-cells from Days 0 to 28 (AUC_{28d}) was 767.2 cells·day/μL. In the phase II part, the median C_{max} and AUC_{28d} were 38.3 cells/μL and 453.4 cells·day/μL, respectively.

The biological disposition of YESCARTA by state of response was investigated (Figure 2). In patients who achieved complete response (CR) or partial response (PR), the median C_{max} and AUC_{28d} were 43.2 cells/μL and 550.1 cells·day/μL, respectively, while in patients who did not achieve CR or PR, the median C_{max} and AUC_{28d} were 15.6 cells/μL and 105.7 cells·day/μL, respectively. Of patients who maintained the CR or PR state at Month 24, 32 patients provided concentrations of anti-CD19 CAR T-cells in blood at Month 24, and of these 21 patients (66%) were found to have anti-CD19 CAR T-cells in blood. As shown in the above, the applicant explained that C_{max} and AUC_{28d} tended to be higher in patients who achieved PR or CR than patients who did not.

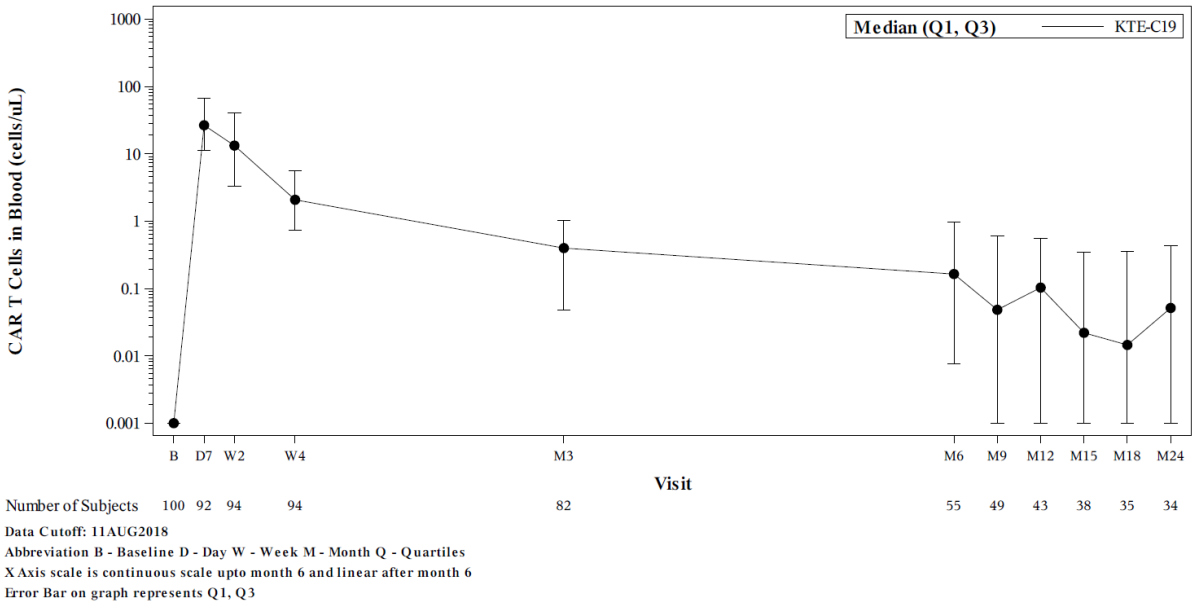

Figure 1. Change over time in concentrations of anti-CD19 CAR T-cells in blood in Study ZUMA-1

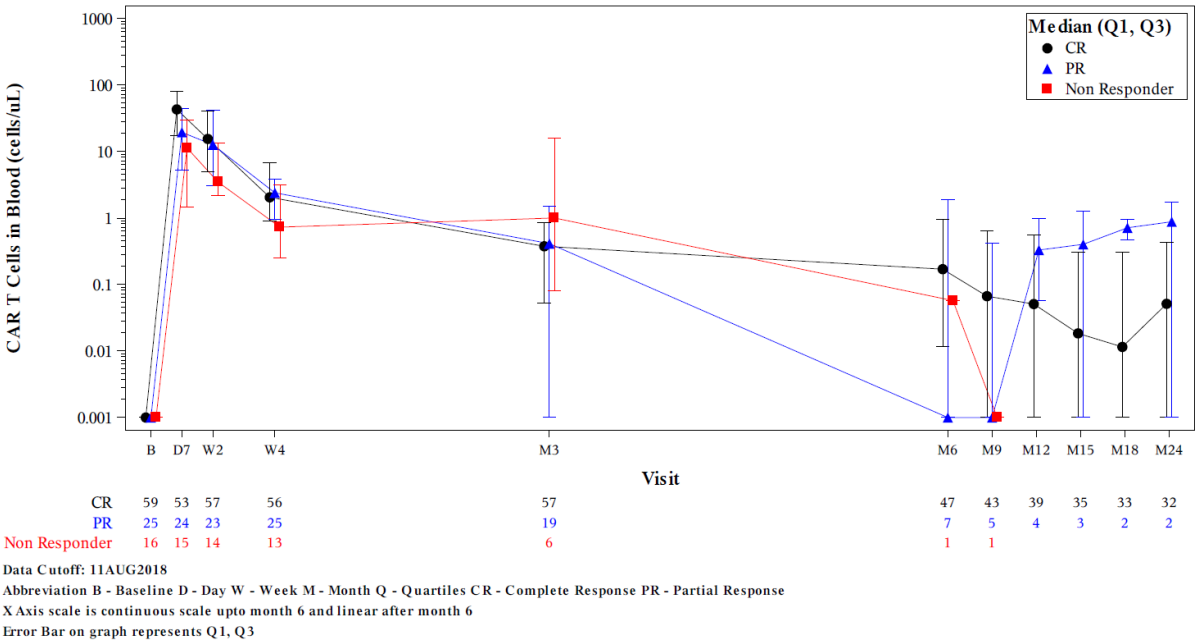

Figure 2. Change over time in concentrations of anti-CD19 CAR T-cells in blood in Study ZUMA-1 by state of response

5.2.2 Study J201 (CTD 5.3.5.2-2)

Change over time of concentrations of anti-CD19 CAR T-cells in blood were investigated in 16 patients in Study J201. In Study J201, patients with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL intravenously received YESCARTA at 2.0×10^6 cells/kg (for patients weighing >100 kg, fixed dose of 2.0×10^8 cells/body) as a single dose. Blood specimens were collected at the enrollment, just before the first dose of YESCARTA, and on Day 8 as well as at Weeks 2 and 4, and Months 3, 6, 9, 12, 15, 18, and 24, and concentrations of anti-CD19 CAR T-cells in the blood specimens were determined by qPCR.

In Study J201, the concentration of anti-CD19 CAR T-cells in blood increased immediately after administration of YESCARTA and reached the maximum on Day 11 (median) as done in Study ZUMA-1. Then, the concentration decreased to 0 to 8.5 cells/μL at Month 3 (Figure 3). The median C_{max} and AUC_{28d} were 12.7 cells/μL and 187.5 cells·day/μL, respectively. The limited number of patients in Study J201 precluded comparison of biological disposition parameters between responders and non-responders. The median C_{max} and AUC_{28d} of concentration of anti-CD19 CAR T-cells in blood in Study J201 tended to be lower than those in Study ZUMA-1. The applicant, however, explained that the difference in concentration of anti-CD19 CAR T-cells in blood between Studies ZUMA-1 and J201 was smaller than the individual difference, and the differences in biological disposition parameters between the studies would not affect the efficacy of YESCARTA.

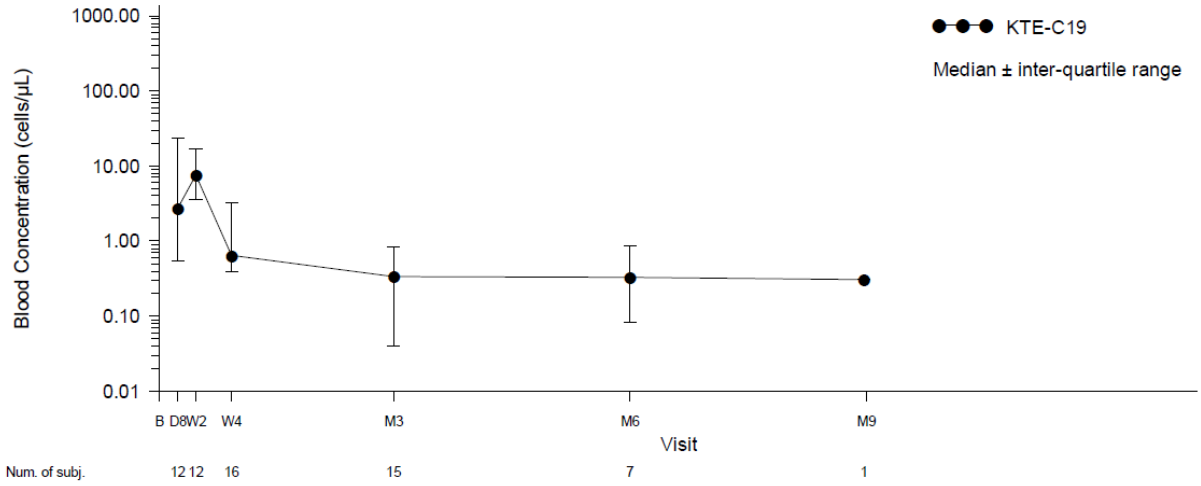

Figure 3. Change over time in concentrations of anti-CD19 CAR T-cells in blood in Study J201

5.R Outline of the review conducted by PMDA

PMDA has concluded that the applicant's explanation on biological disposition of YESCARTA is acceptable based on the submitted data.

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 a total of 2 studies, 1 foreign phase I/II study and 1 Japanese phase II study, as provided in Table 17. In addition, the applicant submitted reference data in the form of results from 1 foreign phase I study, as provided in Table 17.

Table 17. List of clinical studies for efficacy and safety

Data category	Region	Study	Phase	Population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Foreign	ZUMA-1	I/II	Phase I Patients with relapsed or refractory DLBCL, PMBCL, or TFL Phase II Cohort 1: Patients with relapsed or refractory DLBCL Cohort 2: Patients with relapsed or refractory PMBCL or TFL Cohort 3: Patients with relapsed or refractory DLBCL, PMBCL, or TFL	Phase I 8 Phase II Cohort 1: 81 Cohort 2: 30 Cohort 3: 42	Single intravenous administration of 2.0×10^6 CAR T-cells/kg (for patients weighing >100 kg, fixed dose of 2.0×10^8 cells/body)	Efficacy Safety
	Japan	J201	II	Patients with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL	17	Single intravenous administration of 2.0×10^6 CAR T-cells/kg (for patients weighing >100 kg, fixed dose of 2.0×10^8 cells/body)	Efficacy Safety
Reference	Foreign	0082	I	Cohorts 11-14 Patients with CD19 positive B-cell malignant lymphoma	15 Cohort 11: 10 Cohort 12: 1 Cohort 13: 2 Cohort 14: 2	Single intravenous administration of CAR T-cells at the following dose: Cohort 11: 2.0×10^6 cells/kg Cohort 12: 6.0×10^6 cells/kg Cohort 13: 2.0×10^6 cells/kg Cohort 14: 2.0×10^6 cells/kg	Safety

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

6.1 Evaluation data

6.1.1 Foreign clinical studies

6.1.1.1 Foreign phase I/II study (CTD 5.3.5.2-1, Cohort 1-3 in phase I and phase II parts in Study ZUMA-1, ongoing since [redacted] 20[redacted] [data cut-off on August 11, 2018])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of YESCARTA in patients with relapsed or refractory DLBCL, PMBCL, or TFL (target number of patients enrolled, 6-24 patients in the phase I part, 142 patients in the phase II part [72 in Cohort 1, 20 in Cohort 2, 50 in Cohort 3]). The study was conducted at 3 study sites in 1 foreign country during the phase I part, and during the phase II part, 20 study sites in 1 foreign country for Cohort 1, 12 study sites in 2 foreign countries for Cohort 2, and 25 study sites in 4 foreign countries for Cohort 3. Table 18 shows the main inclusion and exclusion criteria.

Table 18. Main inclusion and exclusion criteria

Inclusion criteria • Patients with histologically confirmed DLBCL,[1)] PMBCL, or TFL according to the WHO classification (2008) • Patients with refractory disease meeting any of the following cases: ➢ No response to the first-line chemotherapy (the best response was assessed as PD, or after 4 cycles of the first-line chemotherapy, it was assessed as SD with its duration shorter than 6 months from the last dose). Patients who were intolerant to the first-line therapy were excluded. ➢ No response to second and subsequent lines of chemotherapy (the best response was assessed as PD, or after ≥2 cycles of the last chemotherapy, it was assessed as SD with its duration shorter than 6 months from the last dose) ➢ After autologous SCT, PD or relapse occurred within 12 months. ➢ After autologous SCT, no-response to or relapse after the salvage therapy occurred. • Patients who received the first-line therapy including anti-CD20 monoclonal antibody or an anthracycline-containing chemotherapy • Patients with no evidence of central nervous system (CNS) lymphoma • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 Exclusion criteria • Patients with a history of allogeneic hematopoietic stem cell transplantation • Patients with a history of CD19-targeted therapy • Patients with a history of CAR T-cell therapy or genetically modified T-cell therapy

Objectives of each phase and cohort are as follows:

Phase I part: To evaluate the safety of conditioning chemotherapy (implemented before administration of YESCARTA to enhance survival and proliferation of YESCARTA *in vivo*) and YESCARTA in patients with relapsed or refractory DLBCL, PMBCL, or TFL

Cohort 1 in the phase II part: To evaluate the efficacy and safety of YESCARTA in patients with relapsed or refractory DLBCL

Cohort 2 in the phase II part: To evaluate the efficacy and safety of YESCARTA in patients with relapsed or refractory PMBCL or TFL

Cohort 3 in the phase II part: To examine if preventive treatment with levetiracetam at a dose of 750 mg orally or intravenously twice daily starting on the day of administration of YESCARTA and tocilizumab (Genetical Recombination) (tocilizumab) 8 mg/kg (up to 800 mg/body) 2 days after the administration of YESCARTA would decrease incidences of severe CRS and neurologic toxicity in patients with relapsed or refractory DLBCL, PMBCL, or TFL

Patients intravenously received YESCARTA at the target dose of 2.0×10^6 (±20%) CAR T-cells/kg (for patients weighing >100 kg, fixed dose of 2.0×10^8 cells/body and minimum acceptable dose of 1.0×10^6 cells/kg) as a single dose over ≤30 minutes.

In addition, patients received the following conditioning chemotherapy as pretreatment for 3 consecutive days starting 5 days before administration of YESCARTA. Chemotherapy (bridging chemotherapy) to keep the disease stable while waiting for YESCARTA to be manufactured (from the study enrollment to conditioning chemotherapy) was not permitted.

[1)] The following tissue types of DLBCL were deemed eligible.
- DLBCL, not otherwise specified
- T cell/histiocyte-rich large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Age-related Epstein-Barr virus positive DLBCL

Dosage regimen of conditioning chemotherapy

- Once-daily intravenous infusion of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2

All of 8 patients enrolled in the phase I part underwent leukapheresis, but 1 patient withdrew from the study due to disease progression, and 7 patients received conditioning chemotherapy and YESCARTA. All the 7 patients who received YESCARTA were included in the safety analysis, and 6 patients were included in evaluation of the dose-limiting toxicity (DLT),[2)] excluding 1 patient who received YESCARTA at a lower dose (1.1×10^6 cells/kg) than the target dose ($<1.6 \times 10^6$ cells/kg).

During the DLT evaluation period from administration of YESCARTA to Day 30 in the phase I part, DLT (Grade 4 encephalopathy/Grade 4 CRS) occurred in 1 of 6 patients, but the safety evaluation team determined that YESCARTA at the target dose was tolerable.

In the phase II part, all of 111 patients enrolled in Cohorts 1 and 2 (81 in Cohort 1, 30 in Cohort 2), underwent leukapheresis. After leukapheresis, 8 patients withdrew (because of death due to disease progression in 1 patient, Grade 3 small intestinal obstruction in 1 patient, Grade 3 spinal stenosis in 1 patient, and deep vein thrombosis in 1 patient in Cohort 1; and death due to disease progression in 1 patient, Grade 3 hypoxia/Grade 4 pleural effusion in 1 patient, and regression of measurable lesion in 2 patients[3)] in Cohort 2), and the remaining 103 patients (77 in Cohort 1, 26 in Cohort 2) received conditioning chemotherapy. Furthermore, 2 patients in Cohort 2 withdrew (because of death from tumour lysis syndrome due to conditioning chemotherapy in 1 patient and sepsis due to Grade 3 skin and wound infection in 1 patient), and the remaining 101 patients (77 in Cohort 1, 24 in Cohort 2) received YESCARTA and were included in the efficacy analysis.

The primary endpoint was the response rate (percentage of patients who achieved CR or PR) assessed by investigators according to the International Working Group (IWG) 2007 criteria (*J Clin Oncol.* 2007;25:579-86).

In the phase II part, the following 2 interim analyses and 1 primary analysis were planned:

- The first interim analysis was intended to assess futility and was performed when 20 patients in Cohort 1 who had received YESCARTA at the minimum acceptable dose or more had the opportunity to be assessed for response at Month 3.
- The second interim analysis was intended to assess early termination for efficacy and was performed when 50 patients in Cohort 1 who had received YESCARTA at the minimum acceptable dose or more had the opportunity to be assessed for response at Month 3.
- The primary analysis was intended to be performed when 72 patients in Cohort 1 and 20 patients in Cohort 2 had received YESCARTA at the minimum acceptable dose or more and had the opportunity to be assessed for response at Month 6.

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2) DLT evaluation included patients who received Yescarta at the target dose (2.0×10^6 [±20%] cells/kg) and were followed up for at least 30 days or who received Yescarta at a smaller dose than the target dose but experienced DLT within 30 days.

3) Presence of a measurable lesion was indicated at positron emission tomography-computed tomography (PET-CT) at the time of screening but was not at the imaging reperformed before conditioning chemotherapy.

To control the type 1 error in the entire study to 0.025 (one-sided), the significance levels of 0.022 (one-sided) and 0.0075 (one-sided) were assigned to the analysis in Cohort 1 and that in the overall population (pooled population of Cohorts 1 and 2), respectively, according to a method of Song and Wang, et al. (*Statistics in Medicine.* 2007;26:3535-49 and *Pharmaceutical Statistics.* 2007;6:227-44). Furthermore, for Cohort 1, significance levels of 0.017 (one-sided) and 0.011 (one-sided) were specified in the second interim and primary analyses, respectively, using the Pocock α spending function according to Lan-DeMets method. In the criteria for futility in the first interim analysis, the significance level of 0.393 (one-sided) was specified based on the βspending function.

In addition to the above, the threshold of 20% was specified for the response rate based on the following reports.

- In previous clinical studies in patients with relapsed or refractory NHL (*Br J Haematol.* 2005;130:363-72, *Leuk Lymphoma.* 2012;53:836-41, etc.), the response rate was reported to be 0% to 23%.
- In the SCHOLAR-1 study (*J Clin Oncol.* 2016;34:suppl;abstr 7516, *Blood.* 2017;130:1800-8) in which data from 2 clinical studies in patients with relapsed or refractory DLBCL, PMBCL, or TFL (n = 636) (the LY.12 study [*J Clin Oncol.* 2014;32:3490-6] and the CORAL study [*Bone marrow Transplant.* 2016;51:51-7]) and foreign database (MD Anderson Cancer Center, Mayo Clinic, and University of Iowa) were pooled and analyzed, the response rate was reported to be 26%.

Table 19 shows results from the first interim analysis (data cut-off on [redacted], 20[redacted]), which did not meet the criterion for termination for futility (*P* value [one-sided] in Cohort 1 >0.393). The data safety monitoring board (DSMB) therefore recommended continuation of the study.

Table 19. Results from first interim analysis on response rate (investigator assessment, data cut-off on [redacted], 20[redacted])

	Number of patients (%)	
	Cohort 1 n = 21[*1]	Cohort 2 n = 6
CR	9 (42.9)	6 (100)
PR	8 (38.1)	0
SD	3 (14.3)	0
PD	0	0
Not evaluated	1 (4.8)	0
Response (CR + PR) (response rate [95% CI[*2]] [%]) *P* value (one-sided)[*3]	17 (81.0 [58.1, 94.6]) <0.0001	6 (100 [54.1, 100])

*1 Because the 20th and 21st patients received YESCARTA on the same day, the first interim analysis was performed when 21 patients in Cohort 1 had the opportunity to be assessed for response at Month 3. *2 Clopper-Pearson method; *3 Exact test based on binomial distribution, the threshold of 20% was for response rate, and the criterion for futility was 0.393 (one-sided).

