February 20, 2019

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

Report on the Deliberation Results

Classification	Human cellular/tissue-based products 1. Human somatic cell processed product
Non-proprietary Name	Tisagenlecleucel
Brand Name	Kymriah Suspension for Intravenous Infusion
Applicant	Novartis Pharma K.K.
Date of Application	April 23, 2018 (Application for marketing approval)

Results of Deliberation

In the meeting held on February 20, 2019, the Committee on Regenerative Medicine 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 conditions of approval must be satisfied.

Conditions of Approval

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. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Review Report

February 4, 2019
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	Kymriah Suspension for Intravenous Infusion
Classification	Human cellular/tissue-based products 1. Human somatic cell processed product
Non-proprietary Name	Tisagenlecleucel
Applicant	Novartis Pharma K.K.
Date of Application	April 23, 2018

Shape, Structure, Ingredients, Quantities, or Definition

The product (a regenerative medical product) is autologous T cells transduced with recombinant lentiviral vector containing a transgene encoding chimeric antigen receptor that specifically recognizes CD19.

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	Orphan regenerative medical product (Orphan Regenerative Medicine Designation No. 3 of 2016 [*28 sai*]*;* PSEHB/ELD/OMDE Notification No. 0525-1 dated May 25, 2016, by the Office of Medical Device Evaluation, Evaluation and Licensing 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 a certain level of efficacy in the treatment of relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia and relapsed or refractory CD19-positive diffuse 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

1. Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. Kymriah should be used only in patients meeting any of the following criteria:
   - Newly diagnosed patients who failed to achieve remission with ≥2 lines of standard chemotherapy.
   - Patients with relapsed disease who failed to achieve remission with ≥1 line of chemotherapy.
   - Patients who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.

2. Relapsed or refractory CD19-positive diffuse large B-cell lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are ineligible for, or relapsed after, autologous hematopoietic stem cell transplantation:
   - Newly diagnosed patients who failed to achieve a complete response to ≥2 lines of chemotherapy; newly diagnosed patients who achieved a complete response to ≥2 lines of chemotherapy but subsequently relapsed; patients who received ≥1 line of chemotherapy after relapse but failed to achieve a complete response; or patients who received ≥1 line of chemotherapy after relapse and achieved a complete response but subsequently relapsed again.
   - Patients with diffuse large B-cell lymphoma transformed from follicular lymphoma who failed to achieve a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation, or who achieved a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation but subsequently relapsed.

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 including sufficient T-lymphocytes are collected.

2. Cryopreservation of leukapheresis material
   The leukapheresis material is prepared immediately after collection, and cryopreserved in the vapor phase of liquid nitrogen.

3. Transportation of leukapheresis material
   The cryopreserved leukapheresis material is packed and transported to the manufacturing facility of Kymriah.

Process from acceptance at the medical institution to administration of Kymriah

4. Receipt and storage of Kymriah

Kymriah is received in a frozen condition, and cryopreserved in the vapor phase of liquid nitrogen until immediately before use.

5. Pretreatment before administration of Kymriah

If the peripheral white blood cell count exceeds 1000/μL within 1 week prior to the planned administration of Kymriah, conduct the following lymphodepleting chemotherapy as pretreatment at least 2 days before the administration. The period between pretreatment chemotherapy and administration of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition.

(1) Lymphodepleting chemotherapy for patients with relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia

1) Cyclophosphamide hydrate at 500 mg/m^2 is infused intravenously once daily for 2 days and fludarabine phosphate at 30 mg/m^2 is infused intravenously once daily for 4 days. The dose may be reduced according to the patient's condition.

2) For patients with a history of Grade 4[Note)] hemorrhagic cystitis due to cyclophosphamide hydrate or patients resistant to cyclophosphamide hydrate:
Cytarabine at 500 mg/m^2 is infused intravenously once daily for 2 days and etoposide at 150 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.

(2) Lymphodepleting chemotherapy for patients with relapsed or refractory CD19-positive diffuse large B-cell lymphoma

1) Cyclophosphamide hydrate at 250 mg/m^2 is infused intravenously once daily for 3 days and fludarabine phosphate at 25 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.

2) For patients with a history of Grade 4[Note)] hemorrhagic cystitis due to cyclophosphamide hydrate or patients resistant to cyclophosphamide hydrate:
Bendamustine hydrochloride at 90 mg/m^2 is infused intravenously once daily for 2 days. The dose may be reduced according to the patient's condition.

Note) The Grade is according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

6. Administration of Kymriah

Kymriah is thawed immediately before administration, and intravenously administered as a single dose as described below according to the patient's disease.

(1) Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia

The usual dosage for patients aged ≤25 years (at the time of administration) is determined according to body weight (see below) and administered as a single intravenous dose.

- Body weight ≤50 kg: CAR-positive viable T cells at 0.2×10^6 to 5.0×10^6/kg.
- Body weight >50 kg: CAR-positive viable T cells at 0.1×10^8 to 2.5×10^8 (irrespective of body weight).

(2) Relapsed or refractory CD19-positive diffuse large B-cell lymphoma
The usual adult dosage is 0.6×10^8 to 6.0×10^8 (irrespective of body weight) of CAR-positive viable T cells administered as a single intravenous dose.

Conditions of Approval

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. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Attachment

Review Report (1)

December 19, 2018

Product Submitted for Approval

Brand Name	Kymriah Suspension for Intravenous Infusion
Classification	Human somatic cell processed product
Non-proprietary Name	To be determined
Applicant	Novartis Pharma K.K.
Date of Application	April 23, 2018

Shape, Structure, Ingredients, Quantities, or Definition

The product (a regenerative medical product) is autologous T cells transduced with recombinant lentiviral vector containing a transgene encoding chimeric antigen receptor that specifically recognizes CD19.

Proposed Indications or Performance

Relapsed or refractory CD19-positive diseases below:

1. B-cell acute lymphoblastic leukemia
2. Diffuse large 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 including sufficient T-lymphocytes are collected.

2. Cryopreservation of leukapheresis material
   The leukapheresis material is prepared immediately after collection, and cryopreserved in the vapor phase of liquid nitrogen.

3. Transportation of leukapheresis material
   The cryopreserved leukapheresis material is packed and transported to the manufacturing facility of Kymriah.

Process from acceptance at medical institution to infusion of Kymriah

4. Receipt and storage of Kymriah
   Kymriah is received in a frozen condition, and cryopreserved in the vapor phase of liquid nitrogen until immediately before use.

5. Pretreatment before infusion of Kymriah

The period between pretreatment chemotherapy and infusion of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition.

6. Infusion of Kymriah

Kymriah is thawed immediately before infusion, and administered intravenously as a single dose as described below according to the patient's disease.

- Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia

  The usual dosage for patients aged ≤25 years (at the time of infusion) is selected from the following doses according to body weight and infused as a single intravenous dose:

  - Body weight ≤50 kg: CAR-positive viable T cells at 0.2 to 5.0 × 10^6/kg.
  - Body weight >50 kg: CAR-positive viable T cells at 0.1 to 2.5 × 10^8 (irrespective of body weight).

- Relapsed or refractory CD19-positive diffuse large B-cell lymphoma

  The usual adult dosage is 0.6 to 6.0 × 10^8 (irrespective of body weight) of CAR-positive viable T cells infused 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

Kymriah (tisagenlecleucel), a regenerative medical product, is comprised of cultured autologous peripheral T cells that have been transduced with recombinant lentiviral vector containing a chimeric antigen receptor (CAR) that specifically recognizes CD19. Kymriah is infused intravenously into the patient to obtain a therapeutic effect based on the pharmacological action, in the same manner as drugs.

Kymriah is comprised of genetically modified T cells that have been reprogrammed to include a CAR protein, which consists of a murine single-chain variable fragment (scFv) specifically recognizing CD19, a human CD8α hinge and transmembrane domain, and CD3-ζ and 4-1BB intracellular signaling domains. When recognizing CD19-expressing cells, CAR protein transmits an intracellular signal that drives the genetically modified T cell to proliferate and activate themselves, attack the target cells, and survive. Through these actions, Kymriah is expected to have the long-lasting capability of killing CD19-positive B-cell tumor cells.

Kymriah was designated as an orphan regenerative medical product with the intended indication or performance for treatment of "CD19-positive B-cell acute lymphoblastic leukemia" and "CD19-positive diffuse large B-cell lymphoma" on May 25, 2016 (Orphan Regenerative Medical Product Designation No. 3 of 2016 [*28 sai*]).

1.2 Development history etc.

1.2.1 Development of tisagenlecleucel for treatment of B-ALL in children and adolescents and young adults (AYA) generation

Outside Japan, a phase I/IIa study (Study CTL019B2101J [Study B2101J]) in pediatric and AYA patients with relapsed or refractory acute B-cell lymphoblastic leukemia (B-ALL) was initiated in March 2012 by the University of Pennsylvania (Penn). Then, the applicant concluded a license agreement about development of tisagenlecleucel with Penn. The applicant initiated a foreign phase II study (Study CTL019B2205J [Study B2205J]) in pediatric and AYA patients with relapsed or refractory B-ALL or B-cell lymphoblastic lymphoma in August 2014, and a global phase II study (Study CTL019B2202 [Study B2202]) in pediatric and AYA patients with relapsed or refractory B-ALL in April 2015.

In the US, an application for tisagenlecleucel for treatment of B-ALL based mainly on results from Study B2202 was submitted in February 2017. In August 2017, tisagenlecleucel was approved in the US for the following indication or performance: "KYMRIAH is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of: Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse." In the EU, an application for tisagenlecleucel based mainly on results from Study B2202 was submitted in November 2017. In August 2018, tisagenlecleucel was approved in the EU for the following indication or performance: "Kymriah is indicated for the treatment of: Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse."

As of October 2018, tisagenlecleucel has been approved for the indication or performance of treatment of B-ALL in pediatric and AYA patients in Canada and Switzerland in addition to the US and EU.

In Japan, the applicant started to enroll patients in Study B2202 in [redacted] 20[redacted].

In Japan, the applicant has submitted the present application for tisagenlecleucel based mainly on results from Study B2202.

1.2.2 Development of tisagenlecleucel for treatment of DLBCL

Outside Japan, in March 2014 Penn initiated a phase IIa study (Study CTL019A2101J [Study A2101J]) in adult patients with relapsed or refractory non-Hodgkin lymphoma (NHL) who were aged ≥18 years. In July 2015, the applicant initiated a global phase II study (Study CTL019C2201 [Study C2201]) in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who were aged ≥18 years.