Table 20 shows results from the second interim analysis (data cut-off on August 24, 2016), which met the criterion for early termination for efficacy (*P* value [one-sided] in Cohort 1 <0.017) in a hypothesis test with the threshold of 20% for response rate. In consideration that patient enrollment in Cohorts 1 and 2 was almost completed, the study was continued.

Table 20. Results from second interim analysis on response rate (investigator assessment, data cut-off on August 24, 2016)

	Number of patients (%)	
	Cohort 1 n = 51[*1]	Cohort 2 n = 11
CR	24 (47.1)	8 (72.7)
PR	15 (29.4)	2 (18.2)
SD	8 (15.7)	0
PD	3 (5.9)	0
Not evaluated	1 (2.0)	1 (9.1)
Response (CR + PR) (response rate [95% CI[*2]] [%]) *P* value (one-sided)[*3]	39 (76.5 [62.5, 87.2]) <0.0001	10 (90.9 [58.7, 99.8])

*1 Because the 50th and 51st patients received YESCARTA on the same day, the second interim analysis was performed when 51 patients in Cohort 1 had the opportunity to be assessed for response at Month 3. *2 Clopper-Pearson method; *3 Exact test based on binomial distribution, the threshold of 20% was for response rate, and the significance level (one-sided) was 0.017.

The primary analysis was performed with a cut-off date of January 27, 2017, and results are shown in Table 21.

Table 21. Results from primary analysis on response rate (investigator assessment, data cut-off on January 27, 2017)

	Number of patients (%)		
	Cohort 1 n = 72	Cohort 2 n = 20	Cohorts 1 and 2 pooled n = 92
CR	34 (47.2)	14 (70.0)	48 (52.2)
PR	24 (33.3)	3 (15.0)	27 (29.3)
SD	9 (12.5)	2 (10.0)	11 (12.0)
PD	4 (5.6)	0	4 (4.3)
Not evaluated	1 (1.4)	1 (5.0)	2 (2.2)
Response (CR + PR) (response rate [95% CI[*1]] [%]) *P* value (one-sided)[*2]	58 (80.6 [69.5, 88.9])	17 (85.0 [62.1, 96.8])	75 (81.5 [72.1, 88.9]) <0.0001

*1 Clopper-Pearson method; *2 Exact test based on binomial distribution, the threshold of 20% was for response rate, and the significance level (one-sided) was 0.0075.

Additional analyses were performed with a cut-off date of August 11, 2017 and August 11, 2018 (when all of the 101 patients included in the efficacy analysis completed the follow-up assessment at Months 12 and 24). Tables 22 and 23 show the response rate as of the additional analysis.

Table 22. Results on response rate at Month 12 (investigator assessment, data cut-off on August 11, 2017)

	Number of patients (%)		
	Cohort 1 n = 77	Cohort 2 n = 24	Cohorts 1 and 2 pooled n = 101
CR	41 (53.2)	18 (75.0)	59 (58.4)
PR	23 (29.9)	2 (8.3)	25 (24.8)
SD	8 (10.4)	2 (8.3)	10 (9.9)
PD	4 (5.2)	1 (4.2)	5 (5.0)
Not evaluated	1 (1.3)	1 (4.2)	2 (2.0)
Response (CR + PR) (response rate [95% CI[*]] [%])	64 (83.1 [72.9, 90.7])	20 (83.3 [62.6, 95.3])	84 (83.2 [74.4, 89.9])

* Clopper-Pearson method

Table 23. Results on response rate at Month 24 (investigator assessment, data cut-off on August 11, 2018)

	Number of patients (%)		
	Cohort 1 n = 77	Cohort 2 n = 24	Cohorts 1 and 2 pooled n = 101
CR	41 (53.2)	18 (75.0)	59 (58.4)
PR	23 (29.9)	2 (8.3)	25 (24.8)
SD	8 (10.4)	2 (8.3)	10 (9.9)
PD	4 (5.2)	1 (4.2)	5 (5.0)
Not evaluated	1 (1.3)	1 (4.2)	2 (2.0)
Response (CR + PR) (response rate [95% CI*] [%])	64 (83.1 [72.9, 90.7])	20 (83.3 [62.6, 95.3])	84 (83.2 [74.4, 89.9])

* Clopper-Pearson method

In Cohort 3, which was intended to investigate the effect rate of preventive treatment with tocilizumab and levetiracetam on severe CRS and neurologic toxicity, 42 patients were enrolled, and all patients underwent leukapheresis, but 2 patients withdrew (Grade 3 pleural effusion in 1 patient and failure of YESCARTA manufacture in 1 patient). The remaining 40 patients received conditioning chemotherapy. Furthermore, 2 patients withdrew (disease progression in 1 patient and death from sepsis occurring after conditioning chemotherapy in 1 patient), and the remaining 38 patients received YESCARTA and were included in the safety analysis in Cohort 3. In Cohort 3, CRS occurred in 35 of 38 patients (92.1%) (Grade 1, 13 patients; Grade 2, 21 patients; Grade 4, 1 patient), and neurologic toxicity occurred in 33 of 38 patients (86.8%) (Grade 1, 9 patients; Grade 2, 9 patients; Grade 3, 13 patients; Grade 4, 1 patient; Grade 5, 1 patient).

For the safety, death occurred in 54 of 108 patients in the phase I part as well as Cohorts 1 and 2 in the phase II part during administration of YESCARTA or within 24 months after administration. Causes of the deaths, except for deaths from disease progression (46 patients) and deaths after the next chemotherapy to treat disease progression (4 patients), were brain injury, haemorrhage intracranial, histiocytosis haematophagic, and pulmonary embolism in 1 patient each, and a causal relationship to YESCARTA could not be ruled out for brain injury[4)] and histiocytosis haematophagic[5)] in 1 patient each.

In Cohort 3, death occurred in 18 of 38 patients during administration of YESCARTA or follow-up period (until data cut-off date). Causes of the deaths, except for deaths from disease progression (14 patients) and death from renal failure in 1 patient who underwent allogenic stem cell transplantation after administration of YESCARTA, were bacteraemia, pneumonia necrotising, and brain oedema in 1 patient each, and a causal relationship to YESCARTA could not be ruled out for brain oedema[6)] in 1 patient.

4) A 6[redacted]-year old man received Yescarta to treat the primary disease of TFL and experienced Grade 3 encephalopathy on Day 4 and Grade 4 CRS on Day 5, resulting in cardiac arrest. Approximately 15 minutes later, cardiopulmonary resuscitation led to return of spontaneous circulation, but Grade 4 anoxic brain injury occurred. On Day 34, he died of anoxic brain injury.

5) A 6[redacted]-year old woman received Yescarta to treat the primary disease of DLBCL and experienced CRS (Grade 1) on the same day, which was aggravated to Grade 3 on Day 1. On Day 6, Grade 3 encephalopathy developed. The patient further experienced Grade 3 human herpes virus (HHV)-6 infection on Day 13, Grade 3 lung infection on Day 15, hyperbilirubinaemia (4.7 mg/dL) on Day 18, Grade 3 parvovirus infection on Day 22, and Grade 3 urinary tract infection on Day 28. On Day 29, the patient underwent biopsy bone marrow owing to continuously increasing bilirubin (23.5 mg/dL), encephalopathy, and pancytopenia and was given a diagnosis of histiocytosis haematophagic. On Day 40, she died of histiocytosis haematophagic.

6) A 2[redacted]-year old man received Yescarta to treat the primary disease of PMBCL and experienced CRS (Grade 1) on the same day. On Day 6, CRS was aggravated to Grade 3, and Grade 3 decreased ejection fraction, Grade 2 blood pressure decreased, and Grade 2 confusional state occurred. On Day 7, all of CRS, blood pressure decreased, and depressed level of consciousness became Grade 4. To treat his aggravated respiratory status, mechanical ventilation was started, and CT confirmed brain oedema. On Day 8, brain death was diagnosed, and on Day 9, he died of brain oedema.

6.1.2 Japanese clinical studies

6.1.2.1 Japanese phase II study (CTD 5.3.5.2-2, Study J201, ongoing since October 2018 [data cut-off on October 23, 2019])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of YESCARTA in patients with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL (target sample size, 16 patients [10 in Step 1, 6 in Step 2]) at 6 study sites in Japan. Table 24 shows the main inclusion and exclusion criteria.

Table 24. Main inclusion and exclusion criteria

Inclusion criteria • Patients with histologically confirmed DLBCL,[7] PMBCL, TFL, or HGBCL according to the WHO classification (2016) • Patients with refractory disease meeting any of the following cases: ➢ No response to the first-line chemotherapy (the best response was assessed as PD, or after 4 cycles of the first-line chemotherapy, it was assessed as SD with its duration shorter than 6 months from the last dose). Patients who were intolerant to the first-line therapy were excluded. ➢ No response to second and subsequent lines of chemotherapy (the best response was assessed as PD, or after ≥2 cycles of the last chemotherapy, it was assessed as SD with its duration shorter than 6 months from the last dose) ➢ After autologous SCT, PD or relapse occurred within 12 months. ➢ After autologous SCT, no-response to or relapse after the salvage therapy occurred. • Patients who received prior anti-CD20 monoclonal antibody or an anthracycline-containing chemotherapy • Patients with TFL who received prior chemotherapy for FL and then experienced transformation into DLBCL resistant to chemotherapy • Patients with no evidence of central nervous system (CNS) lymphoma • ECOG PS of 0 or 1 Exclusion criteria • Patients with a history of Richter's transformation of CLL • Patients with a history of allogeneic stem cell transplantation • Patients with a history of CD19-targeted therapy • Patients with a history of CAR T-cell therapy or genetically modified T-cell therapy

Patients intravenously received YESCARTA at the target dose of 2.0×10^6 (±20%) CAR T-cells/kg (for patients weighing >100 kg, fixed dose of 2.0×10^8 cells/body and minimum acceptable dose of 1.0×10^6 cells/kg) as a single dose over ≤30 minutes.

In addition, patients received the following conditioning chemotherapy as pretreatment for 3 consecutive days starting 5 days before administration of YESCARTA. Chemotherapy (bridging therapy) to keep the disease stable while waiting for YESCARTA to be manufactured (from the study enrollment to conditioning chemotherapy) was not permitted (corticosteroids were permitted at an equivalent dose of ≥5 mg/day of prednisolone throughout the study period except for 5 days before administration of YESCARTA).

Dosage regimen of conditioning chemotherapy

- Once-daily intravenous infusion of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2

[7] The following tissue types of DLBCL were deemed eligible:
- DLBCL, not otherwise specified
- Intravascular large B-cell lymphoma
- T cell/histiocyte-rich large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Epstein-Barr virus positive DLBCL, not otherwise specified

The study was initially intended to evaluate DLT (DLT was evaluated for 28 days after administration of YESCARTA), and 3 patients (or 6 patients if DLT has occurred) were firstly enrolled to evaluate the tolerability of YESCARTA. The first 3 patients evaluated for DLT experienced no DLT.

The primary efficacy endpoint was the response rate (percentage of patients who achieved CR or PR) assessed by investigators according to the IWG 2007 criteria (*J Clin Oncol.* 2007;25:579-86).

For evaluation of the efficacy and futility, the following 2-step procedure was applied in accordance with a method of Mander, et al. (*Contemporary Clinical Trials.* 2010;31:572-78) to control the type 1 error in the entire study to 0.05 (two-sided).

In Step 1, the interim analysis should be performed when the first 10 patients (including 3 patients evaluated for DLT) achieved the best response of CR or PR, the study was early terminated, or the 3-month follow-up period was completed, whichever occurred first. The following actions should be taken according to results from the interim analysis: If ≥6 of 10 patients have responded, YESCARTA can be determined to be effective; if ≤2 patients have responded, the study should be terminated for futility; and if 3 to 5 patients have responded, 6 patients should be additionally included in Step 2, the efficacy of YESCARTA should be evaluated based on results from all the 16 patients. If ≥8 of 16 patients have responded in Step 2, YESCARTA can be determined to have efficacy.[8)]

As of data cut-off date for the Step 1 analysis (July 15, 2019), 17 patients were enrolled in the study and underwent leukapheresis, and 15 patients received YESCARTA except for 2 patients (withdrawal from the study owing to disease progression and YESCARTA manufacture ongoing as of data cut-off date in 1 patient each). Furthermore, except for 1 patient who received YESCARTA at $<1.0 \times 10^6$ cells/kg and 3 patients in whom the response was not evaluated, 11 patients were included in the efficacy analysis.

Of the 11 patients in the efficacy analysis population, the first 10 patients who received YESCARTA were included in the Step 1 analysis. Table 25 shows results on the investigator-assessed response rate, the primary endpoint. Because the predetermined ≥6 patients responded, YESCARTA was determined to have efficacy.

Table 25. Results from Step 1 analysis on response rate (investigator assessment, data cut-off on July 15, 2019)

	Number of patients (%)
	n = 10
CR	3 (30.0)
PR	6 (60.0)
SD	1 (10.0)
PD	0
Response (CR + PR) (response rate [95% CI*] [%])	9 (90.0 [55.5, 99.7])

* Clopper-Person method

8) On the basis that the response rate was reported to be 26% in a multi-center research in patients with relapsed or refractory DLBCL, PMBCL, or TFL (n = 636) (the SCHOLAR-1 study [*Blood.* 2017;130:1800-8]), the threshold of 26% was specified for the response rate in Study J201. In addition, on the basis that the response rate in Study ZUMA-1 was 82%, the expected response rate of 60% was conservatively assumed in Study J201.

Table 26 shows results on the response rate in all of the 11 patients as of the interim analysis.

Table 26. Results on response rate as of interim analysis (investigator assessment, data cut-off on July 15, 2019)

	Number of patients (%)
	n = 11
CR	4 (36.4)
PR	6 (54.5)
SD	1 (9.1)
PD	0
Response (CR + PR)	10
(response rate [95% CI*] [%])	(90.9 [58.7, 99.8])

* Clopper-Person method

An additional analysis was performed in 15 patients[9)] with a data cut-off date of October 23, 2019. Table 27 shows the results.

Table 27. Results from additional analysis on response rate (investigator assessment, data cut-off on October 23, 2019)

	Number of patients (%)
	n = 15
CR	4 (26.7)
PR	9 (60.0)
SD	1 (6.7)
PD	1 (6.7)
Response (CR + PR)	13
(response rate [95% CI*] [%])	(86.7 [59.5, 98.3])

* Clopper-Pearson method

Death occurred in 2 of 16 patients (12.5%) during the administration or follow-up period (until the data cut-off date), and causes of the deaths were disease progression for both patients.

6.2 Reference data

6.2.1 Foreign clinical studies

6.2.1.1 Foreign phase I study (CTD 5.3.5.2-3, Cohorts 11-14 in Study NCI 09-C-0082, ongoing since ■ 20■ [data cut-off on ■ ■, 20■])

An open-label, uncontrolled study was conducted to investigate the safety of YESCARTA after conditioning chemotherapy in patients with relapsed or refractory B-cell malignant lymphoma (target sample size, 72 patients) at a single study site in 1 country. The study consisted of 14 cohorts (Cohorts 1-14) using multiple dosage regimens of conditioning chemotherapy in combination with YESCARTA. The applicant submitted results from 4 cohorts (Cohorts 11-14) in which YESCARTA manufactured by a process similar to the proposed process (CLP-2.0) was administered.

The dosage regimens of conditioning chemotherapy and YESCARTA in each cohort are as shown below.

9) When the Step 1 analysis was performed, 17 patients were already enrolled, but 15 patients were included in the efficacy analysis, excluding 2 patients (1 patient who did not receive Yescarta owing to disease progression and 1 patient who received Yescarta at a dose $<1.0 \times 10^6$ cells/kg owing to anaphylactic shock occurring during the administration).

Dosage regimen of conditioning chemotherapy

- Cohorts 11 and 12: Once-daily intravenous infusion of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 for 3 consecutive days starting 5 days before administration of YESCARTA
- Cohorts 13 and 14: Once-daily intravenous infusion of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 for 3 consecutive days starting 5 days before administration of YESCARTA

Dosage regimen of YESCARTA

- Cohort 11: Single intravenous administration of anti-CD19 CAR T-cells at 2.0 × 10^6 cells/kg
- Cohort 12: Single intravenous administration of anti-CD19 CAR T-cells at 6.0 ×10^6 cells/kg
- Cohort 13: Single intravenous administration of anti-CD19 CAR T-cells at 2.0 × 10^6 cells/kg
- Cohort 14: Single intravenous administration of anti-CD19 CAR T-cells at 2.0 ×1 0^6 cells/kg

In Cohorts 11 to 14, 15 patients (10 in Cohort 11, 1 in Cohort 12, 2 in Cohort 13, 2 in Cohort 14) were enrolled. Because the safety analysis was planned to include patients with DLBCL, PMBCL, or TFL, it was performed in 13 patients, excluding 1 patient with mantle cell lymphoma (MCL) in Cohort 13 and 1 patient with FL in Cohort 14.

In the study, incidence of DLT was investigated as a part of the safety evaluation, and DLT occurred in 3 of 10 patients (supraventricular and nodal arrhythmia; somnolence/cognitive disorder/neuropathy [motor]; and hypotension in 1 patient each) in Cohort 11 and 1 of 1 patient (confusion in 1 patient) in Cohort 12.

Death occurred in 3 of 13 patients during the administration or follow-up period (until the data cut-off date), and causes of the deaths were disease progression for all the patients.

6.R Outline of the review conducted by PMDA

6.R.1 Data for review

PMDA determined that, among the clinical studies included in the submitted evaluation data, Cohorts 1 and 2 in the phase II part in Study ZUMA-1 were important in evaluating the efficacy and safety of YESCARTA, and data from the concerned cohorts were mainly used for the evaluation.

The efficacy and safety of YESCARTA in Japanese patients were evaluated based on the data from Study J201 in Japanese patients.

6.R.2 Efficacy

As a result of the following review, PMDA has concluded that YESCARTA was shown to have a certain level of efficacy in patients with relapsed or refractory DLBCL, TFL, PMBCL, or HGBCL.

6.R.2.1 Efficacy endpoint and evaluation results

The applicant's explanation about the efficacy of YESCARTA in patients with DLBCL, TFL, PMBCL, or HGBCL:

In both Studies ZUMA-1 and J201, the response rate was specified as the primary endpoint because the response would lead to tumor reduction, which was expected to alleviate associated symptoms and

improve the quality of life (QOL). The response was assessed according to the IWG 2007 criteria, which are conventionally used in imaging assessment of DLBCL, TFL, PMBCL, or HGBCL.

The second interim analysis in Study ZUMA-1 showed that the investigator-assessed response rate [95% confidence interval (CI)] (%) was 76.5 [62.5, 87.2], which exceeded the predetermined efficacy criterion. The additional analysis at Month 24 further showed that the response rate [95% CI] (%) was 83.1 [72.9, 90.7].

Results on duration of response (DOR) and overall survival (OS), the secondary endpoints, are as follows:
In Cohorts 1 and 2 in Study ZUMA-1, the median DOR [95% CI] (months) at Month 24 was 11.1 [4.2, not estimable]. The median OS [95% CI] (months) at Month 24 was not estimable [12.8, not estimable] (Figure 4).

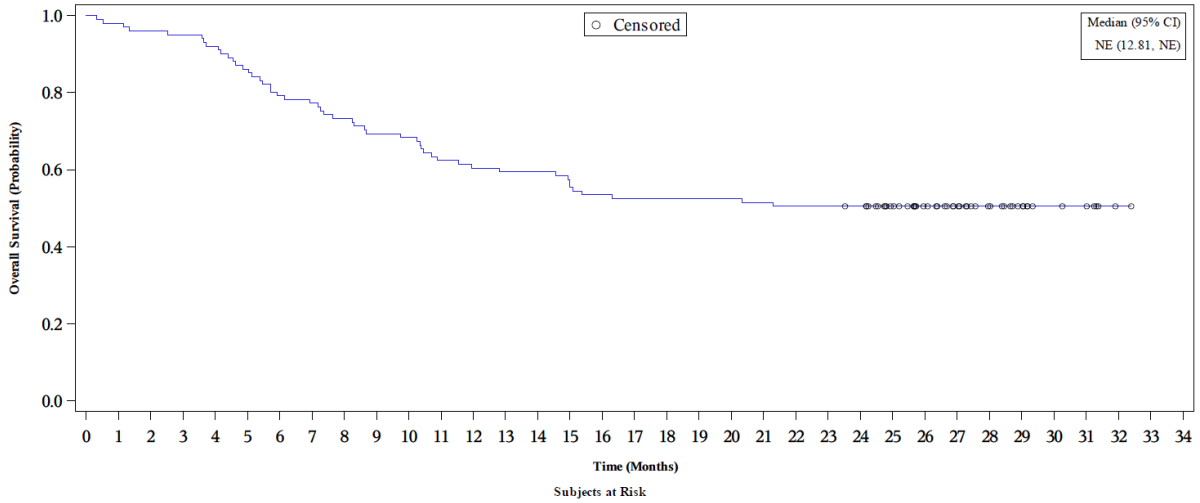

Figure 4. Kaplan-Meier curve of OS until Month 24 in Study ZUMA-1 (efficacy analysis population, data cut-off on August 11, 2018)

In the SCHOLAR-1 study (*Blood.* 2017;130:1800-8) in 636 patients with relapsed or refractory DLBCL, PMBCL, or TFL, the response rate was 26% (7% for CR rate and 18% for PR rate) with the median OS of 6.3 months. Thus the results of Study ZUMA-1 showed the efficacy of YESCARTA.

In Study J201, the investigator-assessed response was observed in 9 of 10 patients in the Step-1 analysis, exceeding the predetermined efficacy criterion as well, and thus the result indicates the potential efficacy of YESCARTA in Japanese patients.

PMDA further asked the applicant to explain the efficacy of YESCARTA by tissue type.

The applicant's response:
When sorted by tissue type (locally assessed), Study ZUMA-1 (n = 101) consisted of 77 patients with DLBCL (76.2%), 8 patients with PMBCL (7.9%), and 16 patients with TFL (15.8%). Of 84 patients in whom the tissue type was also centrally assessed, 82 patients consisted of 69 patients with DLBCL (68.3%), 4 patients with PMBCL (4.0%), and 9 patients with TFL (8.9%), except for 2 patients who

were assessed as DLBCL with small B-cell lymphoma, which fell outside the tissue types of lymphoma subjected to Study ZUMA-1. The diseases locally assessed as PMBCL in 2 patients and TFL in 4 patients were centrally assessed as DLBCL. To identify patients with the disease that fell under HGBCL in the WHO classification (2016), genetic tests were performed in 42 patients who provided the specimens. The diseases centrally assessed as DLBCL in 4 patients and TFL in 2 patients were found to be HGBCL.

Tables 28 and 29 show results on response rate by tissue type (locally assessed or centrally assessed) in Study ZUMA-1. The response was observed in patients with all of the tissue types, indicating the potential efficacy of YESCARTA.

Table 28. Results on response rate by tissue type (locally assessed)
(Study ZUMA-1, investigator assessment, data cut-off on August 11, 2018)

	Number of patients (%)		
	DLBCL n = 77	PMBCL n = 8	TFL n = 16
CR	41 (53.2)	6 (75.0)	12 (75.0)
PR	23 (29.9)	0	2 (12.5)
SD	8 (10.4)	1 (12.5)	1 (6.3)
PD	4 (5.2)	1 (12.5)	0
Not evaluated	1 (1.3)	0	1 (6.3)
Response (CR + PR) (response rate [95% CI*] %)	64 (83.1 [72.9, 90.7])	6 (75.0 [34.9, 96.8])	14 (87.5 [61.7, 98.4]

* Clopper-Pearson method

Table 29. Results on response rate by tissue type (centrally assessed)
(Study ZUMA-1, data cut-off on August 11, 2018)

	Number of patients (%)			
	DLBCL n = 65	PMBCL n = 4	TFL n = 7	HGBCL n = 6
CR	38 (58.5)	3 (75.0)	3 (42.9)	4 (66.7)
PR	17 (26.2)	0	2 (28.6)	2 (33.3)
SD	6 (9.2)	1 (25.0)	1 (14.3)	0
PD	3 (4.6)	0	0	0
Not evaluated	1 (1.5)	0	1 (14.3)	0
Response (CR + PR) (response rate [95% CI*] %)	55 (84.6 [73.5, 92.4])	3 (75.0 [19.4, 99.4])	5 (71.4 [29.0, 96.3])	6 (100 [54.1, 100])

* Clopper-Pearson method

When sorted by tissue type (locally assessed), Study J201 (n = 15) consisted of 14 patients with DLBCL and 1 patient with PMBCL. The tissue type in all patients was also centrally assessed. The type locally assessed as PMBCL in 1 patient and DLBCL in 1 patient was centrally assessed as DLBCL and HGBCL, respectively.[10)] When sorted by tissue type (centrally assessed), the study consisted of 14 patients with DLBCL and 1 patient with HGBCL. In addition, the 1 patient who was excluded from the efficacy analysis population owing to the insufficient dose of $<1.0 \times 10^6$ cells/kg of YESCARTA was locally assessed as TFL[11)] but centrally assessed as DLBCL.

10) At the study site where gene rearrangements of *MYC*, *BCL2*, and *BCL6* were not tested, the patient was diagnosed as DLBCL, but the genetic test centrally performed identified the tissue type as HGBCL (double hit lymphoma).
11) The medical history revealed that the disease was initially FL but transformed into DLBCL 9 years later.

Results on efficacy by tissue type are as follows:

- Of 14 patients with DLBCL, 12 patients were assessed as responders at both local and central laboratory, and the response rate [95% CI] (%) was 85.7 [57.2, 98.2].
- One patient with PMBCL (locally assessed) was assessed to achieve PR.
- One patient with HGBCL (centrally assessed) was assessed to achieve CR.
- One patient with TFL (locally assessed) was assessed to experience progressive disease (PD).

The applicant's explanation:

There are no results from clinical studies indicating that YESCARTA is effective in Japanese patients with TFL, but YESCARTA is expected to be effective even in Japanese patients for the following points:

- Treatment for TFL is provided as done for DLBCL both in Japan and overseas, and Studies ZUMA-1 and J201 show that YESCARTA is expected to show efficacy in patients with DLBCL.
- CD19 remained positive in patients with TFL even after transformation (*Leuk Lymphoma.* 1995;18:385-97), and in view of the mechanism of action, YESCARTA is expected to show efficacy.

PMDA's view:

The above applicant's explanation is understandable. According to the results from Studies ZUMA-1 and J201, YESCARTA was shown to have a certain level of efficacy in patients with DLBCL, PMBCL, TFL, or HGBCL.

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 are CRS, haemophagocytic lymphohistiocytosis, neurologic toxicity, infection, myelosuppression, hypersensitivity, hypogammaglobulinaemia, and tumor lysis syndrome (TLS). Attention should be paid to these adverse events when YESCARTA is used.

In addition, 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 DLBCL, PMBCL, TFL, and HGBCL at medical institutions with adequate equipment capable of taking actions on the above adverse events.

6.R.3.1 Safety profile of YESCARTA and differences in the safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety of YESCARTA:

Table 30 shows the summary of the safety in Study ZUMA-1 (data cut-off on August 11, 2018).

Table 30. Summary of safety (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in phase II part])

	Number of patients (%) n = 108
All adverse events	108 (100)
Grade ≥3 adverse events	106 (98.1)
Serious adverse events	60 (55.6)
Adverse events leading to death	4 (3.7)

Table 31 shows adverse events with an incidence of ≥20% in Study ZUMA-1 (phase I part and Cohorts 1 and 2 in the phase II part).

Table 31. Adverse events with an incidence of ≥20%
(Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part])

System organ class Preferred term (MedDRA ver.21.0)	Number of patients (%) n = 108	
	All Grades	Grade ≥3
All adverse events	108 (100)	106 (98.1)
Blood and lymphatic system disorders		
Anaemia	73 (67.6)	49 (45.4)
Neutropenia	48 (44.4)	42 (38.9)
FN	39 (36.1)	35 (32.4)
Thrombocytopenia	38 (35.2)	26 (24.1)
Metabolism and nutrition disorders		
Decreased appetite	55 (50.9)	2 (1.9)
Hypocalcaemia	43 (39.8)	7 (6.5)
Hypoalbuminaemia	43 (39.8)	1 (0.9)
Hyponatraemia	38 (35.2)	12 (11.1)
Hypokalaemia	36 (33.3)	3 (2.8)
Hypophosphataemia	31 (28.7)	20 (18.5)
Psychiatric disorders		
Confusional state	29 (26.9)	10 (9.3)
Nervous system disorders		
Headache	50 (46.3)	1 (0.9)
Encephalopathy	40 (37.0)	25 (23.1)
Tremor	33 (30.6)	2 (1.9)
Dizziness	23 (21.3)	0
Cardiac disorders		
Tachycardia	43 (39.8)	2 (1.9)
Vascular disorders		
Hypotension	63 (58.3)	15 (13.9)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	34 (31.5)	12 (11.1)
Cough	31 (28.7)	0
Dyspnoea	23 (21.3)	2 (1.9)
Gastrointestinal disorders		
Nausea	63 (58.3)	0
Diarrhoea	48 (44.4)	5 (4.6)
Vomiting	37 (34.3)	1 (0.9)
Constipation	32 (29.6)	0
General disorders and administration site conditions		
Pyrexia	94 (87.0)	15 (13.9)
Fatigue	57 (52.8)	3 (2.8)
Chills	40 (37.0)	0
Investigations		
Neutrophil count decreased	36 (33.3)	35 (32.4)
White blood cell count decreased	33 (30.6)	31 (28.7)
Platelet count decreased	32 (29.6)	17 (15.7)
ALT increased	22 (20.4)	6 (5.6)
Lymphocyte count decreased	22 (20.4)	22 (20.4)

In Study ZUMA-1 (phase I part and Cohorts 1 and 2 in the phase II part), serious adverse events with an incidence of ≥3% were encephalopathy in 20 patients (18.5%), lung infection and pyrexia in 8

patients (7.4%) each, febrile neutropenia (FN) and pneumonia in 6 patients (5.6%) each, B-cells lymphoma and confusional state in 5 patients (4.6%) each, and aphasia, atrial fibrillation, cardiac arrest, and urinary tract infection in 4 patients (3.7%) each. A causal relationship to YESCARTA could not be ruled out for encephalopathy in 20 patients, confusional state in 5 patients, aphasia in 4 patients, lung infection in 3 patients, atrial fibrillation and cardiac arrest in 2 patients each, and pyrexia and FN in 1 patient each.

Within 24 months after administration of YESCARTA, deaths occurred in 54 patients (50.0%) (disease progression in 46 patients, brain injury, haemorrhage intracranial, histiocytosis haematophagic, and pulmonary embolism in 1 patient each; deaths after start of treatment other than YESCARTA for disease progression in 4 patients). A causal relationship to YESCARTA could not be ruled out for brain injury and histiocytosis haematophagic in 1 patient each.

Table 32 shows the summary of the safety in Study J201 (data cut-off on October 23, 2019).

Table 32. Summary of safety (Study J201)

	Number of patients (%) n = 16
All adverse events	16 (100)
Grade ≥3 adverse events	16 (100)
Serious adverse events	13 (81.3)
Adverse events leading to death	0

Table 33 shows adverse events with an incidence of ≥20% in Study J201.

Table 33. Adverse events with an incidence of ≥20% (Study J201)

System organ class Preferred term (MedDRA ver.21.0)	Number of patients (%) n = 16	
	All Grades	Grade ≥3
All adverse events	16 (100)	16 (100)
Blood and lymphatic system disorders		
Anaemia	7 (43.8)	5 (31.3)
FN	7 (43.8)	7 (43.8)
Lymphopenia	6 (37.5)	6 (37.5)
Neutropenia	6 (37.5)	6 (37.5)
Leukopenia	4 (25.0)	4 (25.0)
Thrombocytopenia	4 (25.0)	2 (12.5)
Metabolism and nutrition disorders		
Decreased appetite	9 (56.3)	4 (25.0)
Nervous system disorders		
Headache	5 (31.3)	0
Respiratory, thoracic and mediastinal disorders		
Hypoxia	4 (25.0)	1 (6.3)
Gastrointestinal disorders		
Diarrhoea	8 (50.0)	3 (18.8)
Nausea	8 (50.0)	0
General disorders and administration site conditions		
Pyrexia	14 (87.5)	2 (12.5)
Malaise	6 (37.5)	0
Investigations		
Platelet count decreased	8 (50.0)	8 (50.0)
ALT increased	7 (43.8)	1 (6.3)
AST increased	7 (43.8)	1 (6.3)
Lymphocyte count decreased	7 (43.8)	7 (43.8)
Neutrophil count decreased	7 (43.8)	7 (43.8)
White blood cell count decreased	5 (31.3)	5 (31.3)

In Study J201, serious adverse events with an incidence of ≥10% were pyrexia in 11 patients (68.8%), FN and diarrhoea in 3 patients (18.8%) each, and hypotension, hypoxia, and neutrophil count decreased in 2 patients (12.5%) each. A causal relationship to YESCARTA could not be ruled out for pyrexia in 11 patients, diarrhoea in 3 patients, hypotension, hypoxia, and neutrophil count decreased in 2 patients each, and FN in 1 patient.

Deaths (up to the data cut-off date) occurred in 2 patients (12.5%) both owing to disease progression, and no deaths owing to adverse events occurred.

The applicant's explanation about the safety of YESCARTA by tissue type:
Tables 34 and 35 show the summary of the safety by tissue type (locally assessed or centrally assessed) and incidences of adverse events requiring special attention when using YESCARTA in Study ZUMA-1.

Table 34. Summary of the safety by tissue type (locally assessed) and incidences of adverse events requiring special attention when using YESCARTA (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part])

	Number of patients (%)		
	DLBCL n = 84	PMBCL n = 8	TFL n = 16
All adverse events	84 (100)	8 (100)	16 (100)
Grade ≥3 adverse events	83 (98.8)	8 (100)	15 (93.8)
Serious adverse events	47 (56.0)	4 (50.0)	9 (56.3)
Adverse events leading to death	7 (8.3)*	0	2 (12.5)
CRS	79 (94.0)	8 (100)	13 (81.3)
Neurologic toxicity	56 (66.7)	4 (50.0)	12 (75.0)
Infection	35 (41.7)	4 (50.0)	6 (37.5)
Thrombocytopenia	55 (65.5)	4 (50.0)	8 (50.0)
Neutropenia	74 (88.1)	6 (75.0)	13 (81.3)
Anaemia	60 (71.4)	3 (37.5)	10 (62.5)

* Including deaths in 5 patients owing to disease progression

Table 35. Summary of the safety by tissue type (centrally assessed) and incidences of adverse events requiring special attention when using YESCARTA (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part])

	Number of patients (%)			
	DLBCL n = 75	PMBCL n = 4	TFL n = 9	HGBCL n = 7
All adverse events	75 (100)	4 (100)	9 (100)	7 (100)
Grade ≥3 adverse events	75 (100)	4 (100)	8 (88.9)	7 (100)
Serious adverse events	44 (58.7)	2 (50.0)	6 (66.7)	4 (57.1)
Adverse events leading to death	5 (6.7)*	0	2 (22.2)	0
CRS	69 (92.0)	4 (100)	7 (77.8)	6 (85.7)
Neurologic toxicity	51 (68.0)	2 (50.0)	7 (77.8)	4 (57.1)
Infection	33 (44.0)	2 (50.0)	4 (44.4)	4 (57.1)
Thrombocytopenia	46 (61.3)	3 (75.0)	5 (55.6)	5 (71.4)
Neutropenia	65 (86.7)	3 (75.0)	8 (88.9)	7 (100)
Anaemia	52 (69.3)	2 (50.0)	5 (55.6)	5 (71.4)

* Including deaths in 4 patients owing to disease progression

Tables 36 and 37 show the summary of the safety by tissue type (locally assessed or centrally assessed) and the incidences of adverse events requiring special attention when using YESCARTA in Study J201.

Table 36. Summary of safety by tissue type (locally assessed) (Study J201)

	Number of patients (%)		
	DLBCL n = 14	PMBCL n = 1	TFL n = 1
All adverse events	14 (100)	1 (100)	1 (100)
Grade ≥3 adverse events	14 (100)	1 (100)	1 (100)
Serious adverse events	11 (78.6)	1 (100)	1 (100)
Adverse events leading to death	0	0	0
CRS	11 (78.6)	1 (100)	1 (100)
Neurologic toxicity	0	0	0
Infection	10 (71.4)	1 (100)	1 (100)
Thrombocytopenia	10 (71.4)	1 (100)	1 (100)
Neutropenia	13 (92.9)	1 (100)	1 (100)
Anaemia	6 (42.9)	1 (100)	0

Table 37. Summary of safety by tissue type (centrally assessed) (Study J201)

	Number of patients (%)	
	DLBCL n = 15	HGBCL n = 1
All adverse events	15 (100)	1 (100)
Grade ≥3 adverse events	15 (100)	1 (100)
Serious adverse events	12 (80.0)	1 (100)
Adverse events leading to death	0	0
CRS	12 (80.0)	1 (100)
Neurologic toxicity	0	0
Infection	11 (73.3)	1 (100)
Thrombocytopenia	11 (73.3)	1 (100)
Neutropenia	14 (93.3)	1 (100)
Anaemia	7 (46.7)	0

Because of the limited number of patients with the disease of the other tissue type than DLBCL, strict comparison of the safety among tissue types has limitations, but no clear differences were observed in incidence of adverse events among tissue types in Study ZUMA-1 or Study J201.

The applicant's explanation about differences in the safety profile of YESCARTA between Japanese and non-Japanese patients:
All Grade adverse events with an incidence ≥20% higher in Japanese patients than in non-Japanese patients included platelet count decreased (8 Japanese patients [50.0%], 32 non-Japanese patients [29.6%]), alanine aminotransferase (ALT) increased (7 patients [43.8%], 22 patients [20.4%]), aspartate aminotransferase (AST) increased (7 patients [43.8%], 19 patients [17.6%]), lymphocyte count decreased (7 patients [43.8%], 22 patients [20.4%]), lymphopenia (6 patients [37.5%], 10 patients [9.3%]), and malaise (6 patients [37.5%], 4 patients [3.7%]).

Grade ≥3 adverse events with an incidence ≥20% higher in Japanese patients than in non-Japanese patients included platelet count decreased (8 patients [50.0%], 17 patients [15.7%]), lymphocyte count decreased (7 patients [43.8%], 22 patients [20.4%]), lymphopenia (6 patients [37.5%], 8 patients [7.4%]), and decreased appetite (4 patients [25.0%], 2 patients [1.9%]).

PMDA's view:
In Studies ZUMA-1 and J201, serious adverse events such as CRS frequently occurred. When YESCARTA is used, patients should be carefully monitored, and if an adverse event occurred, multimodal measures should be individually taken according to its nature. In addition, clinical experience with YESCARTA in Japanese patients is limited, and thus strict comparison of the safety of YESCARTA between Japanese and non-Japanese patients has limitations. Even with such limitations, some adverse events such as platelet count decreased more frequently occurred in Japanese patients than in non-Japanese patients; therefore, adverse events should be more carefully controlled in Japanese patients.

6.R.3.2 Safety profile of YESCARTA by event

The following sections show the reviews conducted by PMDA on events occurring frequently and events that was serious in some patients, as indicated by the safety data on YESCARTA mainly from Studies ZUMA-1 and J201.

6.R.3.2.1 CRS

The applicant's explanation about CRS in patients receiving YESCARTA in terms of (a) incidence of CRS in clinical studies, (b) risk factors of onset and aggravation of CRS, and (c) management of CRS:

(a) Incidence of CRS in clinical studies:

In Studies ZUMA-1 and J201, if CRS occurred, terms entered in a case report form (CRF) should be adverse event terms such as "pyrexia" and "hypotension" that led to determination of CRS rather than "CRS", with an additional statement to the effect that the event terms such as "pyrexia" and "hypotension" were related to CRS.

To determine an incidence of CRS, events entered as ones related to CRS in CRFs were counted.

In Studies ZUMA-1 and J201, the grading scale for CRS (Lee's criteria [*Blood.* 2014;124:188-95]) presented in Table 38 was used.

Table 38. Grading scale for CRS

Grade 1	Symptoms are not life threatening and require symptomatic treatment only (e.g., pyrexia, nausea, fatigue, headache, myalgia, and malaise).
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement FiO_2 <40%, Or hypotension responsive to fluids or low dose of 1 vasopressor, Or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement FiO_2 ≥40%, Or hypotension requiring high dose or multiple vasopressors, Or Grade 3 organ toxicity or Grade 4 hypertransaminasaemia
Grade 4	Life-threatening symptoms Requirements for ventilator support, Or Grade 4 organ toxicity (excluding hypertransaminasaemia)
Grade 5	Death

Tables 39 and 40 show incidences of CRS.