In the US, an application for tisagenlecleucel for treatment of DLBCL based mainly on results from Study C2201 was submitted in October 2017. In May 2018, tisagenlecleucel was approved in the US for the following indication or performance: "KYMRIAH is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of: Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma." In the EU, an application for tisagenlecleucel based mainly on results from Study C2201 was submitted in November 2017. In August 2018, tisagenlecleucel was approved in the EU for the following indication or performance: "Kymriah is indicated for the treatment of: Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy."

As of October 2018, tisagenlecleucel has been approved for the indication or performance of treatment of DLBCL in Canada and Switzerland in addition to the US and EU.

In Japan, Study C2201 started to enroll patients in [redacted] 20[redacted].

In Japan, the applicant has submitted the present application for tisagenlecleucel based mainly on results from Study C2201.

2. Data Relating to Manufacturing Process and Specifications and Outline of the Review Conducted by PMDA

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

The manufacturing process of tisagenlecleucel consists of preparation of viral vector, preparation of genetically modified cells, and formulation.

2.1 Viral vector

The gene transfer vector is a lentiviral vector that is derived from human immunodeficiency virus-1 (HIV-1) and has genetically modified self-inactivating (SIN) long terminal repeat (LTR), which deprives the vector from replication competence. The anti-CD19 chimeric antigen receptor (αCD19CAR) gene transferred by the viral vector includes sequences encoding the scFv region of the anti-CD19 mouse monoclonal antibody (mouse hybridoma cell line FMC63), human CD8α hinge and transmembrane domain, and human CD3-ζ and 4-1BB intracellular signaling domains.

2.1.1 Viral vector system

The viral vector is derived from the wild-type HIV-1 genome but defective in *tat*, *vif*, *vpr*, *vpu*, *env*, and *nef*. Components required for production of the viral vector were divided into 4 plasmid vectors (i.e., Gag/Pol packaging component, Env packaging component, Rev packaging component, and viral vector component containing the αCD19CAR expression cassette), in order to minimize homologous recombination to prevent the emergence of a replication competent lentivirus (RCL). A gene encoding the vesicular stomatitis virus g protein (VSV-G) was used in the Env packaging component, to improve vector particle stability and ensure a broad vector tropism.

2.1.2 Plasmids

2.1.2.1 Generation and control of cell substrate for production of plasmids

Under control of [redacted], gene sequences each expressing Gag/Pol, Env, Rev, or αCD19CAR were prepared and inserted in cloning vectors to prepare 4 gene expression constructs. These expression constructs were transfected into *Escherichia coli* (Stbl3 strain). Among clones obtained from the transformed *Escherichia coli* cultures, clones with the target phenotype were selected. These *Escherichia coli* clones were used to generate master cell banks (MCBs) of the plasmid vectors.

Characterization and control tests of the MCBs were performed in terms of host cell identity, host cell purity, bacteriolytic phage, [redacted], DNA uniformity, identification, restriction mapping, plasmid sequences, viability rate, and plasmid retention rate. The MCBs were confirmed to meet the standards.

2.1.2.2 Control of plasmids

The control items of the plasmids include [redacted], [redacted], [redacted], [redacted], [redacted], bacteria endotoxin, [redacted], and bioburden.

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

The viral vector is produced using 293T cells (i.e., human embryo kidney 293 [HEK293] cells expressing Simian Virus 40 [SV40] large T antigen). 293T cells (SD-3515; [redacted]) obtained from the American Type Culture Collection (ATCC) were used to generate MCB and working cell bank (WCB).

The MCB and WCB 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 in the vapor phase of liquid nitrogen. A new MCB will not be prepared, but a new WCB will be prepared as necessary.

Table 1. Tests for adventitious agents

In vivo virus tests (suckling mice, adult mice, guinea pigs, and embryonated eggs)
In vitro virus tests (Vero cells, MRC-5 cells, HeLa cells, and HEK293 cells)
In vitro bovine virus tests (BVDV, BAV, BPV, IBR, and PI3)
In vitro porcine virus tests (PPV)
Transmission electron microscopy
Reverse transcriptase activity test
Porcine circovirus (types 1 and 2) test
Bovine polyoma virus tests
Adeno-associated virus (types 1, 2, 3B, 4, and 6) test
Human virus tests (CMV, EBV, HIV-1, HIV-2, HTLV-1, HTLV-2, HHV-6, HHV-7, HHV-8, BKV, JCV, HBV, SV40, PVB19, HSV-1, HSV-2, HAV, HCV, HBoV, KIPyV, and WUPyV)
Sterility
Mycoplasma test

2.1.4 Manufacturing process of viral vector

The manufacturing process of the viral vector consists of thawing of WCB, cell culture, plasmid transfection, [redacted], harvest, clarification, [redacted], [redacted] chromatography, [redacted], [redacted]/ultrafiltration, [redacted], [redacted], sterile filtration, [redacted], filling, storage, and testing.

Critical steps include [redacted].

Process validation of the manufacturing process of the viral vector has been implemented at the commercial production scale.

2.1.5 Safety evaluation of adventitious agents in the viral vector

Table 2 shows raw materials of biological origin other than 293T cells used in the manufacturing process of the viral vector.

Fetal bovine serum (FBS) is prepared from blood from healthy cattle born in New Zealand or Australia, subjected to gamma-irradiation for inactivation of possible pathogens, and tested for adventitious bovine viruses, bacterial endotoxins, sterility, and mycoplasma.

Casein hydrolysate is prepared from milk from healthy cattle born in New Zealand or Australia, and filtered and sterilized by heat treatment before use.

Table 2. Raw materials of biological origin other than 293T cells

Raw material name	Animal	Material	Process
FBS	Cattle	Blood	[redacted]
Casein hydrolysate	Cattle	Milk	[redacted]

Unpurified bulk harvest after end of production culture of the viral vector or end of production cell bank (EoPC) is subjected to tests for adventitious agents shown in Table 3 for each production batch. The tests shown in Table 3 (except for bioburden) are also used as specification for the viral vector [see Section 2.R.1].

Table 3. Control items for adventitious agents in unpurified bulk harvest of the viral vector and EoPC

Adventitious virus tests (*in vitro* virus tests [Vero cells, MRC-5 cells, and HEK293 cells])
Bovine virus tests (CPE and HAD [BT cells and Vero cells], immunofluorescent staining [BAV, BPV, BRSV, BTV, BVDV, Reo3, and Rabies])
Mycoplasma
Bioburden
RCL test ([redacted] test on [redacted] after coculture with [redacted] cells)

2.1.6 Manufacturing process development of viral vector

Tables 4 and 5 show main changes in the development process of the viral vector. The viral vector manufactured by Process X is used for the product to be marketed.

In association with these changes of genes and manufacturing process of the viral vector, the quality attributes of the pre- and post-change viral vector were compared and shown to be comparable.

The manufacturing process development employs Quality by Design (QbD) concept.

Table 4. Development of viral vector

Manufacturing process	Intended use	Characteristics of genetical modifications, etc.
Process [redacted]	Pharmacology studies	[redacted]
Process [redacted]	Safety, pharmacokinetics, pharmacology, and clinical studies	[redacted]
Process [redacted]	Clinical studies	[redacted]
Process X	Clinical studies and marketing	[redacted] SIN-type lentiviral vector 4-plasmid vector system (transgene, Gag/Pol, Rev, and VSV-G), [redacted], codon-optimized Gag/Pol, [redacted]

Table 5. Changes of manufacturing process of viral vector

Manufacturing process	Changes, etc.
From Process [redacted] to Process X	Changes of [redacted], [redacted], [redacted], [redacted], and [redacted] as well as addition of [redacted]
Process X	Addition of [redacted]

2.1.7 Characterization of viral vector

2.1.7.1 Structure and characterization

Characterization was performed as shown in Table 6.

Table 6. Characterization items

Tests on viral vector	Vector concentration [redacted], vector particles ([redacted] copy number), [redacted] titer, vector particle to infectivity ratio, [redacted] titer, MOI, total residual DNA, host cell DNA, plasmid DNA, [redacted], host cell protein, [redacted], residual BSA, [redacted], mycoplasma, *in vitro* virus, bovine virus, RCL, bioburden, bacterial endotoxin [redacted]
Tests on genetically modified component cells	Cytotoxicity of αCD19CAR-expressing T cells, cytotoxicity of CTL019-transgenic T cells, cytokine production of αCD19CAR-expressing T cells, proliferation and survival of αCD19CAR-expressing T cells, *in vitro* proliferation study of αCD19CAR-expressing T cells and gene insertion site analysis of viral vector [see Sections 4.1.1, 6.2.1, and 6.2.3].

2.1.7.2 Process-related impurities

RCL, host cell DNA, plasmid DNA, Impurity A, Impurity B, host cell protein, and Impurity C were identified as process-related impurities. All product-related impurities have been demonstrated to be adequately removed by the manufacturing process. RCL is controlled by performing the test on EoPC and vector solution.

2.1.8 Control of viral vector

The proposed specifications for the viral vector include [redacted] copy number, description, identification ([redacted]), [redacted], purity (Impurity B, Impurity A, host cell DNA, and plasmid DNA), bacterial endotoxins, sterility, mycoplasma, virus tests (adventitious virus tests and bovine virus tests on unpurified bulk harvest), RCL (infectivity assay), virus titer [redacted], and vector particle to infectivity ratio.

2.2 Component cells and product

2.2.1 Description and composition of product and formulation development

The product contains component cells including CAR-positive viable T cells at the count dependent on the patient's body weight in each of the frozen bags[1)] as specified in the dosage and administration or method of use. Excipients contained in the product include composite electrolytes, dextrose, sodium chloride, human serum albumin, dextran 40, and dimethylsulfoxide (DMSO).

2.2.2 Manufacturing process

The manufacturing process of the component cells and product includes thawing and washing of leukapheresis material, CD3/CD28 magnetic bead [redacted], gene transfer [redacted], [redacted], transduced cell culture [redacted], transduced cell culture [redacted], [redacted], harvesting, preparation, filling, freezing, storage, and testing.

Critical steps include [redacted].

Process evaluation was conducted on the manufacturing process of the component cells and product at the commercial production scale. After the process evaluation of the proposed process, however, there was a deviation from the specification [redacted],

1) Two different size bags filled with up to [redacted]mL or [redacted]mL.

and thus [redacted]. The process evaluation was conducted again [redacted].

In the US where the same process as that proposed in Japan was approved, [redacted] of several post-marketing batches deviated from the specification, and thus the concerned manufacturing process was evaluated in terms of the impact on quality attributes of the product. As a result, the acceptance limit of [redacted] was revised [see Section 2.R.2].

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

Human serum albumin used in preparation of the collected apheresis material is a drug approved for marketing in Japan.

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

Table 7 shows raw materials of biological origin, etc. used in the manufacturing process.