Table 39. Incidence of CRS
(Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part] and Study J201)

PT (MedDRA ver.21.0)	Number of patients (%)			
	Study ZUMA-1 n = 108		Study J201 n = 16	
	All Grades	Grade ≥3	All Grades	Grade ≥3
CRS	100 (92.6)	12 (11.1)	13 (81.3)	1 (6.3)
Pyrexia	83 (76.9)	12 (11.1)	13 (81.3)	2 (12.5)
Hypotension	44 (40.7)	10 (9.3)	2 (12.5)	1 (6.3)
Tachycardia	24 (22.2)	1 (0.9)	0	0
Hypoxia	23 (21.3)	9 (8.3)	2 (12.5)	1 (6.3)
Chills	20 (18.5)	0	0	0
Sinus tachycardia	8 (7.4)	0	0	0
Headache	5 (4.6)	0	1 (6.3)	0
Acute kidney injury	4 (3.7)	3 (2.8)	0	0
Fatigue	4 (3.7)	0	1 (6.3)	0
Myalgia	4 (3.7)	0	0	0
Vomiting	4 (3.7)	0	1 (6.3)	0
Atrial fibrillation	3 (2.8)	2 (1.9)	0	0
Diarrhoea	3 (2.8)	1 (0.9)	3 (18.8)	2 (12.5)
Dyspnoea	3 (2.8)	0	0	0
Ejection fraction decreased	3 (2.8)	1 (0.9)	0	0
Pulmonary oedema	3 (2.8)	0	0	0
Acute left ventricular failure	2 (1.9)	2 (1.9)	0	0
Atrial flutter	2 (1.9)	1 (0.9)	0	0
Blood creatinine increased	2 (1.9)	0	0	0
Capillary leak syndrome	2 (1.9)	0	0	0
Decreased appetite	2 (1.9)	0	0	0
FN	2 (1.9)	2 (1.9)	0	0
Malaise	2 (1.9)	0	1 (6.3)	0
Metabolic acidosis	2 (1.9)	2 (1.9)	0	0
Acidosis	1 (0.9)	1 (0.9)	0	0
ALT increased	1 (0.9)	0	1 (6.3)	1 (6.3)
Anal incontinence	1 (0.9)	0	0	0
Asthenia	1 (0.9)	0	0	0
Cardiac arrest	1 (0.9)	1 (0.9)	0	0
Cough	1 (0.9)	0	0	0
Extrasystoles	1 (0.9)	0	0	0
Histiocytosis haematophagic	1 (0.9)	1 (0.9)	0	0
Hyperhidrosis	1 (0.9)	0	0	0
Localised oedema	1 (0.9)	0	0	0
Nasal congestion	1 (0.9)	0	0	0
Nausea	1 (0.9)	0	0	0
Oedema genital	1 (0.9)	0	0	0
Oedema peripheral	1 (0.9)	0	0	0
Oliguria	1 (0.9)	1 (0.9)	0	0
Periorbital oedema	1 (0.9)	0	0	0
Respiratory rate increased	1 (0.9)	0	0	0
Syncope	1 (0.9)	1 (0.9)	0	0
Tachypnoea	1 (0.9)	0	0	0
Transaminases increased	1 (0.9)	0	0	0
Troponin T increased	1 (0.9)	1 (0.9)	0	0
AST increased	0	0	1 (6.3)	1 (6.3)
Blood alkaline phosphatase increased	0	0	1 (6.3)	0
Blood pressure decreased	0	0	1 (6.3)	0
GGT increased	0	0	1 (6.3)	1 (6.3)
Oxygen saturation decreased	0	0	1 (6.3)	0
Submaxillary gland enlargement	0	0	1 (6.3)	0
Supraventricular tachycardia	0	0	1 (6.3)	1 (6.3)

Table 40. List of patients with Grade ≥3 CRS
(Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part] and Study J201)

Age	Sex	Grade	Seriousness	Causal relationship	Time to onset (days)	Duration (days)	Tocilizumab Number of doses/day	Outcome
Study ZUMA-1 phase I part								
2[redacted]	Female	4	Non-serious	Yes	1	17	3/2, 4, 15	Resolved
Study ZUMA-1 Phase II part								
6[redacted]	Male	3	Serious	Yes	4	6	—	Resolved
6[redacted]	Female	3	Non-serious	Yes	2	7	1/5	Resolved
		5	Serious	Yes	35	7	—	Death
7[redacted]	Male	3	Serious	Yes	5	3	3/5, 6, 7	Resolved
6[redacted]	Male	3	Serious	Yes	7	5	1/7	Resolved
5[redacted]	Female	4	Serious	Yes	10	5	—	Resolved
6[redacted]	Male	3	Non-serious	Yes	5	3	—	Resolved
6[redacted]	Male	4	Serious	Yes	7	2	1/7	Resolved
2[redacted]	Female	3	Serious	Yes	14	5	—	Resolved
4[redacted]	Male	3	Non-serious	Yes	4	2	1/4	Resolved
5[redacted]	Male	3	Serious	Yes	6	4	2/6, 7	Resolved
6[redacted]	Male	4	Serious	Yes	6	8	—	Resolved
Study J201								
5[redacted]	Male	4	Serious	Yes	8	6	4/8, 9*	Not resolved

* On Day 9, 3 doses of tocilizumab were administered.

Fatal CRS occurred in 1 patient in Study ZUMA-1.

In the phase I and II parts in Study ZUMA-1, the median number of days (range) from the start of administration of YESCARTA to the first onset of CRS was 2.0 days (1-4 days) and 2.0 days (1-12 days), respectively.

In Study J201, the median number of days (range) from the start of administration of YESCARTA to the first onset of CRS was 2.0 days (1-11 days).

(b) CRS management algorithm:
In Studies ZUMA-1 and J201, CRS was managed in accordance with the algorithm, which is presented in Table 41.

Table 41. CRS management algorithm (Studies ZUMA-1 and J201)

<table>
<tr><th>Grade</th><th>Management method</th><th>Tocilizumab</th><th>Corticosteroid</th></tr>
<tr><td>Grade 1</td><td>• Symptomatic treatment as per standard of care at the study site
• Careful monitoring for neural conditions</td><td><u>Study ZUMA-1</u>
• Not administered.

<u>Study J201</u>
• If no improvement is observed at 24 hours, intravenously administer tocilizumab 8 mg/kg (up to 800 mg/body).</td><td>• Not administered.</td></tr>
<tr><td rowspan="2">Grade 2</td><td>• Continuously monitor electrocardiogram and oxygen saturation where necessary.
• To treat hypotension, administer a fluid (0.5-1.0 L of an isotonic solution); and if no response to the fluid is observed, administer a vasopressor.
• Administer oxygen where necessary.</td><td><u>Study ZUMA-1</u>
Only for patients with extensive co-morbidities or in elderly, take the following measures:
• Intravenously administer tocilizumab 8 mg/kg (up to 800 mg/body).
• Repeatedly administer up to 3 doses of tocilizumab at an interval of 4-6 hours within 24 hours

<u>Study J201</u>
Irrespective of patient characteristics, take the following measures:
• Intravenously administer tocilizumab 8 mg/kg (up to 800 mg/body).

• If no response to a fluid or oxygen is observed, repeatedly administer at an interval of 8 hours.
• Administer up to 3 doses within 24 hours. If no clinical improvement is observed for CRS signs or symptoms, administer up to 4 doses.

• If any improvement is observed, discontinue the administration.</td><td>• If no improvement is observed within 24 hours after start of tocilizumab administration, intravenously administer methylprednisolone 1 mg/kg (or equivalent dose of dexamethasone) twice daily.

• If improvement is observed, taper the dose.</td></tr>
<tr><td colspan="3">• If no improvement is observed, manage the condition as done for a Grade 3 event.</td></tr>
<tr><td rowspan="2">Grade 3</td><td>• Admit the patient to high care unit or ICU.</td><td>• Manage the condition as done for a Grade 2 event.</td><td>• Intravenously administer methylprednisolone 1 mg/kg (or equivalent dose of dexamethasone) twice daily.

• If improvement is observed, taper the dose.</td></tr>
<tr><td colspan="3">• If no improvement is observed, manage the condition as done for a Grade 4 event.</td></tr>
<tr><td rowspan="2">Grade 4</td><td>• Manage the condition as done for a Grade 3 event.
• Mechanical ventilation and/or renal replacement therapy may be required.</td><td>• Manage the condition as done for a Grade 2 event.</td><td>• Intravenously administer methylprednisolone 1,000 mg once daily for 3 days.

• If improvement is observed, taper the dose.</td></tr>
<tr><td colspan="3"><u>Study J201</u>
• If no improvement is observed, consider another immunosuppressive drug.</td></tr>
</table>

Unless otherwise specified, the same measures were taken in both Studies ZUMA-1 and J201.

Furthermore, currently ongoing Cohort 4[12] in Study ZUMA-1 has indicated[13] that early intervention on CRS can be expected to prevent the condition from worsening, and thus the company core data sheet (CCDS) of YESCARTA was revised (Version [redacted] dated [redacted], 20[redacted]) to modify the CRS management algorithm as shown in Table 42.

Table 42. CRS management algorithm (CCDS Version [redacted])

Grade	Management method	Tocilizumab	Corticosteroid
Grade 1	• Symptomatic treatment as per standard of care at the study site • Careful monitoring for neural conditions	• If no improvement is observed 24 hours later, manage the condition as done for a Grade 2 event.	• If no improvement is observed after 3 days of the standard of care, intravenously administer dexamethasone 10 mg as a single dose.
Grade 2	• Continuously monitor electrocardiogram and oxygen saturation where necessary. • To treat hypotension, administer a fluid (0.5-1.0 L of an isotonic solution); and if no response to the fluid is observed, administer a vasopressor. • Administer oxygen where necessary.	• Intravenously administer tocilizumab 8 mg/kg (up to 800 mg/body). • If no response to a fluid or oxygen is observed, repeatedly administer at an interval of 8 hours. • Administer up to 3 doses within 24 hours. If no clinical improvement is observed for CRS signs or symptoms, administer up to 4 doses. • If improvement is observed, manage the condition as done for a Grade 1 event.	• Intravenously administer dexamethasone 10 mg once daily. • If improvement is observed, continue corticosteroid treatment until Grade ≤1 (or until CRS resolves), and then taper the dose. • If no improvement is observed, manage the condition as done for the applicable grade event below.
Grade 3	• Admit the patient to high care unit or ICU	• Manage the condition as done for a Grade 2 event. • If improvement is observed, manage the condition as done for the applicable lower grade event.	• Intravenously administer dexamethasone 10 mg 3 times a day. • If improvement is observed, manage the condition as done for the applicable lower grade event, and continue corticosteroid treatment until Grade ≤1 (or until CRS resolves), and then taper the dose. • If no improvement is observed, manage the condition as done for a Grade 4 event.
Grade 4	• Manage the condition as done for a Grade 3 event. • Mechanical ventilation and/or renal replacement therapy may be required.	• Manage the condition as done for a Grade 2 event. • If improvement is observed, manage the condition as done for the applicable lower grade event.	• Intravenously administer methylprednisolone 1,000 mg once daily for 3 days. • If improvement is observed, manage the condition as done for the applicable above grade event, and continue corticosteroid treatment until Grade ≤1 (or until CRS resolves), and then taper the dose. • If no improvement is observed, consider methylprednisolone 1,000 mg 2 to 3 times a day or the other treatment (intravenous administration of immunoglobulin).

12) It is a safety management cohort in the phase II part in Study ZUMA-1, and the study in this cohort is currently ongoing to evaluate whether early intervention with tocilizumab and corticosteroids to manage CRS and neurologic toxicity (started at the Grade 1 stage) can prevent the condition from worsening.

13) An incidence of Grade ≥3 CRS was 11.1% in Cohorts 1 and 2 and 2% in Cohort 4, while the response rate in Cohort 4 was 73% with the CR rate of 51%. These results led to a determination that early intervention with tocilizumab and corticosteroids would facilitate CRS management but would not compromise the efficacy.

(c) Risk factors of onset and aggravation of CRS:

CRS is defined as a systemic inflammatory reaction caused by inflammatory cytokines (e.g., IFN-γ) released by CAR T-cells or tumor cells. At present, no risk factors related to onset or aggravation of CRS have been identified.

PMDA's view:

Attention should be paid to CRS especially early after administration of YESCARTA because (1) the incidence of CRS associated with YESCARTA was high; (2) CRS became serious or fatal in some patients; and (3) CRS occurs approximately 2 days after the start of YESCARTA therapy. Accordingly, information about the incidence of CRS and the management methods used in clinical studies should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions. Furthermore, information should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions, in order to ensure that YESCARTA is administered by a physician with sufficient knowledge and experience in systemic control on hematopoietic malignancy and critical conditions such as CRS, at a medical institution with intensive care unit (ICU), etc. that can implement systemic control immediately in an emergency case.

6.R.3.2.2 Haemophagocytic lymphohistiocytosis

The applicant's explanation about haemophagocytic lymphohistiocytosis associated with YESCARTA:

Adverse events related to haemophagocytic lymphohistiocytosis were identified using the database (data cut-off on April 17, 2020) consisting of the safety information from clinical studies and post-marketing experience with YESCARTA in foreign countries, and are listed in Table 43.

Table 43. List of patients with haemophagocytic lymphohistiocytosis

Study	Age	Sex	PT*	Grade	Serious/ Non-serious	Time to onset (days)	Onset of CRS	Causal relationship to YESCARTA
ZUMA-1	6[redacted]	Female	Histiocytosis haematophagic	5	Serious	34	Yes	Yes
Post-marketing experience in foreign countries	6[redacted]	Female	Haemophagocytic lymphohistiocytosis	Unknown	Serious	29	Yes	Yes
	7[redacted]	Female	Haemophagocytic lymphohistiocytosis	Unknown	Serious	4	Yes	Yes
	6[redacted]	Female	Haemophagocytic lymphohistiocytosis	Unknown	Serious	Unknown	Yes	Yes
	7[redacted]	Male	Haemophagocytic lymphohistiocytosis	4	Serious	8	Yes	Yes
	5[redacted]	Male	Haemophagocytic lymphohistiocytosis	5	Serious	Unknown	Yes	Yes
	4[redacted]	Male	Haemophagocytic lymphohistiocytosis	Unknown	Serious	7	No	Yes
	6[redacted]	Female	Haemophagocytic lymphohistiocytosis	Unknown	Serious	Unknown	Yes	Yes
	7[redacted]	Female	Haemophagocytic lymphohistiocytosis	5	Serious	Unknown	Yes	Yes
	6[redacted]	Male	Haemophagocytic lymphohistiocytosis	Unknown	Serious	Unknown	Yes	Yes
	Unknown	Unknown	Haemophagocytic lymphohistiocytosis	Unknown	Serious	Unknown	Yes	Yes
	6[redacted]	Unknown	Haemophagocytic lymphohistiocytosis	Unknown	Serious	9	Yes	Yes
	6[redacted]	Male	Haemophagocytic lymphohistiocytosis	Unknown	Serious	Unknown	Yes	Yes

* Medical Dictionary for Regulatory Activities (MedDRA) ver. 21.0 for Study ZUMA-1 and MedDRA ver. 22.1 for post-marketing experience in foreign countries

Haemophagocytic lymphohistiocytosis is developed and pathologically formed by cytokines released from activated T-cells and macrophages and presents clinical characteristics similar to those of CRS. Development of haemophagocytic lymphohistiocytosis is considered to be triggered by onset of CRS.

PMDA's view:
Haemophagocytic lymphohistiocytosis for which a causal relationship to YESCARTA could not be ruled out occurred in Study ZUMA-1 and post-marketing experience in foreign countries, and attention should be paid to haemophagocytic lymphohistiocytosis in addition to CRS when using YESCARTA. Accordingly, information about the incidence of haemophagocytic lymphohistiocytosis in clinical studies and caution statements should be appropriately presented to healthcare professionals using the package insert, etc. to ensure that appropriate measures can be taken in case of haemophagocytic lymphohistiocytosis.

6.R.3.2.3 Neurologic toxicity

The applicant's explanation about neurologic toxicity associated with YESCARTA:
Events applicable to neurologic toxicities listed in Table 44 were categorized and are listed in Table 45. In Study J201, no events applicable to neurologic toxicity occurred.

Table 44. List of events applicable to neurologic toxicity for tabulation (MedDRA ver. 21.0)

Acalculia, hypertonia, acquired epileptic aphasia, hypoaesthesia, action tremor, hypogeusia, adenoviral encephalitis, hypokinesia, adenoviral meningitis, hypotonia, ageusia, 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, measles meningitis, 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, autonomic failure syndrome, myoclonic epilepsy, autonomic nervous system imbalance, myoclonus, autonomic neuropathy, myotonia, autonomic seizure, nervous system disorder, balance disorder, nervous system injury, Bergman's triad, 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, neuromyotonia, cerebellar ataxia, neurotoxicity, cerebellar syndrome, nystagmus, cerebral ataxia, optic disc pigmentation, cerebral congestion, oromandibular dystonia, cerebral disorder, orthostatic intolerance, cerebral oedema management, paraesthesia, cervicogenic vertigo, paralysis, change in seizure presentation, paraparesis, clonic convulsion, paresis, clonus, partial seizures, clumsiness, 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, phaeohyphomycotic brain abscess, cytotoxic oedema, phonasthenia, delirium, posterior reversible encephalopathy syndrome, delusion, postictal state, dementia, preictal state, depressed level of consciousness, prosopagnosia, disorientation, psychomotor disadaptation syndrome, disturbance in attention, psychomotor hyperactivity, dysaesthesia, pyramidal tract syndrome, dysarthria, reduced facial expression, dyscalculia, reflexes abnormal, dysgraphia, resting tremor, dyskinesia, restlessness, dyslalia, retrograde amnesia, dystonia, right hemisphere deficit syndrome, dystonic tremor, sedation, encephalopathy, seizure, epilepsy, seizure cluster, epileptic aura, seizure like phenomena, essential tremor, sensorimotor disorder, extraischaemic cerebral haematoma, sensory disturbance, fine motor delay, sensory loss, fine motor skill dysfunction, simple partial seizures, focal dyscognitive seizures, sleep deficit, frontal lobe epilepsy, slow speech, fumbling, somnolence, gait apraxia, speech disorder, gait spastic, spinal cord oedema, generalised non-convulsive epilepsy, status epilepticus, generalised tonic-clonic seizure, stupor, gray matter heterotopia, supranuclear palsy, 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 global amnesia, hallucinations-mixed, tremor, head discomfort, unresponsive to stimuli, hemihyperaesthesia, vasogenic cerebral oedema, hemiplegia, vertigo CNS origin, hyperaesthesia, vestibulocerebellar syndrome, hypergeusia, visual perseveration, hyperkinesia, visuospatial deficit, hyperpathia, Yersinia meningitis, hypersomnia

Table 45. Incidences of neurologic toxicity reported by ≥2% of patients (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part])

PT (MedDRA ver.21.0)	Number of patients (%) Study ZUMA-1 n = 108	
	All Grades	Grade ≥3
Neurologic toxicity	72 (66.7)	35 (32.4)
Encephalopathy	40 (37.0)	25 (23.1)
Tremor	33 (30.6)	2 (1.9)
Confusional state	29 (26.9)	10 (9.3)
Aphasia	19 (17.6)	8 (7.4)
Somnolence	18 (16.7)	9 (8.3)
Agitation	10 (9.3)	5 (4.6)
Memory impairment	8 (7.4)	0
Mental status changes	7 (6.5)	3 (2.8)
Dysarthria	5 (4.6)	2 (1.9)
Hallucination	5 (4.6)	0
Ataxia	4 (3.7)	1 (0.9)
Restlessness	4 (3.7)	2 (1.9)
Seizure	4 (3.7)	1 (0.9)
Delirium	3 (2.8)	3 (2.8)
Disturbance in attention	3 (2.8)	2 (1.9)
Lethargy	3 (2.8)	0
Speech disorder	3 (2.8)	2 (1.9)

Table 46 shows characteristics of the patients who experienced serious or Grade ≥3 neurologic toxicity in Study ZUMA-1.