Human serum albumin (1) is prepared from plasma collected from donors qualified by the interview, and the plasma or plasma pool has been demonstrated to be negative for HBV, HCV, and HIV by the serological test and nucleic acid amplification test. Human transferrin is prepared from plasma collected from a donor qualified by the interview, and the plasma/serum or plasma pool has been demonstrated to be negative for HBV, HCV, HIV, and syphilis by the serological test and for HBV, HCV, HIV, and PB19 by the nucleic acid amplification test. In the manufacturing process of human transferrin, cold ethanol fractionation and heat treatment are conducted to inactivate or remove virus, etc. [see Section 2.R.3].

Human serum albumin (2) is the same material as the drug approved for marketing in Japan but provided in a different volume.

Casamino acid is prepared from milk from healthy cattle born in New Zealand or Australia and subjected to heat treatment for inactivation or removal of virus, etc. before use.

Human off-the-clot serum is prepared from blood collected from donors qualified by the interview, and the blood or blood pool has been demonstrated to be negative for HBV, HCV, HIV, and syphilis by the serological test and for HBV, HCV, and HIV by the nucleic acid amplification test. In the manufacturing process of human off-the-clot serum, heat treatment and gamma-irradiation are conducted to inactivate or remove virus, etc.

Anti-[redacted] antibody and anti-[redacted] antibody are prepared using mouse hybridomas as cell substrates. Their MCBs, EoPCs, and unpurified bulk harvests are tested for adventitious agents (*in vitro* virus test, *in vivo* virus test, mouse antibody production test, bovine virus test, bovine polyoma virus test, porcine virus test, transmission electron microscopy, XC plaque assay, S + L-focus assay, *Mus Dunni* cell infectivity assay [direct and extended methods], 293T-cell infectivity assay, MVM test, and mycoplasma). In the manufacturing process of these antibodies, inactivation and removal of virus, etc. are conducted.

All of these raw materials except for human serum albumin (1) and human transferrin have been confirmed to conform to the Standard for Biological Ingredients (MHLW Ministerial Announcement No. 210 in 2003).

Table 7. Raw materials of biological origin, etc. other than patient's peripheral blood mononuclear cells used in the manufacturing process

Raw material name	Animal	Material	Process
Human serum albumin (1)	Human	Blood	[redacted]
Human transferrin	Human	Blood	[redacted]
Human serum albumin (2)	Human	Blood	[redacted]
Casamino acid	Cattle	Milk	[redacted]
Human off-the-clot serum	Human	Blood	[redacted]
Anti-[redacted] antibody	Mouse	Hybridoma cells	[redacted]
Anti-[redacted] antibody	Mouse	Hybridoma cells	[redacted]

2.2.4 Manufacturing process development

Table 8 shows main changes in the development process of the component cells and product. Table 9 shows processes of the component cells used in clinical studies. The component cells manufactured by Process D are used for the product to be marketed.

In association with these changes of the manufacturing process, the quality attributes of the pre- and post-change component cells were compared and shown to be comparable.

The manufacturing process development employs QbD concept.

Table 8. Changes of manufacturing process of component cells

Manufacturing process	Changes, etc.
From Process A to Process B	Change to [redacted] Process X, change to [redacted], and change of [redacted], etc.
From Process B to Process C	Addition of [redacted], addition of [redacted] process by [redacted], change from [redacted] to [redacted], addition of [redacted], addition of [redacted], addition of [redacted], etc.
From Process C to Process D	Standardization of [redacted] process to [redacted], standardization of [redacted], change of [redacted], addition of [redacted], etc.

Table 9. Manufacturing process of component cells used in clinical studies

Manufacturing process	Changes, etc.
Process A	Studies [redacted], [redacted], [redacted], and [redacted]
Process B	Studies [redacted], [redacted], and [redacted]
Process C	Studies [redacted], [redacted], and [redacted]

2.2.5 Characterization

2.2.5.1 Structure and characterization

Characterization was performed as shown in Table 10.

Table 10. Characterization of component cells

Structure and physicochemical properties	Transgene analysis, gene insertion site analysis of viral vector/insertion mutation analysis [see Section 6.2.3], immunophenotype (T cells, B cells, monocytes, and NK cells), T-cell subset analysis (CAR, CD4, CD8, [redacted]), viability rate, repeat number of transgene, CAR-expression rate, and [redacted]
Biological properties	[redacted], release of IFN-γ in response to CD19 antigen specific stimulation, CD19 antigen specific cytotoxicity, and cell proliferation ability
Purity	Non-target cells (B lineage cells, monocytes, granulocytes, NK cells, and erythrocytes), dead cells, RCL, residual viral vector, [redacted], off-the-clot serum, [redacted], human transferrin, [redacted]

2.2.6 Manufacturing process evaluation

2.2.6.1 Verification

At present, potential variables in the manufacturing process have not been clearly identified, but the control strategy of the quality has been constructed by verification to ensure the intended quality in each manufacturing session. Monitoring items in the verification have been specified considering the potential quality risk due to variations in quality attribute of a raw material such as the apheresis material. The specified items include critical process parameter and in-process control tests, specifications of the component cells as well as characterization of the component cells [redacted] shown in Table 11 [see Section 2.R.2].

Table 11. Monitoring items on component cells [redacted] (characterization)

Evaluation item
[redacted] condition*1
[redacted] *1
[redacted] cells*1
[redacted] cells*1
[redacted] cells*1
[redacted] cells*1
[redacted] T cells*1
[redacted] T cells*1
[redacted] T cells*1
[redacted] T cells*1
[redacted] activity*2

*1 Evaluated by [redacted]
*2 Evaluated by [redacted]

2.2.6.2 Removal of process-related impurities

Process-related impurities include RCL, residual viral vector, Impurity D, off-the-clot serum, Impurity E, human transferrin, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, and Impurity L.

The process-related impurities except for RCL, residual viral vector, and Impurity D are unlikely to raise 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. RCL and Impurity D, on the other hand, are controlled by the specifications of the product.

Residual viral vector was subjected to process evaluation for Process B, and the amounts in a specimen after [redacted] process and in supernatant of the final product were demonstrated to be below the detection limit (qPCR, [redacted] copies/[redacted]μg DNA). The proposed process and Process B were shown to have a comparable capability to remove the viral vector.

2.2.7 Control of product

The proposed specifications for the product include description, identification (CAR transgene), purity (copy number of transgene, percentage of T-cells, percentage of residual CD19-positive B-cells, cell viability rate, and residual bead count), bacterial endotoxins, mycoplasma, sterility, RCL (VSV-G DNA), percentage of CAR-expressing T-cells, IFN-γ release, and content (number of CAR-positive viable T cells and total number of viable cells[2)]).

QbD concepts were used to develop the product, and based on the information obtained through the development of the product and related knowledge, etc., the following critical quality attributes (CQAs) and potential CQAs (pCQAs) were identified.

CQA: [redacted], bacterial endotoxins, mycoplasma, sterility, and RCL

pCQA: Items shown in Table 11

2.R Outline of the review conducted by PMDA

2.R.1 Control of viral vector

According to the application data, the viral vector was handled as a material used to transfer the gene into component cells and thus was not controlled by any specifications.

Because the quality of the viral vector is critical in the manufacturing of the product, PMDA asked the applicant to take measures on the following points.

In the manufacture of the viral vector, control of raw materials of biological origin, etc. and in-process control tests should be appropriately performed to ensure the safety against viruses, etc. that are derived from the manufacturing process of the viral vector and potentially contaminate the product. To transfer the gene into autologous cells appropriately, the performance of the viral vector should be controlled. The control tests on the viral vector only are not adequate for the quality control of the viral vector, and thus an appropriate control strategy of the quality should be constructed including control of raw materials, etc. and process parameters to assure the quality. For the quality assurance, the

2) Only when used for treatment of pediatric ALL.

process validation and evaluation of the manufacturing process should be implemented to ensure the consistent quality. Accordingly, the viral vector should be positioned as a critical intermediate product, but not as a material for the manufacture, and thus its manufacturing process should be also controlled as a part of the manufacturing process of the product. The critical intermediate product should be controlled as a material equivalent to the drug substance, and its quality should be defined in the attached specifications. Furthermore, because the manufacturing process of the viral vector does not include processes that can inactivate and remove adventitious virus, etc., the test for adventitious agents performed on the unpurified bulk harvest should be controlled as a part of the specifications.

The applicant submitted results from the process validation for manufacture of the viral vector and validation of analytical procedures for the test methods, explained justification of the specifications, and stated as follows:
The applicant will control the manufacturing process of the viral vector as a part of the manufacturing process of the product and establish the attached specifications to control the quality tests on the viral vector, including virus tests and mycoplasma test performed on the unpurified bulk harvest. Thereby, the applicant will appropriately implement the manufacture and quality control of the viral vector.

PMDA accepted the applicant's response and has concluded that the quality of the viral vector is appropriately controlled.

2.R.2 Control strategy of the quality of the product

In the US where the same process as that proposed in Japan was approved, [redacted] of several post-marketing batches deviated from the specification [see Section 2.2.2]. PMDA asked the applicant to explain whether there are any problems with manufacturing process or whether these product batches differed in quality attributes.

The applicant's explanation about the US product batches in which [redacted] deviated from the specification (the minimum value, [redacted]% for pediatric ALL and [redacted]% for DLBCL):
CAR-expressing viable T [redacted] and IFN-γ releasing capacity are not largely different from those in the previous batches, and in clinical studies, batches not meeting the specification for [redacted] have been demonstrated to be clinically effective. Therefore, [redacted] of the final product is not clearly correlated with the cell proliferation capacity in the body after the administration or with the efficacy or safety in clinical studies. The US post-marketing product batches in which [redacted] deviated from the specification are considered to have quality consistent with that of the investigational product. The approved specification for [redacted] in the US was tighter than that for the investigational product, and therefore the specification for [redacted] will be changed so that it becomes the same as that for the investigational product. Further, this specification is also used for products marketed in Japan. The reasons for frequent deviations from the specification occurring in the US post-marketing settings were investigated in detail, but no definite causes have been identified. Multiple actions will be taken continuously to reduce the risk of deviation from the specification.

PMDA's view:

PMDA largely accepted the applicant's explanation. In the process validation, however, [redacted] deviated from the specification as a result of variations in process performance. In the manufacturing process using an autologous raw material, variable factors are difficult to control and varied results are generated by the process evaluation; therefore, at present, there is no choice but to control the processes in a broader way. At present, PMDA cannot conclude that the applicant confirmed that the target product quality attributes would be ensured consistently in commercial production, and thus considers that the quality of the product should be ensured by verification in the future manufacturing processes. In particular, pCQAs should be controlled as a part of the quality control strategy because, at present, they are assumed to be related to the efficacy.

The applicant's explanation:
It is difficult to control the specification tightly, and the product is to be controlled by verification so that quality attributes including pCQAs can be assessed [redacted]. When adequate data are collected in the future, the position of pCQAs will be reviewed, and the control method will be revised.