Table 46. List of patients with serious or Grade ≥3 neurologic toxicity

Age	Sex	PT (MedDRA ver.21.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to YESCARTA	Outcome
Study ZUMA-1 phase I part								
5[redacted]	Male	Encephalopathy	3	Non-serious	5	2	Yes	Resolved
6[redacted]	Male	Agitation	3	Non-serious	5	1	Yes	Resolved
		Restlessness	3	Non-serious	5	1	Yes	Resolved
		Tremor	3	Non-serious	5	1	Yes	Resolved
		Delirium	3	Non-serious	6	1	Yes	Resolved
		Somnolence	3	Non-serious	6	1	Yes	Resolved
6[redacted]	Male	Encephalopathy	3	Non-serious	9	1	Yes	Resolved
2[redacted]	Female	Encephalopathy	4	Serious	1	16	Yes	Resolved
		Somnolence	3	Non-serious	1	2	No	Resolved
Study ZUMA-1 phase II part								
5[redacted]	Male	Encephalopathy	3	Serious	3	2	Yes	Resolved
		Aphasia	3	Non-serious	5	8	Yes	Resolved
		Encephalopathy	3	Non-serious	5	11	Yes	Resolved
		Somnolence	3	Non-serious	5	9	Yes	Resolved
		Encephalopathy	3	Non-serious	32	3	Yes	Resolved
6[redacted]	Female	Encephalopathy	3	Non-serious	9	1	Yes	Resolved
4[redacted]	Male	Mental status changes	3	Serious	475	4	No	Resolved
6[redacted]	Male	Encephalopathy	3	Serious	4	5	Yes	Resolved
6[redacted]	Female	Encephalopathy	3	Serious	6	14	Yes	Resolved
2[redacted]	Male	Encephalopathy	3	Serious	6	2	Yes	Resolved
4[redacted]	Female	Encephalopathy	3	Serious	2	1	Yes	Resolved
		Encephalopathy	4	Serious	4	13	Yes	Resolved
		Seizure	4	Serious	5	2	Yes	Resolved
		Leukoencephalopathy	3	Serious	9	17	Yes	Resolved
6[redacted]	Male	Encephalopathy	3	Serious	6	8	Yes	Resolved
5[redacted]	Male	Encephalopathy	3	Serious	6	1	Yes	Resolved
3[redacted]	Female	Encephalopathy	3	Serious	8	8	Yes	Resolved
5[redacted]	Female	Somnolence	3	Non-serious	6	13	Yes	Resolved
		Encephalopathy	3	Serious	8	7	Yes	Resolved
6[redacted]	Male	Encephalopathy	3	Serious	6	7	Yes	Resolved
6[redacted]	Male	Confusional state	3	Non-serious	5	7	Yes	Resolved
		Dysarthria	3	Non-serious	5	2	Yes	Resolved
		Encephalopathy	3	Serious	5	7	Yes	Resolved
		Somnolence	3	Non-serious	5	2	Yes	Resolved
		Restlessness	3	Non-serious	7	7	Yes	Resolved
6[redacted]	Female	Aphasia	3	Serious	4	6	Yes	Resolved
		Confusional state	3	Serious	4	6	Yes	Resolved
		Depressed level of consciousness	3	Serious	4	6	Yes	Resolved
		Somnolence	3	Serious	4	6	Yes	Resolved
6[redacted]	Male	Aphasia	3	Serious	6	10	Yes	Resolved
		Confusional state	3	Serious	6	10	Yes	Resolved
		Encephalopathy	3	Serious	6	10	Yes	Resolved
		Somnolence	3	Serious	6	9	Yes	Resolved
2[redacted]	Female	Agitation	3	Serious	10	3	Yes	Resolved
		Aphasia	3	Serious	10	11	Yes	Resolved
		Confusional state	3	Serious	10	8	Yes	Resolved
		Encephalopathy	3	Serious	10	8	Yes	Resolved
		Somnolence	4	Serious	10	8	Yes	Resolved
7[redacted]	Male	Encephalopathy	3	Serious	1	11	Yes	Resolved
5[redacted]	Female	Lethargy	1	Serious	7	8	Yes	Resolved
6[redacted]	Female	Mental status changes	2	Serious	−5	5	No	Resolved
7[redacted]	Male	Mental status changes	3	Non-serious	4	8	Yes	Resolved
6[redacted]	Male	Confusional state	3	Non-serious	6	3	Yes	Resolved
		Delirium	3	Serious	6	4	Yes	Resolved

Age	Sex	PT (MedDRA ver.21.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to YESCARTA	Outcome
5[redacted]	Female	Confusional state	3	Non-serious	5	17	Yes	Resolved
		Dysarthria	3	Non-serious	5	14	Yes	Resolved
		Mental status changes	3	Non-serious	5	17	Yes	Resolved
		Speech disorder	3	Non-serious	6	14	Yes	Resolved
		Agitation	3	Non-serious	7	7	Yes	Resolved
		Aphasia	3	Non-serious	7	13	Yes	Resolved
		Encephalopathy	3	Serious	7	14	Yes	Resolved
6[redacted]	Male	Encephalopathy	3	Serious	7	9	Yes	Resolved
		Confusional state	3	Non-serious	8	5	Yes	Resolved
		Depressed level of consciousness	3	Non-serious	9	3	Yes	Resolved
		Speech disorder	3	Non-serious	9	3	Yes	Resolved
5[redacted]	Male	Aphasia	3	Non-serious	7	2	Yes	Resolved
		Ataxia	3	Non-serious	7	2	Yes	Resolved
		Disturbance in attention	3	Non-serious	7	2	Yes	Resolved
5[redacted]	Male	Aphasia	3	Serious	4	3	Yes	Resolved
		Confusional state	3	Serious	4	7	Yes	Resolved
		Stupor	3	Non-serious	4	2	Yes	Resolved
		Confusional state	3	Serious	12	2	Yes	Resolved
6[redacted]	Male	Encephalopathy	3	Non-serious	8	11	Yes	Resolved
		Somnolence	3	Non-serious	12	4	Yes	Resolved
		Agitation	3	Serious	47	2	No	Resolved
2[redacted]	Female	Tremor	3	Non-serious	3	10	Yes	Resolved
		Encephalopathy	3	Serious	4	6	Yes	Resolved
		Encephalopathy	3	Serious	17	1	Yes	Resolved
6[redacted]	Male	Encephalopathy	3	Serious	5	2	Yes	Resolved
		Encephalopathy	2	Serious	7	4	Yes	Resolved
		Encephalopathy	3	Non-serious	219	6	No	Resolved
6[redacted]	Female	Encephalopathy	3	Serious	4	3	Yes	Resolved
		Encephalopathy	3	Serious	9	3	Yes	Resolved
6[redacted]	Male	Encephalopathy	3	Non-serious	4	31	Yes	Resolved
6[redacted]	Female	Confusional state	3	Non-serious	1	12	Yes	Resolved
		Disturbance in attention	3	Non-serious	1	12	Yes	Resolved
		Psychomotor hyperactivity	3	Non-serious	1	11	Yes	Resolved
		Agitation	3	Serious	5	8	Yes	Resolved
		Delirium	3	Serious	5	8	Yes	Resolved
3[redacted]	Male	Confusional state	1	Serious	16	2	Yes	Resolved
		Confusional state	3	Non-serious	205	2	No	Resolved
		Dysarthria	2	Serious	205	1	No	Resolved
3[redacted]	Male	Aphasia	3	Non-serious	6	2	Yes	Resolved

No fatal neurologic toxicity was observed in Study ZUMA-1.

In the phase I and II parts in Study ZUMA-1, the median number of days (range) from the start of administration of YESCARTA to the first onset of neurologic toxicity was 4.5 days (2-5 days) and 5.0 days (1-17 days), respectively.

The effect of preventive treatment with tocilizumab and levetiracetam on neurologic toxicity, which was planned to be investigated in Cohort 3, will be reviewed when results from currently ongoing Cohort 4 and subsequent cohorts in Study ZUMA-1 become available.

PMDA asked the applicant to explain reasons for absence of neurologic toxicity in Study J201 and the risk of neurologic toxicity in Japanese patients.

The applicant's response:
There is no clear difference in neurologic toxicity monitoring method, patient characteristics (age, sex, stage, and serum IFN-γ concentration), or percentage of patients treated with tocilizumab and corticosteroid between Studies ZUMA-1 and J201. The median hospital follow-up period (range) in patients in Study J201 was 39 days (27-302 days), which is considered long enough in light of the time to onset of neurologic toxicity in Study ZUMA-1 (see Table 46). The reason for absence of neurologic toxicity in Study J201, therefore, remains unknown.

A risk of neurologic toxicity in Japanese patients, however, cannot be ruled out, and a caution statement about neurologic toxicity should be included in the package insert, etc.

PMDA's view:
Although no neurologic toxicity was observed in Study J201, the incidence of neurologic toxicity associated with YESCARTA was high in Study ZUMA-1, and some patients experienced serious neurologic toxicity. When using YESCARTA, therefore, attention should be paid to neurologic toxicity. Furthermore, serious neurologic toxicity such as encephalopathy observed in clinical studies requires special attention, and patients who have received YESCARTA should be carefully monitored. Accordingly, information about the incidence of neurologic toxicity in clinical studies and their details should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions.

6.R.3.2.4 Infection

The applicant's explanation about infection associated with YESCARTA:
Preferred terms (PTs) of adverse events that occurred after administration of YESCARTA and were coded as Medical Dictionary for Regulatory Activities (MedDRA) high level group terms (HLGT) "Bacterial infectious disorders," "Chlamydial infectious disorders (HLGT distinguished from other bacterial infection)," "Viral infectious disorders," "Fungal infectious disorders," "Mycobacterial infectious disorders (HLGT distinguished from other bacterial infection)," and "Infections - pathogen unspecified" were categorized as infection and are listed in Table 47.

Table 47. Incidences of infection reported by ≥5% of patients in either study (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part] and Study J201)

PT (MedDRA ver.21.0)	Number of patients (%)			
	Study ZUMA-1 n = 108		Study J201 n = 16	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infection	45 (41.7)	30 (27.8)	12 (75.0)	2 (12.5)
Herpes zoster	8 (7.4)	1 (0.9)	0	0
Pneumonia	10 (9.3)	7 (6.5)	1 (6.3)	0
Lung infection	9 (8.3)	8 (7.4)	0	0
Upper respiratory tract infection	9 (8.3)	0	3 (18.8)	0
Urinary tract infection	9 (8.3)	5 (4.6)	0	0
Sinusitis	7 (6.5)	0	1 (6.3)	0
Nasopharyngitis	1 (0.9)	0	3 (18.8)	0
Oral herpes	1 (0.9)	1 (0.9)	1 (6.3)	0
Oral candidiasis	0	0	1 (6.3)	0
Abdominal infection	0	0	1 (6.3)	1 (6.3)
Acute sinusitis	0	0	1 (6.3)	1 (6.3)
Folliculitis	0	0	1 (6.3)	0
Infection	0	0	1 (6.3)	1 (6.3)
Pharyngitis	0	0	1 (6.3)	0
Pyelonephritis	0	0	1 (6.3)	0
Skin infection	0	0	1 (6.3)	0

No fatal infection was observed.

Serious infection was lung infection in 8 patients, pneumonia in 6 patients, urinary tract infection in 4 patients, bacteraemia and Escherichia bacteraemia in 2 patients each, and bacterial sepsis, Clostridium difficile colitis, Clostridium difficile infection, Cytomegalovirus enteritis, device related sepsis, herpes zoster, influenza, Klebsiella infection, oral herpes, pneumonia staphylococcal, sepsis, and viral upper respiratory tract infection in 1 patient each in Study ZUMA-1; and abdominal infection in 1 patient in Study J201.

Table 48 shows patients who experienced reactivation of herpesvirus or hepatitis virus in Studies ZUMA-1 and J201. Furthermore, reports from post-marketing experience in foreign countries included 3 events of human herpesvirus 6 encephalitis, 2 events each of herpes zoster and herpes simplex, and 1 event each of meningoencephalitis herpetic, human herpes virus 6 infection and herpes zoster disseminated.

Table 48. List of patients with reactivation of herpesvirus or hepatitis virus (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part], Study J201, and post-marketing experience in foreign countries)

Age	Sex	PT*	Grade	Seriousness	Time to onset (days)	Causal relationship to YESCARTA	Outcome
Study ZUMA-1							
6[redacted]	Male	Herpes zoster	2	Non-serious	251	No	Resolved
		Post herpetic neuralgia	1	Non-serious	368	No	Resolved
3[redacted]	Female	Herpes zoster	2	Non-serious	51	No	Resolved
6[redacted]	Male	Oral herpes	2	Non-serious	367	No	Resolved
6[redacted]	Female	Human herpes virus 6 infection	3	Non-serious	13	No	Resolved
6[redacted]	Male	Herpes zoster	2	Non-serious	723	No	Resolved
5[redacted]	Male	Herpes zoster	2	Non-serious	69	No	Resolved
		Herpes zoster	1	Non-serious	108	No	Resolved
4[redacted]	Female	Hepatitis B reactivation	1	Non-serious	392	No	Not resolved
3[redacted]	Female	Oral herpes	3	Serious	7	No	Resolved
		Herpes simplex	1	Non-serious	16	No	Resolved
7[redacted]	Male	Herpes zoster	2	Non-serious	76	No	Resolved
		Herpes zoster	2	Non-serious	79	No	Resolved
2[redacted]	Male	Herpes simplex	2	Non-serious	5	No	Resolved
2[redacted]	Female	Oral herpes	3	Non-serious	−5	No	Resolved
		Oral herpes	2	Non-serious	0	No	Not resolved
6[redacted]	Male	Herpes zoster	2	Serious	93	Yes	Resolved
2[redacted]	Female	Herpes zoster	2	Non-serious	97	Yes	Resolved
5[redacted]	Male	Herpes zoster	1	Non-serious	89	No	Resolved
6[redacted]	Male	Herpes zoster	3	Serious	152	No	Resolved
5[redacted]	Female	Herpes zoster oticus	2	Non-serious	184	No	Resolved
		Post herpetic neuralgia	2	Non-serious	184	No	Resolved
Study J201							
6[redacted]	Female	Oral herpes	2	Non-serious	83	No	Resolved
Post-marketing experience in foreign countries							
3[redacted]	Male	Herpes zoster	Unknown	Non-serious	Unknown	Unknown	Unknown
Unknown	Unknown	Herpes zoster	3	Serious	29	Unknown	Not resolved
4[redacted]	Male	Herpes simplex	Unknown	Non-serious	Unknown	Unknown	Unknown
7[redacted]	Male	Herpes zoster disseminated	Unknown	Serious	Unknown	Unknown	Unknown
Unknown	Unknown	Meningoencephalitis herpetic	Unknown	Serious	Unknown	Unknown	Unknown
6[redacted]	Female	Human herpes virus 6 encephalitis	Unknown	Serious	Unknown	Yes	Resolved
5[redacted]	Female	Human herpes virus 6 infection	Unknown	Non-serious	25	Unknown	Unknown
6[redacted]	Male	Human herpes virus 6 encephalitis	Unknown	Serious	Unknown	Unknown	Resolved
Unknown	Unknown	Herpes simplex	Unknown	Non-serious	Unknown	Yes	Unknown
6[redacted]	Male	Human herpes virus 6 encephalitis	Unknown	Serious	6	Unknown	Resolved

* MedDRA ver. 21.0 for Study ZUMA-1 and MedDRA ver. 22.1 for the other study and use experience

In the post-marketing experience in foreign countries, progressive multifocal leukoencephalopathy (PML) associated with reactivation of John Cunningham (JC) virus occurred in 3 patients. In response to the above, progressive multifocal leukoencephalopathy was specified as the event requiring a special attention in CCDS of YESCARTA (Version [redacted] dated [redacted], 20[redacted]).

PMDA's view:

Attention should be paid to infection associated with YESCARTA because patients treated with YESCARTA experienced fatal infection, Grade ≥3 infection, and serious infection. Accordingly, information about the incidence of infection in clinical studies should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions.

6.R.3.2.5 Myelosuppression

The applicant's explanation about myelosuppression associated with YESCARTA:

Adverse events coded as MedDRA standardised MedDRA queries (SMQ) (broad) "Haematopoietic cytopenias" were classified as myelosuppression, and are listed in Table 49.

Table 49. Incidence of myelosuppression (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part] and Study J201)

PT (MedDRA ver.21.0)	Number of patients (%)			
	Study ZUMA-1 n = 108		Study J201 n = 16	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression	101 (93.5)	95 (88.0)	16 (100)	16 (100)
Anaemia	73 (67.6)	49 (45.4)	7 (43.8)	5 (31.3)
Neutropenia	48 (44.4)	42 (38.9)	6 (37.5)	6 (37.5)
FN	39 (36.1)	35 (32.4)	7 (43.8)	7 (43.8)
Thrombocytopenia	38 (35.2)	26 (24.1)	4 (25.0)	2 (12.5)
Leukopenia	20 (18.5)	18 (16.7)	4 (25.0)	4 (25.0)
Lymphopenia	10 (9.3)	8 (7.4)	6 (37.5)	6 (37.5)
Neutrophil count decreased	36 (33.3)	35 (32.4)	7 (43.8)	7 (43.8)
White blood cell count decreased	33 (30.6)	31 (28.7)	5 (31.3)	5 (31.3)
Platelet count decreased	32 (29.6)	17 (15.7)	8 (50.0)	8 (50.0)
Lymphocyte count decreased	22 (20.4)	22 (20.4)	7 (43.8)	7 (43.8)

No fatal myelosuppression was observed.

Serious myelosuppression were FN in 6 patients (6%), neutropenia in 2 patients (2%), and thrombocytopenia in 1 patient (1%) in Study ZUMA-1; and FN in 3 patients (18.8%) and neutrophil count decreased in 2 patients (12.5%) in Study J201.

Table 50 shows time to onset, duration, and recovery period of myelosuppression.

Table 50. Time to onset, duration, and recovery period of myelosuppression

Classification	Study	Median (range) (days) of time to onset (number of days after administration of YESCARTA)	Median (range) (days) of duration (days)	Median (range) (days) of recovery period (days)
Erythrocyte lineage	ZUMA-1	4.0 (1-113)	12.0 (1-541)	14.0 (3-545)
	J201	9.5 (2-26)	7.0 (2-21)	15.0 (11-36)
Leukocyte lineage	ZUMA-1	3.0 (1-159)	44.5 (1-727)	54.0 (3-729)
	J201	2.0 (1-15)	17.0 (12-22)	27.5 (26-29)
Thrombocyte lineage	ZUMA-1	3.0 (1-85)	44.0 (1-366)	55.0 (1-374)
	J201	5.5 (1-72)	26.0 (26-26)	36.0 (36-36)

PMDA's view:

Attention should be paid to myelosuppression associated with YESCARTA because serious myelosuppression occurred in clinical studies. Accordingly, information about the incidence and time to onset of myelosuppression in clinical studies and others should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions. In addition, caution statements should be appropriately provided to healthcare professionals using the package insert, etc. to ensure that a blood test is periodically performed after administration of YESCARTA and appropriate measures can be taken in case of myelosuppression.

6.R.3.2.6 Hypersensitivity

The applicant's explanation about hypersensitivity associated with YESCARTA:

Adverse events coded as MedDRA SMQ (narrow) "Hypersensitivity" were classified as hypersensitivity, and are listed in Table 51. The Studies ZUMA-1 and J201 had prespecified in the protocols that patients receive premedication with acetaminophen and diphenhydramine, etc. 1 hour before administration of YESCARTA.

Table 51. Incidences of hypersensitivity occurring in either study (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in phase II part] and Study J201)

PT (MedDRA ver.21.0)	Number of patients (%)			
	Study ZUMA-1 n = 108		Study J201 n = 16	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypersensitivity	22 (20.4)	1 (0.9)	4 (25.0)	1 (6.3)
Rash	5 (4.6)	0	0	0
Infusion related reaction	4 (3.7)	0	0	0
Rash maculo-papular	4 (3.7)	0	2 (12.5)	0
Rhinitis allergic	3 (2.8)	0	0	0
Hypersensitivity	2 (1.9)	0	1 (6.3)	0
Periorbital oedema	1 (0.9)	0	0	0
Lip swelling	1 (0.9)	0	0	0
Face oedema	1 (0.9)	0	0	0
Scrotal oedema	1 (0.9)	0	0	0
Rash erythematous	1 (0.9)	0	0	0
Shock	1 (0.9)	1 (0.9)	0	0
Anaphylactic reaction	0	0	1 (6.3)	1 (6.3)
Dermatitis acneiform	0	0	1 (6.3)	0

Table 52 shows characteristics of the patients who experienced serious or Grade ≥3 hypersensitivity in Studies ZUMA-1 and J201.