PMDA's view:
Controlling the specification tightly is difficult at present, and the quality of the product can be ensured with careful control through verification [redacted]. PMDA thus accepted the applicant's response.

2.R.3 Ensuring viral safety of human serum albumin and human transferrin

Human serum albumin (1) and human transferrin are used in manufacturing processes such as component cell culture. The application data, however, did not include detailed results of process evaluation of viral inactivation/removal in the manufacturing processes of these raw materials.

PMDA asked the applicant to submit the evaluation results of viral inactivation/removal in the manufacturing processes of the raw materials and clarify the results using the specific data, but the applicant responded that they were checking the results at that time.

The viral safety of human serum albumin (1) and human transferrin is reported in Review Report (2).

3. Data Relating to Stability and Outline of the Review Conducted by PMDA

3.1 Stability of viral vector

Table 12 shows a summary of major stability studies for the viral vector.

Table 12. Summary of major stability studies for the viral vector

Study[*1]	Number of batches	Storage condition	Study period	Storage form
Long-term testing	8	−90°C to −60°C	[redacted][*2, 3]	Bromobutyl rubber stopper and glass vial
Accelerated testing	1	−20°C	[redacted]	
Stress testing	2	[redacted]°C	[redacted]	
	2	[redacted]°C	[redacted]	
	2	[redacted]°C	[redacted]	

*1 [redacted]
*2 [redacted]
*3 [redacted]

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

The accelerated testing showed a clear decrease in [redacted] at [redacted] months.

The stress testing showed a clear decrease in [redacted] at [redacted] hours under the storage condition at [redacted]°C. Under the storage conditions at [redacted]°C and [redacted]°C, a decreasing trend in [redacted] was found from [redacted] hours, and a clear decrease was found at [redacted] hours.

Based on the above, a shelf life of [redacted] months has been proposed for the viral vector when stored in a glass vial sealed with a bromobutyl rubber stopper at [redacted]°C.

3.2 Stability of product

Table 13 shows a summary of major stability studies for the product.

Table 13. Summary of major stability studies for the product

Study	No. of batches	Manufacturing process	Origin	Storage condition	Filling volume	Study period	Storage form
Long-term testing	4	Process B	Healthy subjects	≤−120°C	10 mL	[redacted]	Gamma-irradiation EVA bag
	3	Process B	Pediatric patients with ALL	≤−120°C	15.8-39.0 mL	[redacted][*1]	
	3	Process C	Patients with DLBCL	≤−120°C	12-14 mL	[redacted][*2]	
	6	Proposed process	Pediatric patients with ALL and healthy subjects	≤−120°C	10-12 mL	9 months[*3]	
	3	Proposed process[*4]	Healthy subjects	≤−120°C	10-13 mL	9 months[*3]	
In-use stability testing	3[*5]	Process B	Healthy subjects	5°C 20°C-25°C 37°C	17-19 mL	[redacted]	

*1 [redacted]
*2 [redacted]
*3 The stability testing is ongoing until 24 months.
*4 Manufacture was further optimized during the process validation.
*5 Number of batches for each storage condition

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

The in-use stability testing included the stability evaluation criteria ([redacted]) in addition to the stability specifications. Under the storage condition at [redacted]°C, all the specimens met the stability specifications, but [redacted]

[redacted] at [redacted] hours was below the stability evaluation criteria. Under the storage condition at [redacted]°C, [redacted] hours failed to meet the stability specifications, and [redacted] hours and thereafter were below the stability evaluation criteria, showing a decreasing trend. Neither [redacted] nor [redacted] showed any clear decreasing trend, but both were below the stability evaluation criteria at [redacted] and [redacted] hours. Under the storage condition at [redacted]°C, [redacted] hours were decreased, failing to meet the stability specifications, and [redacted] at [redacted] minutes and thereafter were below the stability evaluation criteria, showing a decreasing trend. [redacted] did not show any clear decreasing trend, but [redacted] hours was below the stability evaluation criteria.

Based on the above, a shelf life of 9 months has been proposed for the product when stored in a gamma-irradiated sterile EVA bag at ≤−120°C, and the administration should be started immediately after thawing and completed within 30 minutes at room temperature.

3.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA accepted the proposed storage and shelf life of the product and results from stability evaluation of the administration fluid.

4. Data Relating to Indication or Performance and Outline of the Review Conducted by PMDA

The applicant submitted data relating to the indication or performance of tisagenlecleucel: the results from *in vitro* and *in vivo* pharmacology studies.

4.1 Primary pharmacodynamics

4.1.1 *In vitro* studies (CTD 4.2.1.1-1)

Table 14 shows *in vitro* studies conducted as primary pharmacodynamic studies of tisagenlecleucel. In addition to the above, studies listed in Table 10 were conducted for quality-related characterization [see Section 2.2.5.1].

Table 14. Summary of *in vitro* studies

Study	Major findings
Cytotoxicity of tisagenlecleucel on K562-CD19 (n = 3)	The CD19-positive-cell specific cytotoxicity of tisagenlecleucel was evaluated in coculture with CD-19 untransduced K562 cells (Kwt) or CD19-transduced K562 cells (K562-CD19). Tisagenlecleucel was not cytotoxic on Kwt but was cytotoxic on K562-CD19.
Evaluation of the impact of TCRζ domain on the cytotoxicity of αCD19CAR-expressing T cells on human B-ALL tumor cells (n = 3)	The cytotoxicity of tisagenlecleucel or αCD19CAR-expressing T cells with defective TCRζ domain on human B-ALL tumor cells was evaluated in the coculture system. Tisagenlecleucel was cytotoxic on human B-ALL tumor cells. On the other hand, αCD19CAR-expressing T cells with defective TCRζ domain was not cytotoxic on human B-ALL tumor cells.
Cytokine production in various types of αCD19CAR-expressing T cells in coculture with K562-CD19 cells (n = 2)	In coculture with K562-CD19 cells, amounts of cytokines released from tisagenlecleucel and T cells expressing modified αCD19CAR with a different structure from that of tisagenlecleucel, were evaluated. Tisagenlecleucel released smaller amounts of IL-4 and IL-10, Th2 cytokines, than αCD19CAR-expressing T cells that do not express 4-1BB. In addition, tisagenlecleucel produced a greater amount of IFN-γ in coculture with K562-CD19 cells than in coculture with Kwt cells.
Proliferation and survival of various types of αCD19CAR-expressing T cells in the absence of CD19 antigen (n ≥3)	Tisagenlecleucel and T cells expressing modified αCD19CAR with a different structure from that of tisagenlecleucel, were cultured in the presence of IL-2, to monitor the cell count over time. The results suggested tisagenlecleucel was superior in proliferation and survival to αCD19CAR-expressing T cells that do not express 4-1BB.

4.1.2 *In vivo* studies (CTD 4.2.1.1-2)

Table 15 shows *in vivo* studies conducted as primary pharmacodynamic studies.

Table 15. Summary of *in vivo* studies

Animal species	Major findings
NOD/SCID-β_2m^{null} mouse (n = 7-10)	Tisagenlecleucel at 2×10^6 cells was administered to immunodeficient mice implanted with primary human B-ALL cells. The tumor cell count in peripheral blood decreased at 1 to 4 weeks.
NOD/SCID-$\gamma_c^{-/-}$ mouse (n ≥4)	Immunodeficient mice implanted with primary human B-ALL cells were given 8 × 106 cells of tisagenlecleucel or T cells expressing modified αCD19CAR with a different structure from that of tisagenlecleucel. At 4 weeks, mice given tisagenlecleucel had more CAR-expressing T cells in peripheral blood than mice given the other αCD19CAR-expressing T-cells. The disease-free survival period was significantly longer in mice given tisagenlecleucel than in those given the other αCD19CAR-expressing T-cells (log-rank test, P = 0.009).

4.R Outline of the review conducted by PMDA

The applicant's explanation about the effects of tisagenlecleucel on tumor:

The *in vitro* studies showed that tisagenlecleucel released cytokines such as IFN-γ and proliferated in a CD19-antigen dependent manner. In addition, tisagenlecleucel recognized CD19-expressing cells specifically and presented the cytotoxicity on these cells.

In the *in vivo* studies, tisagenlecleucel cells survived continuously in cancer-bearing model mice implanted with human B-ALL tumor cells and significantly extended the disease-free survival of the mice.

The above results indicate that tisagenlecleucel specifically recognizes malignant B cells and exerts the cytotoxic action on these cells.

PMDA accepted the applicant's explanation.

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

The applicant did not conduct non-clinical studies to evaluate the biological disposition of tisagenlecleucel. The following sections describe the applicant's explanation about the biological disposition and survival period of tisagenlecleucel based on data from the non-clinical pharmacology study (CTD 4.2.1.1-2) and toxicity studies in cancer-bearing model mice (i.e., NOD/SCID IL-2Rγc^{null} [NOG] mice implanted with human B-ALL cells) (CTD 4.2.2.3-1, 4.2.2.3-2, and 4.2.2.3-3).

5.1. Non-clinical biological disposition

5.1.1. Toxicity studies (CTD 4.2.2.3-1, 4.2.2.3-2, and 4.2.2.3-3)

Test article (1×10^6, 5×10^6, or 20×10^6) was comprised of a 1:1 mixture of 2 different αCD19CAR-expressing T-cells: (1) T-cells expressing αCD19-ζ CAR and (2) T-cells expressing αCD19-BB-ζ CAR, the same domain structure as that of tisagenlecleucel. The test article (1×10^6, 5×10^6, or 20×10^6) was intravenously administered to a cancer-bearing mouse model (n = 16/group), to evaluate the cell distribution into organs by PCR. The results showed that DNA derived from tisagenlecleucel was detected in the spleen, lungs, kidneys, bone marrow, liver, brain, heart, and blood. Table 16 shows the evaluation results in the spleen, lungs, kidneys and bone marrow (adequate data are available for these organs).

Table 16. Evaluation results of biological distribution
(number of animals with tisagenlecleucel DNA detected/number of animals evaluated)

Dose (cells/body)	Observation period[*1] (days)	αCD19-ζ CAR[*2]				αCD19-BB-ζ CAR[*2]			
		Spleen	Lung	Kidney	Bone marrow	Spleen	Lung	Kidney	Bone marrow
1×10^6	21	0/4	0/3	0/4	0/1	0/3	0/3	0/4	2/3
	35	0/4	0/3	0/3	0/2	2/4	1/4	0/2	0/1
	196	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
5×10^6	21	1/4	2/3	1/4	1/2	1/4	2/3	0/3	0/1
	35	0/4	3/4	0/3	0/1	0/4	2/3	0/3	0/2
	196	1/3	1/2	0/4	1/2	1/2	0/1	1/5	1/2
20×10^6	21	3/3	4/4	4/4	1/1	4/4	3/3	4/4	0/0
	35	3/3	4/4	3/4	3/3	3/3	4/4	2/3	3/3
	196	0/1	0/3	0/3	0/2	0/1	0/3	0/3	0/3

*1 Number of days after administration of CAR-expressing T cells. The test cells were administered 21 days after implantation of human B-ALL cells.
*2 The lower detection limit was 10 copies/μg DNA.

5.1.2 Non-clinical pharmacology study (CTD 4.2.1.1-2)

After administration of tisagenlecleucel at 8×10^6 to NOG mice and cancer-bearing model mice (i.e., NOG mice implanted with human B-ALL cells) (n ≥4/group), tisagenlecleucel in peripheral blood at 4 weeks was evaluated by flow cytometry (FCM). Tisagenlecleucel was detected in both animals groups irrespective of implanted human B-ALL cells.

5.2 Clinical pharmacology

The biological disposition by therapeutic effect in pediatric and AYA patients with relapsed or refractory B-ALL was investigated based on combined data on biological disposition of tisagenlecleucel from Studies B2202 and B2205J (Figure 1).

In patients (n = 80) who achieved complete remission (CR)/complete remission with incomplete hematologic recovery (CRi), the CAR transgene level in peripheral blood increased immediately after administration and reached the maximum (geometric mean C_{max}, 32,700 copies/μg DNA) around Day 10. In patients (n = 11) who failed to achieve CR/CRi, the CAR transgene level in peripheral blood increased more slowly than in patients with CR/CRi and reached the maximum (geometric mean C_{max}, 19,500 copies/μg DNA) around Day 20. In both patient groups, the CAR transgene level in peripheral blood decreased in a biphasic manner.

The maximum time to the last measurable concentration (T_{last}), an indicator of the tisagenlecleucel survival period in the body, was 617 days after administration of tisagenlecleucel in patients who achieved CR/CRi and 376 days in patients who failed to achieve CR/CRi.

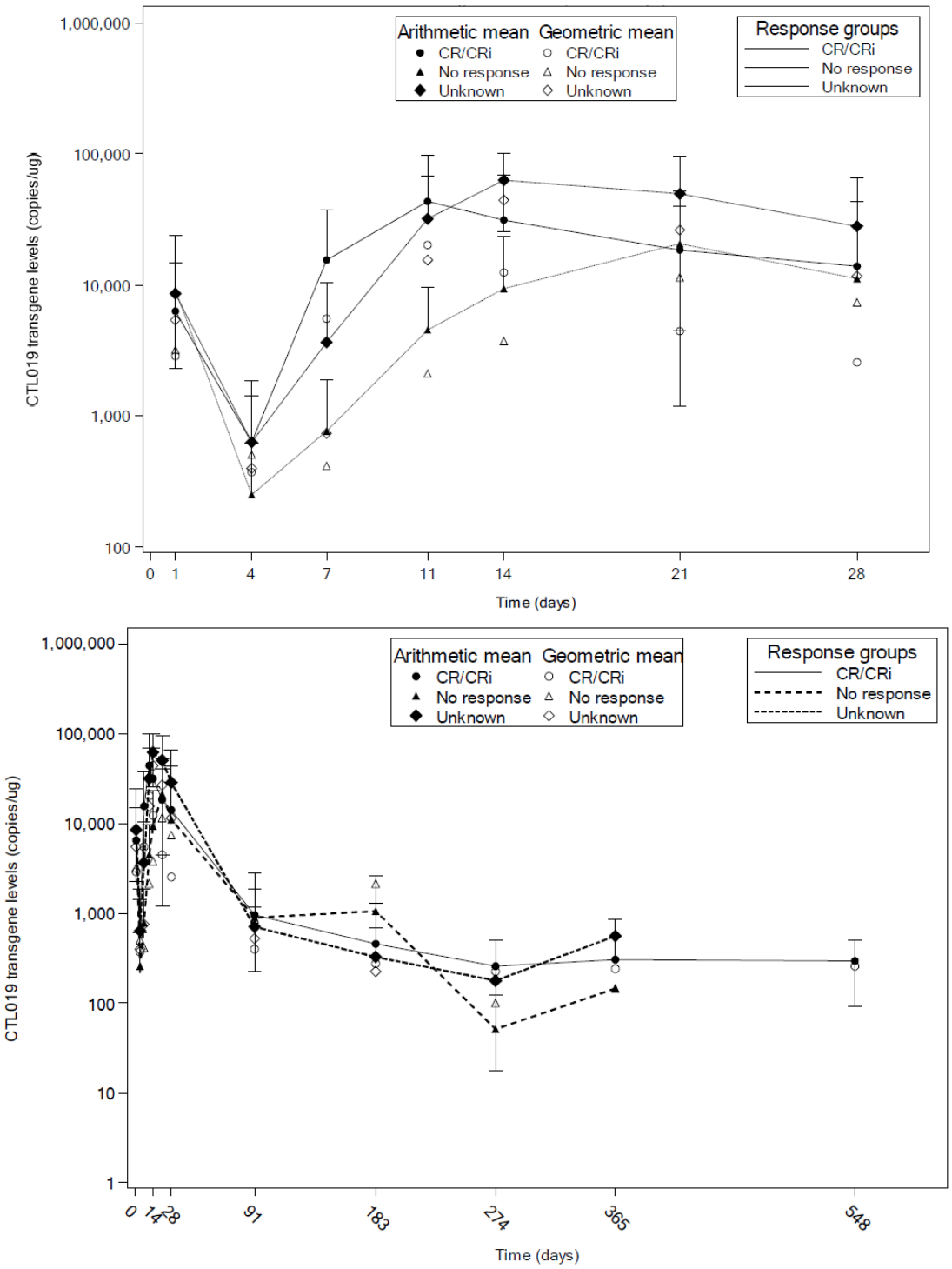

Figure 1. Changes in CAR transgene level in peripheral blood in Studies B2202 and B2205J (top, up to Day 28; bottom, up to Day 548)

Using data from Study C2201, the applicant investigated the biological disposition of tisagenlecleucel by therapeutic effect in patients with relapsed or refractory DLBCL (Figure 2).

The CAR transgene level in peripheral blood increased immediately after administration. In both patients (n = 35) who achieved CR/partial response (PR) and patients (n = 58) who failed to achieve CR/PR, the level reached the maximum around Day 9 (geometric mean C_{max}, 6210 copies/μg DNA and 5100 copies/μg DNA, respectively) and then decreased in a biphasic manner.

T_{last}, an indicator of the tisagenlecleucel survival period in the body, was 693 days after administration of tisagenlecleucel in patients who achieved CR/PR and 374 days in patients who failed to achieve CR/PR.

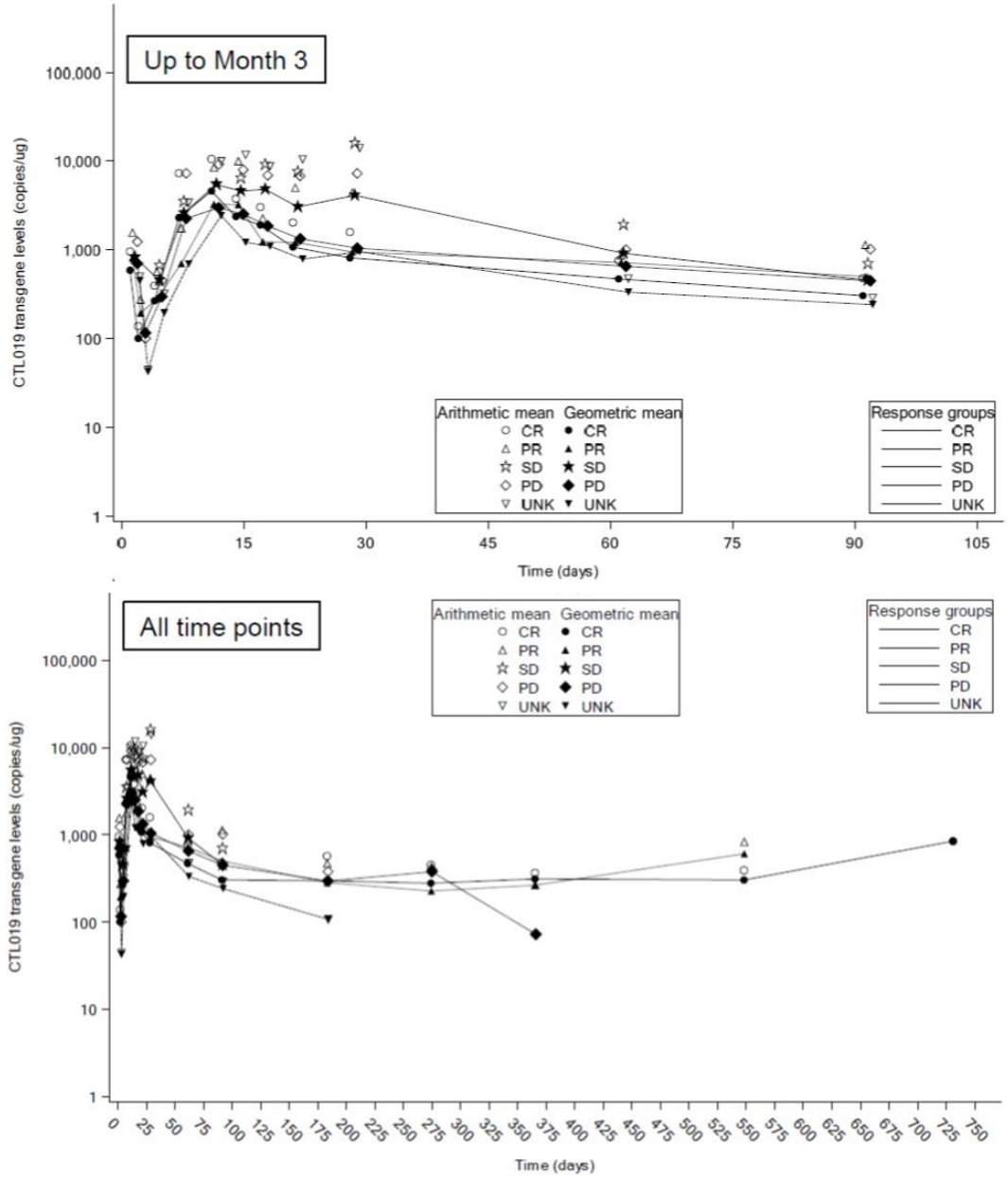

Figure 2. Changes in CAR transgene level in peripheral blood in Study C2201 (top, up to Day 90; bottom, up to Day 730)

5.R Outline of the review conducted by PMDA

The applicant's explanation about the biological disposition and survival period of tisagenlecleucel:

In the toxicity studies, DNA derived from tisagenlecleucel was detected not only in the spleen, lungs, kidneys, and bone marrow but also, data were limited though, the liver, brain, heart, and blood in some animals. This indicates that tisagenlecleucel given intravenously is widely distributed into organs. In the 20×10^6 dose group, DNA derived from tisagenlecleucel was detected in the spleen, lungs, kidneys, and bone marrow in all the animals except for one 35 days after administration of

tisagenlecleucel. In the non-clinical pharmacology study, DNA derived from tisagenlecleucel was also detected in peripheral blood 4 weeks after administration of tisagenlecleucel. These findings suggest that tisagenlecleucel survives in the body for a certain period.