Table 52. List of patients with serious or Grade ≥3 hypersensitivity

Age	Sex	PT (MedDRA ver.21.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to YESCARTA	Outcome
Study ZUMA-1								
6[redacted]	Female	Shock	4	Serious	8	2	No	Resolved
Study J201								
7[redacted]	Male	Anaphylactic reaction	3	Serious	1	1	Yes	Resolved

No fatal hypersensitivity was observed in Study ZUMA-1 or J201.

In Studies ZUMA-1 and J201, the median number of days (range) from administration of YESCARTA to the first onset of hypersensitivity was 7.0 days (1-455 days) and 6.0 days (1-36 days), respectively.

PMDA's view:

Attention should be paid to hypersensitivity associated with YESCARTA because patients treated with YESCARTA experienced Grade ≥3 and serious hypersensitivity. Accordingly, information about the incidence of hypersensitivity and details of the premedication prespecified in clinical studies should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions.

6.R.3.2.7 Hypogammaglobulinaemia

The applicant's explanation about hypogammaglobulinaemia associated with YESCARTA:

Adverse events coded as MedDRA PT "Blood immunoglobulin A abnormal," "Blood immunoglobulin A decreased," "Blood immunoglobulin D decreased," "Blood immunoglobulin E abnormal," "Blood immunoglobulin E decreased," "Blood immunoglobulin G abnormal," "Blood immunoglobulin G decreased," "Blood immunoglobulin M abnormal," "Blood immunoglobulin M decreased," "Hypogammaglobulinaemia," "Immunoglobulins abnormal," "Immunoglobulins decreased," "IgA immunodeficiency," "Selective IgG subclass deficiency," and "IgM immunodeficiency" were classified as hypogammaglobulinaemia and are listed in Table 53.

Table 53. Incidence of hypogammaglobulinaemia or agammaglobulinaemia (Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part] and Study J201)

PT (MedDRA Version 21.0)	Number of patients (%)			
	Study ZUMA-1 n = 108		Study J201 n = 16	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypogammaglobulinaemia or agammaglobulinaemia	17 (15.7)	0	3 (18.8)	2 (12.5)
Hypogammaglobulinaemia	16 (14.8)	0	3 (18.8)	2 (12.5)
Blood immunoglobulin G decreased	2 (1.9)	0	0	0

Table 54 shows characteristics of the patients who experienced Grade ≥3 hypogammaglobulinaemia after being treated with YESCARTA in Study J201.

Table 54. List of patients with Grade ≥3 hypogammaglobulinaemia (Study J201)

Age	Sex	PT (MedDRA Version 21.0)	Grade	Seriousness	Time to onset (days)	Causal relationship to YESCARTA	Outcome
4[redacted]	Male	Hypogammaglobulinaemia	3	Non-serious	46	Yes	Not resolved
		Hypogammaglobulinaemia	3	Non-serious	88	Yes	Not resolved
4[redacted]	Male	Hypogammaglobulinaemia	3	Non-serious	93	Yes	Not resolved

In Studies ZUMA-1 and J201, neither fatal hypogammaglobulinaemia nor serious hypogammaglobulinaemia occurred.

In Studies ZUMA-1 and J201, the median number of days (range) from administration of YESCARTA to the first onset of hypogammaglobulinaemia was 44.0 days (9-448 days) and 93.0 days (46-94 days), respectively.

PMDA's view:

Attention should be paid to hypogammaglobulinaemia associated with YESCARTA because patients treated with YESCARTA experienced Grade ≥3 hypogammaglobulinaemia. Accordingly, information about the incidence of hypogammaglobulinaemia in clinical studies and caution statements should be appropriately presented to healthcare professionals using the package insert, etc. to ensure that serum γ globulin is periodically measured and appropriate measures can be taken in case of hypogammaglobulinaemia.

6.R.3.2.8 TLS

The applicant's explanation about TLS associated with YESCARTA:

Adverse events coded as MedDRA SMQ (narrow) "Tumour lysis syndrome" were classified as TLS. No TLS occurred in Study J201.

In Study ZUMA-1, TLS occurred in 2 patients. Table 55 shows characteristics of the patients who experienced TLS after being treated with YESCARTA.

Table 55. List of patients with TLS
(Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part])

Age	Sex	Primary disease	Clinical stage	Grade	Seriousness	Time to onset (days)	Causal relationship to YESCARTA	Outcome	Remarks
5[redacted]	Male	DLBCL	III	3	Non-serious	90	No	Death	The patient was treated with YESCARTA, experienced TLS after disease progression on Day 84, and died from disease progression on Day 163.
4[redacted]	Male	TFL	III	5	Serious	TLS occurred on the day after conditioning chemotherapy.	No	Death	Death on the day after onset of TLS

PMDA's view:

Attention should be paid to TLS when using YESCARTA because (1) TLS occurred in 1 patient treated with YESCARTA in Study ZUMA-1, although a causal relationship was denied; and (2) it is classified as an event requiring attention in the package insert of tisagenlecleucel, which is a product of anti-CD19 CAR T-cells with the same mechanism of action as that of YESCARTA. Accordingly, information about the incidence of TLS in clinical studies and caution statements should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions to ensure that appropriated measures can be taken in case of TLS.

6.R.3.2.9 Others

6.R.3.2.9.1 Secondary malignant tumor

The applicant's explanation about secondary malignant tumor:

Adverse events related to secondary malignant tumor were identified using the database (data cut-off on April 17, 2020) consisting of the safety information from clinical studies and post-marketing experience with YESCARTA in foreign countries, and are listed in Table 56.

Table 56. List of patients with secondary malignant tumor

Study	Age	Sex	Primary disease	PT*	Grade	Serious/ Non-serious	Time to onset	Causal relationship to YESCARTA
ZUMA-1	6[redacted]	Male	DLBCL	Myelodysplastic syndrome	4	Serious	176 days (42 days after re-administration)	No
	3[redacted]	Female	DLBCL	Myelodysplastic syndrome	4	Serious	120 days	No
	6[redacted]	Male	TFL	Myelodysplastic syndrome	4	Serious	574 days	No
Post-marketing experience in foreign countries	6[redacted]	Female	Unknown	Myelodysplastic syndrome	Unknown	Serious	Unknown	Unknown
	Unknown	Unknown	Unknown	Myelodysplastic syndrome	Unknown	Serious	2 months and 24 days	Unknown
	Unknown	Male	DLBCL	Basal cell carcinoma	Unknown	Serious	Unknown	Unknown
	5[redacted]	Male	DLBCL	Acute leukaemia	Unknown	Serious	Approx. 2 months	Unknown
	6[redacted]	Male	DLBCL	Myelodysplastic syndrome	Unknown	Serious	Approx. 4 months	No

* MedDRA ver. 21.0 for Study ZUMA-1 and MedDRA ver. 22.1 for post-marketing experience in foreign countries

At present, whether YESCARTA increases a risk of secondary malignant tumor remains unclear because (1) many factors (age, genetic predisposition, prior chemotherapy, etc.) are involved in onset of secondary malignant tumor; and (2) the number of patients who experienced secondary malignant tumor after administration of YESCARTA is limited. Accordingly, the relevant information should be continuously collected also in post-marketing settings of YESCARTA.

PMDA's view:
For secondary malignant tumor, a relationship to the primary disease or prior chemotherapy cannot be ruled out, and at present, the relationship to YESCARTA remains unclear. For some of the events, however, a causal relationship to YESCARTA cannot be ruled out. In consideration of this, attention should be paid to secondary malignant tumor, and the relevant information should be continuously collected also in post-marketing settings of YESCARTA.

6.R.4 Clinical positioning and indications or performance

The proposed "Indication or Performance" of YESCARTA was "Relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma, and high grade B-cell lymphoma."

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

- YESCARTA should be used in patients who did not respond to ≥1 line of standard therapy or relapsed after the treatment.
- 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 prior treatment, etc. of patients enrolled in the clinical studies.

PMDA's view:
On the basis of reviews in Sections "6.R.2 Efficacy," "6.R.3 Safety," and the review presented below, the "Clinical Studies" section of the package insert should include details of the prior treatment of the patients enrolled in Studies ZUMA-1 and J201, and the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections of YESCARTA should be specified as shown below:

Indications or Performance (Underline denotes additions or modifications.)
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 transfusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.
- In patients indicated for autologous hematopoietic stem cell transplantation, ≥2 lines of chemotherapy in the newly diagnosed patients and ≥1 line of chemotherapy after relapse in the relapsed patients, which failed to lead to response or result in relapse after the treatment.

Precautions Concerning Indications or Performance (Underline denotes additions. Strikethrough denotes deletion.)
- ~~YESCARTA should be used in patients who did not respond to ≥1 line of standard therapy or relapsed after the treatment.~~
- 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.

6.R.4.1 Clinical positioning and target population of YESCARTA
The Japanese and foreign clinical guidelines include the following description about use of YESCARTA in patients with malignant lymphoma.

Clinical guidelines
- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas (NCCN guideline) (v.4.2020): YESCARTA is recommended for patients with large B-cell lymphoma (including DLBCL not otherwise specified, PMBCL, TFL, and HGBCL) who have ≥2 lines of prior chemotherapy (Category 2A[14)]). Treatment with anti-CD19 CAR T-cells including YESCARTA is recommended for patients indicated for stem cell transplant (SCT) who have achieved partial response to pre-SCT chemotherapy (Category 2A).

The applicant's explanation about clinical positioning and "Indications or Performance" of YESCARTA:
Since results from Studies ZUMA-1 and J201 demonstrated the efficacy and safety of YESCARTA, YESCARTA will be one of the treatment options for the patient population of Studies ZUMA-1 and

14) Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

J201 such as patients with DLBCL, PMBCL, TFL, or HGBCL who have failed to respond to at least 1 line of the standard therapy (refractory) or relapsed after the treatment.

In Studies ZUMA-1 and J201, the inclusion criteria specified that patients who experienced PD or relapse after autologous SCT should be eligible, but patients who relapsed after autologous SCT received ≥2 lines of chemotherapy. Thus, a description about autologous SCT may be omitted because the proposed "Indications or Performance" and "Precautions Concerning Indications or Performance" sections have already implied that such patients are eligible. It is still important that patients who experienced PD or relapse after autologous SCT were the population eligible for clinical studies, and the "Clinical Studies" section of the package insert will include details of prior treatment of the patients enrolled in Studies ZUMA-1 and J201, and the "Precautions Concerning Indications or Performance" section will include 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 prior treatment, etc. of patients enrolled in the clinical studies.

Of 101 patients enrolled in Cohorts 1 and 2 in the phase II part in Study ZUMA-1, 3 patients had received only 1 line of prior chemotherapy, and 98 patients had received ≥2 lines of prior chemotherapy (77 did not respond to ≥2 lines of chemotherapy, 21 experienced relapse after autologous SCT). All of the 16 patients enrolled in Study J201 had received ≥2 lines of prior chemotherapy. PMDA asked the applicant to explain whether YESCARTA can be recommended for patients with only 1 line of prior chemotherapy.

The applicant's explanation:
Table 57 shows details of the 3 patients with only 1 line of prior chemotherapy in Study ZUMA-1. None of the patients had received prior treatment with autologous SCT.

Table 57. List of patients with only 1 line of prior chemotherapy (Study ZUMA-1)

Age	Sex	Primary disease	Stage	Best response	Duration of response (months)	Main adverse events
7[redacted]	Male	DLBCL	IV	PR	2.07	Hypotension (Grade 3) Hypoxia (Grade 3)
5[redacted]	Female	DLBCL	III	PR	1.84	Pyrexia (Grade 3) Anaemia (Grade 3)
5[redacted]	Male	DLBCL	IV	PD	—	Neutropenia (Grade 3)

In the 3 patients with only 1 line of prior chemotherapy, the response rate was 66.7%. In view of this result and the following findings, YESCARTA can be also recommended for patients with only 1 line of prior chemotherapy.

- In Study ZUMA-1, the response rate was 85.7% in the 77 patients who had received ≥2 lines of prior chemotherapy and 76.2% in the 21 patients who had experienced relapse after autologous SCT. These results show that YESCARTA has efficacy irrespective of the number of lines or content of prior therapy.
- In the SCHOLAR-1 study, which is used as an external control of Study ZUMA-1, the response rate was 23.7% in the patients who had received only 1 line of prior chemotherapy. Compared with

this figure, the results from Study ZUMA-1 indicate that YESCARTA can be expected to have efficacy.

Furthermore, the Japanese clinical guidelines recommends that for the patients aged ≤65 years with only 1 line of prior chemotherapy who are indicated for autologous SCT, and if a response is observed as a result of chemotherapy, high-dose chemotherapy in combination with autologous SCT should be then indicated. For the following reasons, however, YESCARTA can be recommended even for the patients with only 1 line of prior chemotherapy who are indicated for autologous SCT. A foreign phase III study (Study ZUMA-7) is ongoing to compare the efficacy and safety of YESCARTA with those of conventional standard therapy, when used as the second line therapy in patients with large B-cell lymphoma (including DLBCL, TFL, and HGBCL) which were refractory to the first-line therapy or relapsed after responding to the first-line therapy.

- The efficacy of currently available therapies is limited for the patients with only 1 line of prior chemotherapy and are indicated for autologous SCT, taking into account that approximately half of such patients have not undergone autologous SCT despite their eligibility, and even high-dose chemotherapy in combination with autologous SCT was effective only in approximately 40% of such patients (*Hematology Am Soc Hematol Educ Program.* 2011;2011:498-505 and *J Clin Oncol.* 2010;28:4184-90).

PMDA's view:
It is mostly acceptable to specify the "Indications or Performance" of YESCARTA on the basis of Studies ZUMA-1 and J201. However, the statement about the tissue type and prior treatment should be modified from those proposed by the applicant based on the following views:

For the tissue type, Studies ZUMA-1 and J201 included patients with DLBCL, PMBCL, TFL, or HGBCL, which are a part of the diseases classified as large B-cell lymphoma according to the WHO classification (revised fourth edition). Transfer from fourth edition to revised fourth edition of the WHO classification has involved many changes, and the histological diagnosis is assumed to be performed based on the revised fourth edition. The "Indications or Performance" section of YESCARTA, therefore, should clarify that the target diseases of YESCARTA are DLBCL, PMBCL, TFL, and HGBCL, which are a part of the diseases classified as large B-cell lymphoma in accordance with the WHO classification (revised fourth edition).

Then, for the patients with only 1 line of prior chemotherapy who are indicated for autologous SCT, at present, YESCARTA cannot be recommended because (1) autologous SCT is recommended after a response to chemotherapy is obtained; and (2) there are no results from clinical studies comparing usefulness between YESCARTA and autologous SCT in such patient. Of the patients indicated for autologous SCT, only patients with the disease relapsed after or refractory to the last therapy who had received ≥2 lines of prior chemotherapy should be eligible for YESCARTA. For the patients with only 1 line of prior chemotherapy who are not indicated for autologous SCT, on the other hand, use of YESCARTA may not have to be restricted in consideration of no therapies recommended in the Japanese clinical guidelines. Information about prior treatment in the target patient population of YESCARTA is considered important. The "Indications or Performance" section should clarify the

population potentially eligible for YESCARTA as "In patients indicated for autologous hematopoietic stem cell transplantation, ≥2 lines of chemotherapy in the newly diagnosed patients and ≥1 line of chemotherapy after the relapse in the relapsed patients, which failed to lead to response or result in relapse after the treatment."

Furthermore, the "Clinical Studies" section of the package insert should include tissue type and details of prior treatment of patients enrolled in Studies ZUMA-1 and J201. The "Precautions Concerning Indications or Performance" section should include the statement to the effect that 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.

6.R.4.2 SCT after administration of YESCARTA

The applicant's explanation about SCT after administration of YESCARTA:
In Study ZUMA-1, at least 6[15)] of the patients enrolled in the phase II part underwent allogeneic SCT. Outcome of the SCT, however, was not reported, and thus the efficacy and safety of SCT after administration of YESCARTA remain unclear.

In Study J201, 3 patients underwent allogeneic SCT (peripheral SCT in all cases) (4 sessions) after administration of YESCARTA. After the transplant, 1 patient was subjected to assessment and assessed to experience PD. In addition, 1 patient died of hepatic veno-occlusive disease 2 months after SCT, but a causal relationship to YESCARTA was denied.

PMDA's view:
At present, information about patients who underwent SCT after administration of YESCARTA is very limited, and thus the relevant information should be continuously collected also in post-marketing settings of YESCARTA.

6.R.4.3 Necessity of confirming CD19 antigen expression before administration of YESCARTA

PMDA asked the applicant to explain the necessity of confirming CD19 antigen expression before administration of YESCARTA.

The applicant's response:
For the following reasons, expression of the CD19 antigen does not have to be confirmed before administration of YESCARTA.

- The following results from Studies ZUMA-1 and J201 show that it is difficult to predict a therapeutic effect of YESCARTA based on findings from a conventional immunohistochemistry (IHC method) performed to confirm the CD19 expression, and patients with the CD19 expression below the detection sensitivity can be expected to respond to YESCARTA.
  - Of 101 patients enrolled in the phase II part of Study ZUMA-1, 82 patients (74 in the CD19 antigen positive population, 8 in the CD19 antigen negative population) were available for an

[15)] In the analysis on progression free survival (PFS), the 6 patients were censored at the event of SCT.

IHC method for expression of the CD19 antigen. In these patients, a relationship between CD19 expression status and efficacy of YESCARTA was retrospectively investigated. The response rate [95% CI] (%) at Month 24 was 86.5 [76.5, 93.3] in the CD19 antigen positive population and 75.0 [34.9, 96.8] in the CD19 antigen negative population, which were similar to the response rate [95% CI] (%) of 83.2 [74.4, 89.9] in all patients in the phase II part. Furthermore, the survival rate [95% CI] (%) at Month 24 estimated by the Kaplan-Meier method was 52.7 [40.8, 63.3] in the CD19 antigen positive population and 62.5 [22.9, 86.1] in the CD19 antigen negative population, which were similar to the estimated survival rate of 50.5 [40.4, 59.7] in all patients in the phase II part.

  - In Study J201, 1 patient negative for CD19 antigen at baseline was enrolled and achieved CR as the best response.

- DLBCL, PMBCL, TFL, and HGBCL to be indicated for YESCARTA are all classified into B-cell lymphoma, which express CD19 (*Clin Cancer Res.* 2011;17:6448-58). In light of this, all patients to be indicated for YESCARTA are deemed positive for CD19 antigen.
- There may be cases where a specimen to confirm expression of the CD19 antigen is not available owing to the extremely serious condition of the patient or difficult-to-access location of the lesion.

PMDA's view:
The above applicant's explanation is understandable. At present, it is considered unnecessary to check expression status of CD19 antigen before administration of YESCARTA. The applicant, however, should continuously explore a scheme to predict the efficacy of YESCARTA beforehand.

6.R.4.4 Use of YESCARTA in patients with prior anti-CD19 CAR T-cell therapy

The applicant's explanation about use of YESCARTA in patients with prior anti-CD19 CAR T-cell therapy other than YESCARTA:
In clinical studies and post-marketing experience with YESCARTA, YESCARTA has not been administered to the concerned patients, and thus the efficacy and safety of YESCARTA in these patients remain unclear.

In general, anti-CD19 CAR T-cell therapy may deprive the patient of the CD19 antigen, and thus YESCARTA is not recommended.

Accordingly, the applicant will appropriately inform healthcare professionals using materials, etc. that YESCARTA is not recommended for the concerned patients owing to the limited clinical experience with YESCARTA.

PMDA's view:
The above applicant's explanation that YESCARTA is not recommended for the concerned patients is acceptable. This content is critical in selecting patients for YESCARTA, and it should be clearly stated not only in the materials but also in the "Indications or Performance" section of YESCARTA.

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

The proposed "Dosage and Administration or Method of Use" of YESCARTA is shown below.

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 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 following lymphodepleting chemotherapy is conducted as pretreatment for 3 consecutive days starting 5 days before administration of YESCARTA.
   Cyclophosphamide 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.
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.

In addition, the proposed "Precautions Concerning Dosage and Administration or Method of Use" section included the following statements:
For the details of a series of the procedures from leukapheresis in the patient to administration of YESCARTA, refer to the manual, etc. provided by the manufacturer.