Results of the CAR transgene level in peripheral blood in the clinical pharmacology studies suggest that tisagenlecleucel rapidly proliferates after the administration, then decreases slowly in a biphasic manner, and survives for a long period in both patients with B-ALL and those with DLBCL, irrespective of whether they are responders or non-responders.

C_{max} in patients with DLBCL was lower than that in pediatric and AYA patients with B-ALL. The difference is considered to reflect a difference of the localized site of cancer cells between these diseases.

PMDA accepted the applicant's explanation.

6. Data Relating to Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted data relating to non-clinical safety of tisagenlecleucel: the results from toxicity studies in NOG mice, *in vitro* proliferation tests of various αCD19CAR-expressing T cells including tisagenlecleucel, tissue cross-reactivity studies, gene insertion site analysis of the lentiviral vector, and safety evaluation of impurities and excipients.

6.1 Toxicity study in immunodeficient mice (CTD 4.2.2.3-1, 4.2.2.3-2, and 4.2.2.3-3)

Test article (1×10^6, 5×10^6, or 20×10^6) comprised of a 1:1 mixture of tisagenlecleucel cells and αCD19-ζ CAR-expressing T-cells, was administered to NOG mice with or without human B-ALL cells. None of the mice showed test article-related toxicity or cell proliferation suggesting tumorigenicity (Table 17).

Table 17. Toxicity studies in immunodeficient mice

Test system	Route of administration	Observation period*	B-ALL cell implantation	Test cells	Dose (cells/body)	No. of animals (n)	Major findings	CTD
NOG mouse	Intravenous	21, 35, and 196 days after administration of CAR-expressing T cells	Yes	Test article	20×10^6	16	Animals implanted with B-ALL cells showed proliferation of B-ALL cells and associated changes. Animals receiving the test article or mock T cells showed changes in clinical signs and histopathological findings associated with GVHD. No toxicity related to the test article was observed.	4.2.2.3-1 4.2.2.3-2 4.2.2.3-3
			Yes	Test article	5×10^6	16		
			Yes	Test article	1×10^6	16		
			Yes	Mock T cells	20×10^6	16		
			Yes	Mock T cells	5×10^6	16		
			Yes	Mock T cells	1×10^6	16		
			Yes	-	0	4		
			No	Test article	20×10^6	4		

* The test cells were administered 21 days after implantation of human B-ALL cells.

6.2 Other safety

6.2.1 *In vitro* proliferation study of αCD19CAR-expressing T cells (CTD 4.2.3.7.7-1, 4.2.3.7.7-2, and 4.2.3.7.7-3)

In the proliferation study of human αCD19CAR-expressing T cells, no uncontrolled cell growth was observed (Table 18).

Table 18. *In vitro* proliferation study of αCD19CAR-expressing T cells

Study	Test cells*	Culture period (days)	Result	CTD
Proliferation study using peripheral blood lymphocytes derived from healthy donors	αCD19-BB-ζ or αCD19-ζ-transduced peripheral lymphocytes from healthy donors	38	T cells expressing αCD19-BB-ζ proliferated more persistently than T cells expressing αCD19-ζ, and decreases in cell viability rate were observed on Day ≥28.	4.2.3.7.7-1
Proliferation study using peripheral lymphocytes from patients with chronic lymphocytic leukemia	αCD19-BB-ζ-transduced peripheral lymphocytes from patients with chronic lymphocytic leukemia	28	The cell viability rate decreased over a period from Day 21 to Day 28 of culture, and cell death was observed.	4.2.3.7.7-2
Proliferation study using peripheral lymphocytes from healthy donors and patients with hairy cell leukemia	αCD19-BB-ζ-transduced peripheral lymphocytes from healthy donors or patients with hairy cell leukemia	33	The cell viability rate decreased over a period from Day 18 to Day 20 of culture, and cell death was observed.	4.2.3.7.7-3

* αCD19-BB-ζ and αCD19-ζ were transduced using LTG119 and LTG118 vectors, respectively.

6.2.2 Tissue cross-reactivity studies (CTD 4.2.3.7.7-4, 4.2.3.7.7-5, and 4.2.3.7.7-6)

A study for cross-reactivity of CD19scFv to human membrane proteins was conducted. Transient adverse events in the central nervous system were observed in clinical studies after administration of tisagenlecleucel. Therefore, to elucidate the relationship between these events and tisagenlecleucel, cross-reactivity of CD19scFv and CD19-expression was investigated using human and monkey brain tissues (Table 19).

Table 19. Tissue cross-reactivity study

Study	Study method	Result	CTD
A study for cross-reactivity of CD19scFv to human membrane proteins	Protein array using HEK293* cells	Mouse CD19CARscFv did not bind to any membrane proteins other than CD19.	4.2.3.7.7-4
Investigation of CD19 expression using human and monkey brain tissues	• Immunohistochemical examination • *In situ* hybridization method • RT-PCR method	Mouse CD19CARscFv did not bind to human and cynomolgus monkey brain tissues (cerebrum and cerebellum). Neither CD19 protein nor gene was expressed.	4.2.3.7.7-5 4.2.3.7.7-6

* HEK293 cells express about 3550 full-length human membrane proteins.

6.2.3 Gene insertion site analysis of lentiviral vector (CTD 4.2.3.7.7-7 and 4.2.3.7.7-8)

To identify the gene insertion site and distribution of tisagenlecleucel, the analysis was performed using INSPIIRED and GENE-IS (Table 20). The results showed that the gene insertion site was characterized by a highly multiclonal pattern, a typical insertion pattern of a lentiviral vector (insertion in the vicinity of DNase I highly sensitive sites, CpG islands, and GC-rich regions).

Table 20. Gene insertion site analysis of lentiviral vector

Test system	Study method	Result	CTD
Analysis using INSPIIRED	Tisagenlecleucel batches derived from pediatric patients with B-ALL (n = 6), patients with DLBCL (n = 6), and healthy donors (n = 2) were subjected to identification of the insertion site sequence by Bushman laboratory and gene insertion site analysis using the INSPIIRED analysis pipeline.*1	All the gene insertion sites analyzed were characterized by a highly multiclonal pattern. Neither specific gene insertion in the vicinity of potentially carcinogenic genes such as oncogenes nor selective single-clonal expansion was observed.	4.2.3.7.7-7
Analysis using GENE-IS	Tisagenlecleucel batches derived from pediatric patients with B-ALL (n = 6), patients with DLBCL (n = 6), and healthy adults (n = 2) were subjected to identification of the insertion site sequence by Genewerk Shearing-Extension Primer Tag Selection/Ligation-Mediated PCR and gene insertion site analysis using the GENE-IS analysis pipeline.*2	All the gene insertion sites analyzed were characterized by a highly multiclonal pattern. Neither specific gene insertion in the vicinity of potentially carcinogenic genes such as oncogenes nor selective expansion of such cells was observed.	4.2.3.7.7-8

*1 *Mol Ther Methods Clin Dev*. 2016;4:17-26 and *Mol Ther Methods Clin Dev*. 2017;4:39-49
*2 *Mol Ther Nucleic Acids*. 2017;6:133-39

6.2.4 Safety evaluation of impurities

Impurities potentially present in the final product include Impurity G, Impurity D, Impurity F, Impurity I, Impurity E, transferrin, Impurity N, Impurity O, and medium components (Impurity H, Impurity K, Impurity J, and Impurity L). The applicant conducted the safety evaluation of these impurities at the estimated or actual residual amounts based on the permitted daily dose and pharmacologically or physiologically active concentration, and concluded that these impurities would not put humans at a safety risk.

6.2.5 Safety evaluation of excipients

Among the excipients of tisagenlecleucel, the following have never been used in other drugs or are contained at a greater amount in tisagenlecleucel than in other drugs:

The composite electrolyte solution, DMSO, dextran 40 contained in 10% dextran 40 and 5% dextrose solutions, and human serum albumin contained in 25% human serum albumin solution.

The applicant conducted the safety evaluation of these excipients based on the literature information, clinical use experience, and physiologically active concentration, and concluded that these excipients would raise no safety concerns.

6.R Outline of the review conducted by PMDA

Based on the data submitted and the following investigations, PMDA has concluded that tisagenlecleucel raises no particular concerns about the non-clinical safety.

6.R.1 Potential effect of tisagenlecleucel on normal tissues

PMDA asked the applicant to explain a potential effect of tisagenlecleucel on the normal tissues.

The applicant's response:

For the following reasons, tisagenlecleucel shows specifically high cytotoxicity to a CD19 and thus considered to have no effect on the normal tissues not expressing CD19:

- In the cross-reactivity study, scFv comparable to that expressed on tisagenlecleucel bound to CD19 at a high affinity but did not bind to any other molecules other than CD19.

- In the *in vitro* cytokine release study [see Section 4.1.1], tisagenlecleucel presented the cytokine release pattern corresponding to the T-cell subgroup only when the target cells were CD19-transduced K562 cells (K562-CD19).

- In the *in vitro* cytotoxicity study [see Section 4.1.1], tisagenlecleucel showed cytotoxicity only on CD19-positive cells.

CD19 is expressed on B cells throughout their differentiation process from pre-B cells to plasma cells, but is not found on normal tissues other than pluripotent hematopoietic stem cells and B cells, and only the CD19 gene expression is slightly detected in a subset of dendritic cells (*Blood*. 2005;105:3087-93, *Blood*. 1988;71:13-29, and *Annu Rev Immunol*. 2000;18:393-422). The CD19 expression on the normal tissues is thus limited, and tisagenlecleucel is expected to be effective against B-cell tumors in a relatively safe manner. Actually, findings from clinical use experience have indicated that CD19-positive B cells are only normal cells that are affected by tisagenlecleucel (*Molecular Therapy-Oncolytics.* 2016;3:16011).

PMDA accepted the applicant's explanation.

6.R.2 Reproductive and developmental toxicity

PMDA asked the applicant to explain the effect of tisagenlecleucel on fetuses in pregnant women.

The applicant's response:

The effects of CD19-positive B cells on pregnancy maintenance and fetal development remain unknown, but no reproductive abnormalities were found in CD19-knockout mice (The Jaxson Laboratory Mouse Strain Datasheet-006785). Therefore, there are no particular concerns about the effect of decreased CD19-positive B cells on fetuses in pregnant women receiving tisagenlecleucel.

The human placenta, however, is not an intact barrier against blood cells; circulating maternal cells may transfer to the fetus during pregnancy and integrate with the fetal immune and organ systems, potentially creating a state of maternal microchimerism (*Lab invest.* 2006;86:1185-92 and *Best Pract Res Clin Obset Gynaecol.* 2016;31:121-30). Microchimerism can persist throughout the human's life and is involved in triggering or perpetuating inflammatory autoimmune diseases. Therefore, immunologically activated tisagenlecleucel can transfer to the fetus via the placenta, potentially causing a decrease in fetal B cells. At present, whether tisagenlecleucel administered to a pregnant woman can cause decreased B cells or autoimmune disease in the fetus remains unknown, but the risk cannot be completely ruled out.

The search for pregnant cases in the applicant's safety database (data cut-off on [redacted], 20[redacted]) detected 2 cases. One case was reported from a female patient who was found pregnant about 3 months and 2 weeks after administration of tisagenlecleucel and then terminated the pregnancy. Pathological examinations of the placenta and aborted fetus showed no histological abnormalities. The other case was reported from a male patient whose partner delivered a healthy newborn about 2 years after he had received tisagenlecleucel. These cases raise no safety concerns.

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

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

The applicant submitted evaluation data on the efficacy and safety from 3 studies: 2 global phase II studies and 1 foreign phase II study (Table 21). In addition, the applicant submitted reference data from 3 studies: 1 foreign phase I study, 1 foreign phase I/IIa study, and 1 foreign phase II study (Table 21).

Table 21. List of clinical studies for efficacy and safety

Data category	Region	Study	Phase	Population	No. of patients enrolled	Dosage regimen*	Main endpoints
Evaluation	Global	B2202	II	Patients with relapsed or refractory B-ALL (≥3 years of age at the time of screening to ≤21 years of age at the initial diagnosis)	92	A single dose at the following number of cells • Patients weighing ≤50 kg Target dose: 2.0×10^6 to 5.0×10^6 cells/kg Acceptable dose: 0.2×10^6 to 5.0×10^6 cells/kg • Patients weighing >50 kg Target dose: 1.0×10^8 to 2.5×10^8 cells Acceptable dose: 0.1×10^8 to 2.5×10^8 cells	Efficacy Safety
		C2201	II	Patients with relapsed or refractory DLBCL (≥18 years of age)	165	A single dose at the following number of cells Target dose: 5.0×10^8 cells Acceptable dose: 1.0×10^8 to 5.0×10^8 cells	Efficacy Safety
	Foreign	B2205J	II	Patients with relapsed or refractory B-ALL or B-cell lymphoblastic lymphoma (≥3 years of age at the time of screening to ≤21 years of age at the initial diagnosis)	35	Same as in Study B2202	Efficacy Safety
Reference	Foreign	B2102J	I	Patients with relapsed or refractory B-cell leukemia or malignant lymphoma (≥18 years of age)	26	3 divided infusions at the following number of cells Target dose: 5.0×10^9 cells Acceptable dose: 1.5×10^7 to 5.0×10^9 cells	Safety
		B2101J	I/IIa	Patients with relapsed or refractory B-cell leukemia or malignant lymphoma (1-24 years of age)	73	3 divided infusions at 1.5×10^7 to 5.0×10^9 cells	Efficacy Safety
		A2201	II	Patients with relapsed or refractory CLL (≥18 years of age)	30	A single dose at low number of cells (1.0×10^7 to 5.0×10^7 cells) or high number of cells (1.0×10^8 to 5.0×10^8 cells)	Safety

* Tisagenlecleucel was intravenously administered.
Target dose: the target number of the cells in the manufacturing of tisagenlecleucel
Acceptable dose: the number of the cells acceptable for administration

Each clinical study is summarized below. The main adverse events excluding deaths observed in each clinical study are presented in Section "9 Adverse events observed in clinical studies."

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global phase II study (CTD 5.3.5.2-1, Study B2202, ongoing since April 2015 [data cut-off on April 25, 2017])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of tisagenlecleucel in patients with relapsed or refractory[3] B-ALL at 3 years of age (at the time of screening) to ≤21 years of age (at the initial diagnosis of B-ALL)[4] (target number of patients enrolled,

[3] Patients meeting any of the criteria (a) to (f) were included:
(a) ≥2 relapses occurred in the bone marrow; (b) relapse occurred in the bone marrow after allogeneic hematopoietic stem cell transplantation (HSCT), and tisagenlecleucel is to be administered ≥6 months after the allogeneic HSCT; (c) ineligible for allogeneic HSCT; (d) newly diagnosed ALL that failed to achieve CR after 2 cycles of the same standard chemotherapy; (e) relapsed ALL that failed to achieve CR after 1 cycle of chemotherapy; and (f) patients positive for Philadelphia chromosome who are intolerant to, or have a contraindication to, tyrosine kinase inhibitors (TKIs), or who have not responded to ≥2 TKIs.

[4] Patients aged 3 to 23 years were included.

95 patients; target number of patients treated, 76 patients) at 25 study sites in 11 countries including Japan.

Tisagenlecleucel was intravenously administered as a single dose. Patients weighing ≤50 kg received the target dose of 2.0×10^6 to 5.0×10^6 cells/kg (acceptable dose, 0.2×10^6-5.0×10^6 cells/kg), and patients weighing >50 kg received the target dose of 1.0×10^8 to 2.5×10^8 cells (acceptable dose, 0.1×10^8-2.5×10^8 cells).

In addition, to stabilize the disease during the manufacturing period of tisagenlecleucel (from study enrollment to lymphodepleting [LD] chemotherapy), patients were allowed to receive bridging chemotherapy selected by the investigator. Further, patients showing a peripheral white blood cell count >1000/μL within 1 week before the planned infusion of tisagenlecleucel were required to complete the following LD chemotherapy as pretreatment until 2 days before the infusion, in order to enhance the survival and proliferation of tisagenlecleucel in the patient's body.

LD chemotherapy

- Intravenous infusion of cyclophosphamide hydrate (cyclophosphamide) at 500 mg/m^2 once daily for 2 days and intravenous infusion of fludarabine phosphate (fludarabine) at 30 mg/m^2 once daily for 4 days

- For patients ineligible for treatment with cyclophosphamide and fludarabine,[5)] intravenous infusion of cytarabine 500 mg/m^2 once daily for 2 days and intravenous infusion of etoposide 150 mg/m^2 once daily for 3 days

A total of 92 patients enrolled in Study B2202 underwent leukapheresis, and 75 patients received tisagenlecleucel.[6)] All of patients who received tisagenlecleucel were included in the efficacy analysis population, which also served as the safety analysis population. In total, 96.0% (72 of 75) of patients[7)] received the LD chemotherapy.

The primary endpoint in Study B2202 was the overall remission rate (percentage of patients who achieved CR or CRi) determined by the independent review committee (IRC) according to the following efficacy criteria prepared by the applicant based on the National Comprehensive Cancer Network (NCCN) guideline 2013 version. At the start of the study, no interim analysis was planned, but the efficacy was planned to be evaluated when the follow-up period of ≥6 months elapsed in 50 patients who had received tisagenlecleucel.

Efficacy criteria

According to the following definitions, results were classified into 5 categories: CR, CRi, no-response, relapse, and unknown:

---

5) Patients with a history of Grade 4 hemorrhagic cystitis due to cyclophosphamide or patients resistant to cyclophosphamide

6) Dropout occurred in 17 patients (18.5%) before administration of tisagenlecleucel because of death in 7 patients, manufacturing failure in 7 patients, and adverse events occurring before administration of tisagenlecleucel in 3 patients (systemic mycosis, graft versus host disease, and pneumonia fungal in 1 patient each). In addition, the median period (range) from enrollment to administration of tisagenlecleucel was 45 days (30-105 days).

7) One patient died of respiratory failure during the period between LD chemotherapy and administration of tisagenlecleucel.

- "CR" is defined as a state that meets all of the following criteria:
  - <5% of blast cells in the bone marrow
  - Neutrophil count >1 × 10^9/L, platelet count >100 × 10^9/L, and <1% of blast cells in peripheral blood
  - No clinical finding of extramedullary lesion, and remission state shown by an additional assessment, if any (lumbar puncture, imaging examination of the central nervous system, etc.)
  - No dependence on blood transfusion (neither platelet nor neutrophil transfusion was implemented within 7 days before collection of the peripheral blood specimen for disease assessment)

- "CRi" is defined as a state that meets all of the CR criteria except for the following:
  - Neutrophil count ≤1 × 10^9/L, platelet count ≤100 × 10^9/L in peripheral blood, or platelet or neutrophil transfusion within 7 days before collection of the peripheral blood specimen for disease assessment

- "No-response (NR)" is defined as a state that has not achieved CR or CRi.

- "Relapse" is defined as a state of patients who previously achieved CR or CRi but now have ≥1% of blast cells in peripheral blood, ≥5% of blast cells in the bone marrow, or an extramedullary lesion again.

- "Unknown" is defined as a state of not undergoing baseline assessment or efficacy judgment; the efficacy judgment is not complete; or the judgment is not possible or was not implemented within the specified period. (However, patients with evident relapse should be categorized as "relapse.")

After start of the study, its protocol was revised ([redacted], 20[redacted]) as follows:

- The cut-off data from Study B2202 (as of [redacted] 20[redacted]) and published literature (*N Engl J Med.* 2013;368:1509-18, *N Engl J Med.* 2014;371:1507-17) indicated that pediatric and AYA patients with relapsed or refractory B-ALL could achieve CR or CRi within 3 months after administration of tisagenlecleucel, and thus the follow-up period for assessment of the overall remission rate, the primary endpoint, was changed from 6 to 3 months.

- One interim analysis was planned to evaluate the efficacy of tisagenlecleucel for the application in the US when the initial 50 patients who had received infusion of tisagenlecleucel completed the 3-month follow-up period or prematurely discontinued the study. The final analysis was planned when all the subjects who had received tisagenlecleucel (target number of patients treated, 76 patients) completed the 3-month follow-up period or prematurely discontinued the study. To adjust the type 1 error probability associated with the interim analysis, significance levels for the interim and final analyses were calculated according to the O'Brien-Fleming-type alpha spending function.

- Initially, tisagenlecleucel was manufactured only at a facility in the US, but later another facility in Germany also started to manufacture the product. To evaluate the efficacy and safety of

tisagenlecleucel manufactured in Germany in up to 14 patients, the target number of patients enrolled was changed from 78 to 95.