Pretreatment

1. In order to facilitate the engraftment of transplanted cells, administer chemotherapeutic agents with a cytocidal effects such as DNA synthesis inhibitory activity or with immunosuppressive activity associated with a decrease in lymphocyte count, before administration of YESCARTA. Refer to the "Clinical Studies" section for chemotherapeutic agents used in clinical studies.

Administration

2. Before administration, check the label on the infusion bag of YESCARTA to confirm that the bag is for the patient.
3. If any of the following conditions is observed before administration of YESCARTA, postpone the administration until the concerned condition resolves.
   - Serious adverse drug reactions due to the pretreatment chemotherapy (especially, lung disorder, cardiac disorder, hypotension) occurred and have not resolved.
   - Active infection is observed.
   - Acute or chronic extensive graft-versus-host disease (GVHD) is observed.
4. To alleviate the infusion reaction (pyrexia, chills, nausea, etc.) potentially occurring during administration of YESCARTA, pre-medicate antihistamine and antipyretic analgesic

approximately 1 hour before the administration of YESCARTA. Except for a life-threatening emergency case, do not use corticosteroids. To cope with treatment-emergent severe events such as anaphylaxis, emergency measures should be prepared.

5. To cope with emergency due to cytokine release syndrome, keep tocilizumab (genetical recombination) available for prompt treatment.
6. Place the frozen YESCARTA infusion bag in a constant-temperature water bath or dry thawing device at 37°C until the content completely thaws. Remove the bag from the constant-temperature water bath or dry thawing device immediately after thawing. Do not re-freeze the bag after thawing.
7. If any damage or leakage is observed in the YESCARTA infusion bag, do not use YESCARTA.
8. When discarding the residual fluid of YESCARTA, discard the infusion bag containing the residual content itself as an infectious substance according to the procedure at the medical institution.
9. After thawing of YESCARTA, do not wash the cells. Administer the entire content in the infusion bag.
10. Do not irradiate YESCARTA.
11. Administer YESCARTA using latex-free intravenous tubing without a leukocyte depleting filter.
12. Use physiological saline to prime the intravenous tubing before administration of YESCARTA. After administration of the full volume of YESCARTA, rinse the YESCARTA infusion bag with physiological saline by back priming to ensure that as many cells as possible are administered.
13. Administer YESCARTA over ≥5 minutes and <30 minutes. Once thawed, YESCARTA is stable at room temperature for up to 3 hours.
14. During administration, mix gently the content of the infusion bag to disperse cells.

PMDA's view

On the basis of Sections "6.R.2 Efficacy" and "6.R.3 Safety" as well as the review presented below, the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections of YESCARTA should be specified after modification of these sections as shown below.

Dosage and Administration or Method of Use (Underline denotes additions.)

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 <u>in a refrigerated container maintained at 2°C to 8°C</u> 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 lymphocyte count is confirmed to be ≥100/μL. The following lymphodepleting chemotherapy is conducted as pretreatment for 3 consecutive days starting 5 days before administration of YESCARTA.

Cyclophosphamide 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.

Precautions Concerning Dosage and Administration or Method of Use (Underline denotes additions or modifications. Strikethrough denotes deletion.)

For the details of a series of the procedures from leukapheresis in the patient to administration of YESCARTA, refer to the manual, etc. provided by the manufacturer.

Pretreatment

1. In order to facilitate the engraftment of transplanted cells, administer chemotherapeutic agents with a cytocidal effects such as DNA synthesis inhibitory activity or with immunosuppressive activity associated with a decrease in lymphocyte count, before administration of YESCARTA. ~~Refer to the "Clinical Studies" section for chemotherapeutic agents used in clinical studies.~~

Administration

2. Before administration, check the label on the infusion bag of YESCARTA to confirm that the bag is for the patient.
3. If any of the following conditions is observed before administration of YESCARTA, postpone the administration until the concerned condition resolves.
   - Serious adverse drug reactions due to the pretreatment chemotherapy (especially, lung disorder, cardiac disorder, hypotension) occurred and have not resolved.
   - Active infection is observed.
   - Acute or chronic extensive graft-versus-host disease (GVHD) is observed.
4. To alleviate the infusion reaction (pyrexia, chills, nausea, etc.) potentially occurring during administration of YESCARTA, pre-medicate antihistamine and antipyretic analgesic approximately 1 hour before the administration of YESCARTA. Except for a life-threatening emergency case, do not use corticosteroids. To cope with treatment-emergent severe events such as anaphylaxis, emergency measures should be prepared.
5. To cope with emergency due to cytokine release syndrome, keep tocilizumab (genetical recombination) available for prompt treatment.
6. Place the frozen YESCARTA infusion bag in a constant-temperature water bath or dry thawing device at 37°C until the content completely thaws. Remove the bag from the constant-temperature water bath or dry thawing device immediately after thawing. Do not re-freeze the bag after thawing.
7. If any damage or leakage is observed in the YESCARTA infusion bag, do not use YESCARTA.

8. When discarding the residual fluid of YESCARTA, discard the infusion bag containing the residual content itself as an infectious substance according to the procedure at the medical institution.
9. After thawing of YESCARTA, do not wash the cells. Administer the entire content in the infusion bag.
10. Do not irradiate YESCARTA.
11. Administer YESCARTA using latex-free intravenous tubing without a leukocyte depleting filter.
12. Use physiological saline solution to prime the intravenous tubing before administration of YESCARTA. After administration of the full volume of YESCARTA, rinse the YESCARTA infusion bag with physiological saline solution by back priming to ensure that as many cells as possible are administered.
13. ~~Administer YESCARTA over ≥5 minutes and <30 minutes.~~ Once thawed, YESCARTA is stable at room temperature for up to 3 hours, thus, complete the administration within 3 hours after thawing.
14. During administration, mix gently the content of the infusion bag to disperse cells.

6.R.5.1 Dosage regimen of YESCARTA and conditioning chemotherapy

The applicant's explanation about the rationale for establishing the "Dosage and Administration or Method of Use" of YESCARTA and conditioning chemotherapy:

Dosage regimen of YESCARTA and conditioning chemotherapy

The dosage regimen of YESCARTA and conditioning chemotherapy were established based on those in Studies ZUMA-1 and J201 for the following reasons:

- In Study NCI09-C-0082, multiple cohorts using various conditioning chemotherapies and numbers of anti-CD19 CAR T-cells in combination were conducted to optimize the conditioning chemotherapy and number of anti-CD19 CAR T-cells based on the extent of decreased lymphocyte count by conditioning chemotherapy, development of DLT, and the efficacy information. The safety of the regimen used in Cohorts 13 and 14 was confirmed. The concerned regimen consisted of once-daily intravenous infusion of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 for 3 consecutive days starting 5 days before administration of YESCARTA, followed by a single intravenous administration of anti-CD19 CAR T-cells at 2.0×10^6 cells/kg. Of 13 patients with DLBCL, PMBCL, or TFL who received YESCARTA, 8 patients responded (8 patients achieved CR and 1 patient achieved PR).
- In Study ZUMA-1, which was designed based on results from Study NCI09-C-0082, tolerability was confirmed in patients who received anti-CD19 CAR T-cells at 2.0×10^6 cells/kg (body weight) (for patients weighing ≥100 kg, up to 2×10^8 cells) after the above conditioning chemotherapy, and favorable results were also obtained for the efficacy.
- In Study J201 where conditioning chemotherapy and administration of YESCARTA were conducted using the same dosage regimen as those in Study ZUMA-1, the efficacy and safety in Japanese patients were confirmed as well.

Administration time of YESCARTA

The administration time of YESCARTA was specified as ≤30 minutes in Studies ZUMA-1 and J201, but the "Precautions Concerning Dosage and Administration or Method of Use" section of YESCARTA was specified as ≥5 minutes and <30 minutes.

PMDA asked the applicant to explain the rationale for specifying the administration time of YESCARTA.

The applicant's response:

Although YESCARTA is confirmed to be stable at room temperature for up to 3 hours, the upper limit of the administration time of YESCARTA was specified as within 30 minutes with the ≥5-fold safety margin. In Studies ZUMA-1 and J201, the actual administration time (range) of YESCARTA was 3 to 33 and 7 to 30[16)] minutes, respectively.

In addition, the lower limit of the administration time was specified as ≥5 minutes to prevent a rapid increase of blood concentration of potassium, which is contained in CryoStor CS10, an excipient of YESCARTA.

Conditions for conditioning chemotherapy

In Studies ZUMA-1 and J201, a lymphocyte count of ≥100/μL before conditioning chemotherapy was prerequisite for conditioning chemotherapy. For a patient with a lymphocyte count of <100/μL, if any, the patient's feasibility of conditioning chemotherapy had been confirmed with a medical monitor in the clinical study beforehand.

In Studies ZUMA-1 and J201, all patients who received YESCARTA had presented a lymphocyte count of ≥100/μL. Conditioning chemotherapy, accordingly, has not been conducted in patients with a lymphocyte count of <100/μL, but if YESCARTA is decided to be needed based on comprehensive consideration of the disease progression status and clinical course, conduct of the conditioning chemotherapy should be considered.

Re-administration of YESCARTA

In Studies ZUMA-1 and J201, re-administration of YESCARTA was permitted only when meeting the following criteria: (1) The response lasted for 3 months after the first dose; (2) the relapsed lesion was confirmed to be CD19 positive; (3) the general condition was favorable (none of the exclusion criteria in the corresponding clinical study were met, and adverse drug reactions due to the conditioning chemotherapy resolved); and (4) no neutralizing antibody against YESCARTA was detected.

Re-administration of YESCARTA was conducted in 12 patients in Study ZUMA-1 and in 1 patient in Study J201. Table 58 shows characteristics of the patients who received the re-administration.

16) Time in the patients in Study J201 excluding patient who discontinued Yescarta owing to an adverse event (anaphylactic reaction) when approximately 20% of the cells were administered. The administration time in the concerned patient was 4 minutes.

The number of patients who received re-administration of YESCARTA is limited, and thus the applicant considers that re-administration of YESCARTA is not recommended at present.

Table 58. List of patients re-treated with YESCARTA

Study		Age	Sex	Primary disease	Best response	Main adverse events after re-administration of YESCARTA
ZUMA-1	Phase I part	6[redacted]	Male	DLBCL	PR	Lymphocyte count decreased, white blood cell count decreased, CRS, hyponatraemia, platelet count decreased, pyrexia, hypophosphataemia, and anaemia
	Phase II part	3[redacted]	Male	DLBCL	PR	Lymphocyte count decreased, CRS, FN, neutrophil count decreased, white blood cell count decreased, anaemia, hyperglycaemia, and platelet count decreased
		6[redacted]	Female	DLBCL	SD	Lymphocyte count decreased, white blood cell count decreased, neutrophil count decreased, FN, and hyponatraemia
		5[redacted]	Male	DLBCL	PR	Lymphocyte count decreased, white blood cell count decreased, neutrophil count decreased, anaemia, and platelet count decreased
		7[redacted]	Male	TFL	CR	Lymphocyte count decreased, CRS, hypophosphataemia, white blood cell count decreased, anaemia, FN, neutrophil count decreased, hyponatraemia, and hypertension
		2[redacted]	Male	DLBCL	PD	Clostridium difficile colitis and soft tissue infection
		6[redacted]	Male	DLBCL	CR	Tremor and neutrophil count decreased
		6[redacted]	Male	DLBCL	PR	FN and anaemia
		6[redacted]	Male	DLBCL	CR	Herpes zoster and cholecystitis
		7[redacted]	Male	DLBCL	PD	Hypercalcaemia and mental status changes
		5[redacted]	Female	DLBCL	CR	Neutropenia and cardiac failure
		3[redacted]	Male	PMBCL	PD	Lymphocyte count decreased, white blood cell count decreased, neutropenia, dyskinesia, poor sucking reflex, aphasia, and thrombocytopenia
Study J201		4[redacted]	Male	DLBCL	CR	FN and lymphopenia

PMDA's view:

The above applicant's explanation is understandable. Because not only the clinical experience with re-administration of YESCARTA is limited but also methods to check positive for CD19 on the relapsed lesion and to detect the presence of neutralizing antibody have not been established, the re-administration cannot be recommended at present. The following points should be accommodated in the "Dosage and Administration or Method of Use" section.

- Information on administration time of YESCARTA and that re-administration of YESCARTA is not allowed even after disease aggravation is important. The "Dosage and Administration or Method of Use" section of YESCARTA should clearly state the above information.
- Lymphodepleting chemotherapy should be conducted after confirming the lymphocyte count is ≥100/μL.
- The dose in lymphodepleting chemotherapy may be reduced according to the patient's condition as appropriate.

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

The applicant's explanation about a post-marketing surveillance plan for YESCARTA:

In order to investigate the safety of YESCARTA in clinical use, the applicant plans a post-marketing surveillance covering all patients with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL treated with YESCARTA.

The safety specification in this surveillance includes the following:
(1) Events expected to occur in post-marketing settings based on incidences of adverse events in Studies ZUMA-1 and J201
"CRS," "nervous system event," "infection," "hypogammaglobulinaemia," "cytopenia," "tumor lysis syndrome," "secondary malignant tumor," "aggravation of graft versus host disease (when used in patients with prior allogeneic hematopoietic stem cell transplantation)."
(2) Missing information on YESCARTA
"Use in pregnant and breast feeding women," "onset or aggravation of autoimmune disease," and "long-term safety."

The surveillance will cover 300 patients based on (1) the number of patients expected to receive YESCARTA in post-marketing settings (for 3 years after the market launch of YESCARTA) and (2) the incidences of the above events, as included in the safety specification, in Study ZUMA-1.

The follow-up period of at least 5 years and up to 8 years was established for each patient to evaluate each specification items in this surveillance.

PMDA's view:
Since safety information in Japanese patients treated with YESCARTA is very limited, the applicant should conduct the surveillance covering all patients treated with YESCARTA after the market launch to collect information, and provide the obtained safety information to healthcare professionals without delay.

The safety specification in this all-case surveillance should include "haemophagocytic lymphohistiocytosis" and "hypersensitivity" taking account of the review in Section "6.R.3 Safety."

The planned sample size should be re-considered in light of the above specification, incidences of adverse events in Study J201, and the review in Section "6.R.4 Clinical positioning and indications or performance."

The follow-up period proposed by the applicant is acceptable.

The details of the post-marketing use-results survey will be finalized, taking account of comments on the safety evaluation of YESCARTA raised in the Expert Discussion.

8. Adverse Events Observed in Clinical Studies

Data on deaths reported in clinical studies submitted for safety evaluation are presented in Sections "6.1 Evaluation data" and "6.2 Reference data." Main adverse events other than death are shown below.

8.1 Foreign phase I/II study (Study ZUMA-1)

8.1.1 Phase I part and Cohorts 1 and 2 in the phase II part

Adverse events occurred in all patients, and events for which a causal relationship to YESCARTA could not be ruled out occurred in 107 of 108 patients (99.1%). Table 59 shows adverse events with an all Grade incidence of ≥10%.

Table 59. Adverse events with an incidence of ≥10%
(Study ZUMA-1 [phase I part and Cohorts 1 and 2 in the phase II part])

System organ class Preferred term (MedDRA ver.21.0)	Number of patients (%) n = 108	
	All Grades	Grade ≥3
All adverse events	108 (100)	106 (98.1)
Blood and lymphatic system disorders		
Anaemia	73 (67.6)	49 (45.4)
Neutropenia	48 (44.4)	42 (38.9)
FN	39 (36.1)	35 (32.4)
Thrombocytopenia	38 (35.2)	26 (24.1)
Leukopenia	20 (18.5)	18 (16.7)
Immune system disorders		
Hypogammaglobulinaemia	16 (14.8)	0
Metabolism and nutrition disorders		
Decreased appetite	55 (50.9)	2 (1.9)
Hypocalcaemia	43 (39.8)	7 (6.5)
Hypoalbuminaemia	43 (39.8)	1 (0.9)
Hyponatraemia	38 (35.2)	12 (11.1)
Hypokalaemia	36 (33.3)	3 (2.8)
Hypophosphataemia	31 (28.7)	20 (18.5)
Hyperglycaemia	20 (18.5)	5 (4.6)
Hypomagnesaemia	20 (18.5)	0
Dehydration	13 (12.0)	3 (2.8)
Psychiatric disorders		
Confusional state	29 (26.9)	10 (9.3)
Anxiety	15 (13.9)	1 (0.9)
Insomnia	13 (12.0)	0
Nervous system disorders		
Headache	50 (46.3)	1 (0.9)
Encephalopathy	40 (37.0)	25 (23.1)
Tremor	33 (30.6)	2 (1.9)
Dizziness	23 (21.3)	0
Aphasia	19 (17.6)	8 (7.4)
Somnolence	18 (16.7)	9 (8.3)
Cardiac disorders		
Tachycardia	43 (39.8)	2 (1.9)
Sinus tachycardia	21 (19.4)	0
Vascular disorders		
Hypotension	63 (58.3)	15 (13.9)
Hypertension	17 (15.7)	8 (7.4)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	34 (31.5)	12 (11.1)
Cough	31 (28.7)	0
Dyspnoea	23 (21.3)	2 (1.9)
Pleural effusion	17 (15.7)	2 (1.9)
Gastrointestinal disorders		
Nausea	63 (58.3)	0
Diarrhoea	48 (44.4)	5 (4.6)
Vomiting	37 (34.3)	1 (0.9)
Constipation	32 (29.6)	0
Abdominal pain	16 (14.8)	2 (1.9)
Dry mouth	13 (12.0)	0
Musculoskeletal and connective tissue disorders		
Muscular weakness	17 (15.7)	1 (0.9)
Back pain	16 (14.8)	1 (0.9)
Myalgia	16 (14.8)	1 (0.9)
Pain in extremity	13 (12.0)	0

System organ class Preferred term (MedDRA ver.21.0)	Number of patients (%) n = 108 All Grades	 Grade ≥3
Arthralgia	11 (10.2)	0
General disorders and administration site conditions		
Pyrexia	94 (87.0)	15 (13.9)
Fatigue	57 (52.8)	3 (2.8)
Chills	40 (37.0)	0
Oedema peripheral	21 (19.4)	0
Investigations		
Neutrophil count decreased	36 (33.3)	35 (32.4)
White blood cell count decreased	33 (30.6)	31 (28.7)
Platelet count decreased	32 (29.6)	17 (15.7)
ALT increased	22 (20.4)	6 (5.6)
Lymphocyte count decreased	22 (20.4)	22 (20.4)
AST increased	19 (17.6)	7 (6.5)
Weight decreased	17 (15.7)	0

Serious adverse events occurred in 60 of 108 patients (55.6%). Serious adverse events reported by ≥3 patients were encephalopathy in 20 patients (18.5%), lung infection and pyrexia in 8 patients (7.4%) each, FN and pneumonia in 6 patients (5.6%) each, B-cells lymphoma and confusional state in 5 patients (4.6%) each, aphasia, atrial fibrillation, cardiac arrest, and urinary tract infection in 4 patients (3.7%) each, and acute kidney injury, agitation, ejection fraction decreased, hypotension, hypoxia, and somnolence in 3 patients (2.8%) each. A causal relationship to YESCARTA could not be ruled out for encephalopathy in 20 patients, confusional state in 5 patients, aphasia in 4 patients, ejection fraction decreased, hypoxia, lung infection, and somnolence in 3 patients each, acute kidney injury, agitation, atrial fibrillation, and cardiac arrest in 2 patients each, and FN, hypotension, and pyrexia in 1 patient each.

8.1.2 Cohort 3 in the phase II part

Adverse events occurred in all patients, and events for which a causal relationship to YESCARTA could not be ruled out also occurred in all patients. Table 60 shows adverse events with an all Grade incidence of ≥10%.

Table 60. Adverse events with an incidence of ≥10% (Study ZUMA-1 [Cohort 3 in the phase II part])

System organ class Preferred term (MedDRA ver.21.0)	Number of patients (%) N = 38 All Grades	 Grade ≥3
All adverse events	38 (100)	37 (97.4)
Infections and infestations		
Upper respiratory tract infection	5 (13.2)	0
Candida infection	4 (10.5)	0
Blood and lymphatic system disorders		
Anaemia	21 (55.3)	15 (39.5)
Neutropenia	19 (50.0)	17 (44.7)
Thrombocytopenia	12 (31.6)	10 (26.3)
FN	11 (28.9)	10 (26.3)
Leukopenia	4 (10.5)	2 (5.3)
Metabolism and nutrition disorders		
Decreased appetite	10 (26.3)	0
Hypokalaemia	6 (15.8)	3 (7.9)
Hypomagnesaemia	6 (15.8)	0
Hypophosphataemia	5 (13.2)	0
Hypoalbuminaemia	4 (10.5)	1 (2.6)
Hypocalcaemia	4 (10.5)	0
Psychiatric disorders		
Confusional state	17 (44.7)	5 (13.2)

System organ class Preferred term (MedDRA ver.21.0)	Number of patients (%) N = 38 All Grades	 Grade ≥3
Insomnia	4 (10.5)	0
Anxiety	4 (10.5)	0
Nervous system disorders		
Headache	19 (50.0)	2 (5.3)
Tremor	16 (42.1)	0
Encephalopathy	13 (34.2)	9 (23.7)
Aphasia	8 (21.1)	2 (5.3)
Dizziness	5 (13.2)	0
Somnolence	4 (10.5)	2 (5.3)
Paraesthesia	4 (10.5)	1 (2.6)
Cardiac disorders		
Tachycardia	7 (18.4)	1 (2.6)
Sinus tachycardia	5 (13.2)	0
Vascular disorders		
Hypotension	23 (60.5)	9 (23.7)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	11 (28.9)	5 (13.2)
Cough	9 (23.7)	0
Dyspnoea	5 (13.2)	1 (2.6)
Pleural effusion	5 (13.2)	3 (7.9)
Gastrointestinal disorders		
Diarrhoea	16 (42.1)	1 (2.6)
Nausea	15 (39.5)	0
Vomiting	10 (26.3)	1 (2.6)
Constipation	7 (18.4)	0
Dysphagia	6 (15.8)	4 (10.5)
Abdominal pain	5 (13.2)	1 (2.6)
Musculoskeletal and connective tissue disorders		
Myalgia	5 (13.2)	0
Muscular weakness	4 (10.5)	0
Renal and urinary disorders		
Urinary incontinence	4 (10.5)	1 (2.6)
General disorders and administration site conditions		
Pyrexia	35 (92.1)	3 (7.9)
Fatigue	18 (47.4)	5 (13.2)
Chills	10 (26.3)	0
Oedema peripheral	6 (15.8)	0
Pain	5 (13.2)	1 (2.6)
Gait disturbance	4 (10.5)	1 (2.6)
Investigations		
Neutrophil count decreased	10 (26.3)	8 (21.1)
White blood cell count decreased	10 (26.3)	10 (26.3)
Platelet count decreased	9 (23.7)	8 (21.1)
ALT increased	8 (21.1)	2 (5.3)
AST increased	7 (18.4)	2 (5.3)
Blood alkaline phosphatase increased	4 (10.5)	1 (2.6)
Lymphocyte count decreased	4 (10.5)	4 (10.5)

Serious adverse events occurred in 23 of 38 patients (60.5%). Serious adverse events reported by ≥3 patients were encephalopathy in 7 patients (18.4%), hypotension in 4 patients (10.5%), and B-cell lymphoma in 3 patients (7.9%) A causal relationship to YESCARTA could not be ruled out for encephalopathy in 7 patients and hypotension in 3 patients.

8.2 Japanese phase II study (Study J201)

Adverse events occurred in all patients, and events for which a causal relationship to YESCARTA could not be ruled out also occurred in all patients. Table 61 shows adverse events with an all Grade incidence of ≥10%.

Table 61. Adverse events with an incidence of ≥10% (Study J201)

System organ class Preferred term (MedDRA ver.21.0)	Number of patients (%) n = 16	
	All Grades	Grade ≥3
All adverse events	16 (100)	16 (100)
Infections and infestations		
Nasopharyngitis	3 (18.8)	0
Upper respiratory tract infection	3 (18.8)	0
Blood and lymphatic system disorders		
Anaemia	7 (43.8)	5 (31.3)
FN	7 (43.8)	7 (43.8)
Lymphopenia	6 (37.5)	6 (37.5)
Neutropenia	6 (37.5)	6 (37.5)
Leukopenia	4 (25.0)	4 (25.0)
Thrombocytopenia	4 (25.0)	2 (12.5)
Eosinophilia	2 (12.5)	0
Immune system disorders		
Hypogammaglobulinaemia	3 (18.8)	2 (12.5)
Metabolism and nutrition disorders		
Decreased appetite	9 (56.3)	4 (25.0)
Hyponatraemia	3 (18.8)	1 (6.3)
Hypophosphataemia	3 (18.8)	3 (18.8)
Hypercalcaemia	2 (12.5)	1 (6.3)
Hypoglycaemia	2 (12.5)	0
Hypokalaemia	2 (12.5)	0
Psychiatric disorders		
Insomnia	3 (18.8)	0
Nervous system disorders		
Headache	5 (31.3)	0
Vascular disorders		
Hypotension	3 (18.8)	1 (6.3)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	4 (25.0)	1 (6.3)
Gastrointestinal disorders		
Diarrhoea	8 (50.0)	3 (18.8)
Nausea	8 (50.0)	0
Vomiting	3 (18.8)	0
Hepatobiliary disorders		
Hepatic function abnormal	2 (12.5)	1 (6.3)
Skin and subcutaneous tissue disorders		
Dry skin	2 (12.5)	0
Rash maculo-papular	2 (12.5)	0
General disorders and administration site conditions		
Pyrexia	14 (87.5)	2 (12.5)
Malaise	6 (37.5)	0
Fatigue	2 (12.5)	0
Investigations		
Platelet count decreased	8 (50.0)	8 (50.0)
ALT increased	7 (43.8)	1 (6.3)
AST increased	7 (43.8)	1 (6.3)
Lymphocyte count decreased	7 (43.8)	7 (43.8)
Neutrophil count decreased	7 (43.8)	7 (43.8)
White blood cell count decreased	5 (31.3)	5 (31.3)
Blood creatinine increased	2 (12.5)	0
GGT increased	2 (12.5)	2 (12.5)

Serious adverse events occurred in 13 of 16 patients (81.3%). Serious adverse events reported by ≥2 patients were pyrexia in 11 patients (68.8%), FN and diarrhoea in 3 patients (18.8%) each, and hypotension, hypoxia, and neutrophil count decreased in 2 patients (12.5%) each. A causal relationship to YESCARTA could not be ruled out for pyrexia in 11 patients, diarrhoea in 3 patients, hypotension, hypoxia, and neutrophil count decreased in 2 patients each, and FN in 1 patient.

8.3 Foreign phase I study (Study NCI 09-C-0082 [Cohorts 11-14])

Adverse events occurred in all patients, and events for which a causal relationship to YESCARTA could not be ruled out also occurred in all patients. Table 62 shows adverse events with an all Grade incidence of ≥10%.

Table 62. Adverse events with an incidence of ≥10% (Study NCI 09-C-0082)

	Number of patients (%) n = 13	
	All Grades	Grade ≥3
All adverse events	13 (100)	13 (100)
Blood/bone marrow		
Lymphocyte decreased	13 (100)	13 (100)
Haemoglobin decreased	11 (84.6)	11 (84.6)
Neutrophil decreased	11 (84.6)	11 (84.6)
Platelet decreased	2 (15.4)	2 (15.4)
Cardiac system		
Hypotension	4 (30.8)	3 (23.1)
General symptom		
Pyrexia (without neutrophil decreased)	8 (61.5)	3 (23.1)
Gastrointestinal system		
Dysphagia	2 (15.4)	2 (15.4)
Infection		
Febrile neutropenia	6 (46.2)	6 (46.2)
Nervous system		
Language disorder	11 (84.6)	7 (53.8)
Confusion	6 (46.2)	6 (46.2)
Somnolence/depressed level of consciousness	5 (38.5)	5 (38.5)
Neuropathy: Motor	3 (23.1)	1 (7.7)
Mental disease	3 (23.1)	2 (15.4)
Tremor	3 (23.1)	0
Cognitive disorder	2 (15.4)	2 (15.4)

Serious adverse events occurred in 10 of 13 patients (76.9%). Serious adverse events reported by ≥2 patients were language disorder in 8 patients (61.5%), confusion in 6 patients (46.2%), somnolence/depressed level of consciousness in 5 patients (38.5%), febrile neutropenia in 4 patients (30.8%), hypotension and neuropathy (motor) in 3 patients (23.1%) each, and cognitive disorder and dysphagia in 2 patients (15.4%) each. A causal relationship to YESCARTA could not be ruled out for language disorder in 8 patients, confusion in 6 patients, somnolence/depressed level of consciousness in 5 patients, hypotension and neuropathy (motor) in 3 patients each, and cognitive disorder and dysphagia in 2 patients each.

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 new regenerative medical product application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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.

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

The new regenerative medical product application data (CTD 5.3.5.2-2) 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.

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 large B-cell lymphoma," and that YESCARTA has acceptable safety in view of its benefits. PMDA considers that making YESCARTA available in clinical practice is meaningful because it offers a new treatment option for patients with DLBCL, PMBCL, TFL, and HGBCL.

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 13, 2020

Product Submitted for Approval

Brand Name	YESCARTA Intravenous Drip Infusion
Non-proprietary Name	Axicabtagene ciloleucel
Applicant	Daiichi Sankyo Company, Limited
Date of Application	March 30, 2020

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 investigator-assessed response rate, the primary endpoint, exceeded the predefined efficacy criterion in Studies ZUMA-1 and J201 in patients with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL, and therefore that YESCARTA was shown to have a certain level of efficacy in patients with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL.

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 are CRS, haemophagocytic lymphohistiocytosis, neurologic toxicity, infection, myelosuppression, hypersensitivity, hypogammaglobulinaemia, and TLS. Attention should be paid to these adverse events when YESCARTA is used.

In addition, 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 DLBCL, PMBCL, TFL, and HGBCL at medical institutions 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 and indications or performance

As a result of the review in Section "6.R.4 Clinical positioning and indications or performance" of the Review Report (1), PMDA has concluded that the details of prior treatment, etc. of patients enrolled in Studies ZUMA-1 and J201 should be included in the "Clinical Studies" section of the package insert, and the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections of YESCARTA should be established as described in the corresponding sections of the Review Report (1). PMDA, however, considered that the "Indications or Performance" section should include the clear statement to the effect that YESCARTA might be indicated for patients who are not indicated for autologous hematopoietic stem cell transplantation and thus has concluded that the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections of YESCARTA should be specified after modifying as follows:

Indications or Performance

The following relapsed or refractory large B-cell lymphoma classified:

- 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 transfusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.
- Patients who are indicated for autologous hematopoietic stem cell transplantation, have failed to respond with ≥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 not indicated for autologous hematopoietic stem cell transplantation.

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 modify the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections as described above. As the applicant appropriately responded to the request, 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" and

"Precautions Concerning Dosage and Administration or Method of Use" sections should be established as described in the corresponding sections of the Review Report (1).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion, and also the following comments were raised:

- The condition of lymphodepleting chemotherapy conducted as pretreatment is limited to a lymphocyte count of ≥100/μL, but such condition is barely supported by scientific evidence.
- Depending on the patient's general condition, lymphodepleting chemotherapy should not be conducted from a viewpoint of the safety irrespective of the lymphocyte count.

Taking account of the above comments on lymphodepleting chemotherapy and aggravation of graft versus host disease (GVHD) in Section "1.5 Post-marketing surveillance plan (draft)" from the expert advisors, PMDA has concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections should be specified after modifying, as presented below. In addition, the "Clinical Studies" section of the package insert should include that lymphodepleting chemotherapy was conducted after confirming that the lymphocyte count was ≥100/μL in clinical studies.

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.

Precautions Concerning Dosage and Administration or Method of Use

For the details of a series of the procedures from leukapheresis in the patient to administration of YESCARTA, refer to the manual, etc. provided by the manufacturer.

Pretreatment

1. In order to facilitate the engraftment of the transplanted cells, administer chemotherapeutic agents with a cytocidal effects such as DNA synthesis inhibitory activity or with immunosuppressive activity associated with a decrease in lymphocyte count, before administration of YESCARTA. Refer to the "Clinical Studies" section for pretreatment in clinical studies.

Administration

2. Before administration, check the label on the infusion bag of YESCARTA to confirm that the bag is for the patient.
3. If any of the following conditions is observed before administration of YESCARTA, postpone the administration until the concerned condition resolves.
   - Serious adverse drug reactions due to the pretreatment chemotherapy (especially, lung disorder, cardiac disorder, hypotension) occurred and have not resolved.
   - Active infection is observed.
4. To alleviate the infusion reaction (pyrexia, chills, nausea, etc.) potentially occurring during administration of YESCARTA, pre-medicate antihistamine and antipyretic analgesic approximately 1 hour before the administration of YESCARTA. Except for a life-threatening emergency case, do not use corticosteroids. To cope with treatment-emergent severe adverse events such as anaphylaxis, emergency measures should be prepared.
5. To cope with emergency due to cytokine release syndrome, keep tocilizumab (genetical recombination) available for prompt treatment.
6. Place the frozen YESCARTA infusion bag in a constant-temperature water bath or dry thawing device at 37°C until the content completely thaws, Remove the bag from the constant-temperature water bath or dry thawing device immediately after thawing. Do not refreeze the bag after thawing.
7. If any damage or leakage is observed in the YESCARTA infusion bag, do not use YESCARTA.
8. When discarding the residual fluid of YESCARTA, discard the infusion bag containing the residual content itself as an infectious substance according to the procedure at the medical institution.
9. After thawing of YESCARTA, do not wash the cells. Administer the entire content in the infusion bag.
10. Do not irradiate YESCARTA.
11. Administer YESCARTA using latex-free intravenous tubing without a leukocyte depleting filter.
12. Use physiological saline solution to prime the intravenous tubing before administration of YESCARTA. After administration of the full volume of YESCARTA, rinse the YESCARTA infusion bag with physiological saline solution by back priming to ensure that as many cells as possible are administered.
13. Once thawed, YESCARTA is stable at room temperature for up to 3 hours, thus, complete the administration within 3 hours after thawing.

14. During administration, mix gently the content of the infusion bag to disperse cells.

PMDA requested the applicant to modify the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections as described above. As the applicant appropriately responded to the request, PMDA accepted.

1.5 Post-marketing surveillance plan (draft)

At the time of proposal, the applicant proposed a plan of post-marketing surveillance covering all patients treated with YESCARTA in order to evaluate the safety of YESCARTA in clinical use. The planned sample size was 300 with the observation period of up to 8 years.

As a result of the review in Section "7. Data Relating to Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), PMDA has concluded that "haemophagocytic lymphohistiocytosis" and "hypersensitivity" should be added as a safety specification in the post-marketing surveillance plan; and the planned sample size should be re-considered in view of the range of patients indicated for YESCARTA.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion, and also the following comments were raised:

- Concerning the safety specification of "aggravation of graft versus host disease (GVHD) (when used in patients with prior allogeneic hematopoietic stem cell transplantation)," YESCARTA was not used in patients with prior allogeneic hematopoietic stem cell transplantation in Study ZUMA-1 or J201, and thus it is not considered to be recommended for such patients. In light of this, YESCARTA is unlikely to be used in such patients, and thus the concerned item is not appropriate for the safety specification.

In view of the above discussion and the following explanation presented by the applicant, PMDA has concluded that the post-marketing surveillance provided in Table 63 should be conducted.

Major corrections

- "Haemophagocytic lymphohistiocytosis" and "hypersensitivity" are added as the safety specification, and "aggravation of graft versus host disease (when used in patients with prior allogeneic hematopoietic stem cell transplantation)" is removed.
- The planned sample size for the surveillance was reconsidered taking the range of patients indicated for YESCARTA into account, and the number of patients expected to receive YESCARTA in post-marketing settings was considered to remain almost unchanged. The planned sample size is therefore 300.

Table 63. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the safety 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 DLBCL, TFL, PMBCL, or HGBCL
Observation period	Up to 8 years
Planned sample size	300 patients
Main survey items	Safety specification 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

1.6 Others

1.6.1 Designation of specified regenerative medical product

On the basis of "Principles for designation of biological products, specified biological products, and specified regenerative medical products" (PFSB/ELD Notifications No. 1105-1 and 1105-2 dated November 5, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare), PMDA has concluded that YESCARTA need not be designated as a specified regenerative medical product for the following reasons:

- All the human- or animal-derived materials used in manufacture of YESCARTA, except for FBS used in generation of the MCB for manufacture of the viral vector, conformed to the Standard for Biological Ingredients, with a resultant extremely low risk of causing infection.
- Concerning FBS used in generation of the MCB for manufacture of the viral vector, the viral risk attributable to the concerned raw material cannot be completely ruled out, but it is extremely low and acceptable, as reviewed in Section "2.R.1 Viral risk derived from FBS used in generation of MCB of viral vector" of the Review Report (1).

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the 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. Because the product is classified as an orphan regenerative medical product, the re-examination period should be 10 years. The product need not be designated as a specified regenerative medical product.

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 transfusion of chimeric antigen receptor-expressing T-cells targeted at CD19 antigen.

- Patients who are indicated for autologous hematopoietic stem cell transplantation, have failed to respond with ≥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 not indicated for autologous hematopoietic stem cell transplantation

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.

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

Ad	adenovirus
ALT	alanine aminotransferase
Anti-CD19 CAR	Anti-CD19 chimeric antigen receptor
Application	Application for marketing approval
AST	aspartate aminotransferase
BAV	bovine adenovirus
BPV	bovine parvovirus
BRSV	bovine respiratory syncytial virus
BSA	bovine serum albumin
BSE	bovine spongiform encephalopathy
BTV	bluetongue virus
BT-cells	Bovine turbinate cells
BVDV	bovine viral diarrhea virus
CAR	chimeric antigen receptor
CCDS	Company Core Data Sheet
CCR7	C-chemokine receptor-7
CD	cluster of differentiation
CFSE	carboxyfluorescein diacetate succinimidyl ester
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMTMR	5-(and-6)-(((4-chloromethyl)benzoyl)amino) tetramethylrhodamine
CMV	cytomegalovirus
Component cells	Cells serving as a component of the product
Cyclophosphamide	Cyclophosphamide Hydrate
CQA	critical quality attribute
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	data safety monitoring board
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme linked immunosorbent assay
EPC	end of production cell
EVA	ethylene vinyl acetate
FBS	fetal bovine serum
FL	follicular lymphoma
Fludarabine	Fludarabine Phosphate
FN	febrile neutropenia
GALV	gibbon ape leukemia virus
[redacted]	[redacted]
GGT	gamma-glutamyltransferase
GM-CSF	granulocyte macrophage-colony stimulating factor
HBV	hepatitis B virus

HCV	hepatitis C virus
HGBCL	high grade B-cell lymphoma
HHV	human herpes virus
HIV	human immunodeficiency virus
HLGT	high level group terms
HTLV	human T-cell leukemia virus
ICU	intensive care unit
IFN-γ	interferon-gamma
Ig	immunoglobulin
IHC method	immunohistochemistry
IL	interleukin
IWG	International Working Group
JC	John Cunningham
Kite	Kite Pharma, Inc.
LTR	long terminal repeat
MCB	master cell bank
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
MIP	macrophage inflammatory protein
[redacted]	[redacted]
MoMLV	moloney murine leukemia virus
MRC-5 cells	Human fetal lung fibroblasts
MSCV	murine stem cell virus
NCCN	National Comprehensive Cancer Network
NCCN guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas
NCI	National Cancer Institute
NGFR	nerve growth factor receptor
NHL	non-Hodgkin lymphoma
NIH3T3 cells	Mouse embryonic fibroblasts
[redacted]	[redacted]
[redacted]	[redacted]
OIE	International Epizootic Office
OS	overall survival
PAV	porcine adenovirus
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PI3	parainfluenza-3
PMBCL	primary mediastinal large B-cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
PPV	porcine parvovirus
PR	partial response
PS	performance status
PT	preferred term
QbD	quality by design
QOL	quality of life

qPCR	quantitative polymerase chain reaction
RABV	rabies virus
RCR	replication competent retrovirus
REO	reo virus
[redacted]	[redacted]
scFv	single-chain variable fragment
SCT	stem cell transplant
SD	stable disease
sFAS	soluble FAS (receptor)
sFASL	soluble FAS ligand
SMQ	standardised MedDRA queries
Study J201	Study KTEC19-A-J201
Study ZUMA-1	Study KTE-C19-101
SV40	simian virus 40
Tocilizumab	Tocilizumab (Genetical Recombination)
TFL	transformed follicular lymphoma
TGEV	transmissible gastroenteritis virus
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
Vero cells	African green monkey kidney epithelial cells
WCB	working cell bank
WHO	World Health Organization
YESCARTA	YESCARTA Intravenous Drip Infusion