Furthermore, the study protocol was revised ([redacted], 20[redacted]) to investigate the efficacy and safety of tisagenlecleucel in at least 5 Japanese patients. The enrollment of Japanese patients was started on [redacted], 20[redacted].

Efficacy results:

The interim analysis was performed with a cut-off date of [redacted], 20[redacted]. The overall remission rate determined by the IRC, the primary endpoint, is shown in Table 22. The lower limit (64.5%) of 98.9% confidence interval (CI) of the overall remission rate exceeded the predetermined threshold of 20%.[8)]

Table 22. Results from interim analysis of overall remission rate (determined by the IRC, efficacy analysis population at the time of interim analysis, data cut-off on [redacted], 20[redacted])

	Number of patients (%)
	Overall population N = 50
CR	34 (68.0)
CRi	7 (14.0)
NR	4 (8.0)
Unknown	5 (10.0)
Remission (CR + CRi) (overall remission rate [98.9% CI*] [%])	41 (82.0 [64.5, 93.3])

* Clopper-Pearson method

The final analysis was performed with a cut-off date of April 25, 2017, and the overall remission rate at the time of the final analysis is shown in Table 23.

Table 23. Results from final analysis of overall remission rate (determined by the IRC, efficacy analysis population, data cut-off on April 25, 2017)

	Number of patients (%)	
	Overall population n = 75	Japanese population n = 2
CR	45 (60.0)	0
CRi	16 (21.3)	1 (50.0)
NR	6 (8.0)	1 (50.0)
Unknown	8 (10.7)	0
Remission (CR + CRi) (overall remission rate [95% CI*] [%])	61 (81.3 [70.7, 89.4])	1 (50.0 [1.3, 98.7])

*: Clopper-Pearson method

An additional analysis was performed with a cut-off date of [redacted], 20[redacted] to investigate the efficacy and safety of tisagenlecleucel in Japanese patients; the remission rate is shown in Table 24.

8) In a study of clofarabine in pediatric and AYA patients with relapsed or refractory B-ALL who had received ≥2 lines of chemotherapy, the remission rate was 20% (*J Clin Oncol.* 2006;24:1917-23). The threshold of 20% was therefore used.

Table 24. Results from additional analysis of overall remission rate (determined by the IRC, efficacy analysis population, data cut-off on [redacted], 20[redacted])

	Number of patients (%)
	Japanese population n = 6
CR	3 (50.0)
CRi	1 (16.7)
NR	2 (33.3)
Unknown	0
Remission (CR + CRi) (overall remission rate [95% CI*] [%])	4 (66.7 [22.3, 95.7])

* Clopper-Pearson method

Safety results:

In total, 2.7% (2 of 75) of patients died within 30 days after administration of tisagenlecleucel. Causes of the deaths were disease progression and cerebral haemorrhage in 1 patient each. A causal relationship to either or both of tisagenlecleucel and LD chemotherapy could not be ruled out for cerebral haemorrhage in 1 patient.[9)] In addition, 22.7% (17 of 75) of patients died >30 days after administration of tisagenlecleucel. Causes of the deaths were disease progression in 12 patients, and encephalitis, systemic mycosis, lower respiratory tract infection bacterial, hepatobiliary disease, and unknown causes of death in 1 patient each. A causal relationship to either or both of tisagenlecleucel and LD chemotherapy could not be ruled out for encephalitis in 1 patient, and a causal relationship to tisagenlecleucel could not be ruled out for systemic mycosis in 1 patient.[10)] None of the Japanese patients died owing to adverse events.

7.1.1.2 Global phase II study (CTD 5.3.5.2-4, Study C2201, ongoing since July 2015 [data cut-off on December 8, 2017])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of tisagenlecleucel in adult patients with relapsed or refractory[11)] DLBCL[12)] who were aged ≥18 years (target number of patients enrolled, 118 patients [100 in primary cohort,[13)] 18 in Cohort A[14)]]; target number of patients treated, 95 patients [80 in primary cohort, 15 in Cohort A]) at 27 study sites in 10 countries including Japan.

Tisagenlecleucel was intravenously administered as a single dose (target dose, 5.0×10^8 cells; acceptable dose, 1.0×10^8-5.0×10^8 cells).

9) A male patient aged [redacted] years. Down syndrome coexisted. Day 4 of administration of tisagenlecleucel, cytokine release syndrome (CRS) and febrile neutropenia (FN) occurred. On Day 7, hypoxaemia requiring mechanical ventilation and hypotension requiring high-dose vasopressor occurred. Although tocilizumab was started, disseminated intravascular coagulation occurred on Day 9, followed by renal disorder requiring continuous venovenous hemodiafiltration on Day 12, abdominal compartment syndrome on Day 13, and cerebral haemorrhage on Day 15, which resulted in death.

10) A female patient aged 1[redacted] years. Multiple events of viral, bacterial, and fungal infections, febrile neutropenia as well as septic shock occurred during the pre-treatment period. On Day 3 of administration of tisagenlecleucel, Grade 3 *granulicatella* infection occurred, and antimicrobial agents were started. Grade 4 white blood cell count decreased occurred on Day 4 followed by Grade 3 herpes simplex virus Type 1 and human herpes virus type 6 infection on Day 13, and Grade 3 systemic candida infection on Day 17. Hypoxaemia occurred on Day 32, oxygenation with an oxygen mask was started, and tocilizumab was administered to treat Grade 3 CRS. On Day 42, Grade 1 hallucination occurred, but CRS resolved. On Day 61, death occurred owing to systemic mycosis.

11) The study included patients with ≥2 lines of prior chemotherapy (including rituximab [genetical recombination] and anthracycline antineoplastic drugs) who were ineligible for, or relapsed after, autologous HSCT.

12) Patients with DLBCL histologically transformed from follicular lymphoma were also included.

13) Cohort of patients who received tisagenlecleucel manufactured at the facility in the US

14) Cohort of patients who received tisagenlecleucel manufactured at the facility in Germany

In addition, to stabilize the disease during the manufacturing period of tisagenlecleucel (from study enrollment to LD chemotherapy), patients were allowed to receive bridging chemotherapy selected by the investigator. Further, patients showing a peripheral white blood cell count >1000/μL within 1 week before the planned infusion of tisagenlecleucel were required to complete the following LD chemotherapy as pretreatment until 2 days before the infusion, in order to enhance the survival and proliferation of tisagenlecleucel in the patient's body.

LD chemotherapy

- Intravenous infusion of cyclophosphamide at 250 mg/m^2 once daily for 3 days and intravenous infusion of fludarabine at 25 mg/m^2 once daily for 3 days

- For patients ineligible for treatment with cyclophosphamide and fludarabine,[15)] intravenous infusion of bendamustine hydrochloride (bendamustine) at 90 mg/m^2 once daily for 2 days

The primary endpoint in Study C2201 was the response rate (percentage of patients who achieved CR or PR) determined by the IRC according to the Lugano response criteria (*J Clin Oncol.* 2014;32:3059-68) established by the International Conference on Malignant Lymphoma. One interim analysis was planned to be performed to evaluate the efficacy when the initial 50 patients who had received tisagenlecleucel completed the 6-month follow-up period or prematurely discontinued the study. The primary analysis was planned to be performed when all of the patients who had received tisagenlecleucel (target number of patients treated, 80 patients) completed the 3-month follow-up period or prematurely discontinued the study. To adjust the type 1 error probability associated with the interim analysis, significance levels for the interim and primary analyses were calculated according to the O'Brien-Fleming-type alpha spending function.

After the start of Study C2201, its protocol was revised ([redacted], 20[redacted]) as follows:

- Because the clinical research conducted at Penn indicated that patients with DLBCL could achieve CR within 3 months after administration of tisagenlecleucel, the follow-up period for assessment of the response rate was changed from 6 to 3 months.

- Cohort A was added to evaluate the clinical profile of tisagenlecleucel manufactured at the second facility (in Germany). The primary analysis was to be performed in patients receiving tisagenlecleucel manufactured at the facility in the US (primary cohort).

The protocol was further revised ([redacted], 20[redacted]) to investigate the efficacy and safety of tisagenlecleucel in Japanese patients (target number of patients enrolled, 13patients). The enrollment of Japanese patients was started on [redacted], 20[redacted].

As of the interim analysis (data cut-off on [redacted], 20[redacted]), 141 patients enrolled underwent leukapheresis, and 85 patients (82 in primary cohort, 3 in Cohort A) received tisagenlecleucel. Of the

15) Patients with a history of Grade 4 hemorrhagic cystitis due to cyclophosphamide or patients resistant to chemotherapy including cyclophosphamide.

primary cohort, 51 patients who were subjected to the 3-month post-dose follow-up survey (or prematurely discontinued the study) were included in the efficacy analysis population.

As of the primary analysis (data cut-off on March 8, 2017), 147 patients enrolled underwent leukapheresis, and 99 patients (92 in primary cohort, 7 in Cohort A) received tisagenlecleucel.[16] Of the primary cohort, 81 patients who were subjected to the 3-month post-dose follow-up survey (or prematurely discontinued the study) were included in the efficacy analysis population.

Efficacy results:
The interim analysis was performed with a cut-off date of [redacted], 20[redacted], and the response rate determined by the IRC, the primary endpoint, is shown in Table 25. The lower limit (39.8%) of 99.06% CI of the response rate exceeded the predetermined threshold of 20%.[17]

Table 25. Results from interim analysis of efficacy (determined by the IRC, interim analysis population, data cut-off on [redacted], 20[redacted])

	Number of patients (%)	
	Overall population n = 51	Japanese population n = 2
CR	22 (43.1)	1 (50.0)
PR	8 (15.7)	1 (50.0)
SD	6 (11.8)	0
PD	12 (23.5)	0
Unknown	3 (5.9)	0
Response (CR + PR)	30	2
(Response rate [99.06% CI*] [%])	(58.8 [39.8, 76.1])	(100 [6.9, 100])

* Clopper-Pearson method

In addition, the primary analysis was performed with a cut-off date of March 8, 2017, and the response rate at the time of the primary analysis is shown in Table 26.

Table 26. Results from primary analysis of efficacy (determined by the IRC, efficacy analysis population, data cut-off on March 8, 2017)

	Number of patients (%)	
	Overall population n = 81	Japanese population n = 2
CR	32 (39.5)	1 (50.0)
PR	11 (13.6)	1 (50.0)
SD	11 (13.6)	0
PD	18 (22.2)	0
Unknown	9 (11.1)	0
Response (CR + PR)	43	2
(Response rate [95% CI*] [%])	(53.1 [41.7, 64.3])	(100 [15.8, 100])

* Clopper-Pearson method

In addition, the additional analysis was performed with a cut-off date of December 8, 2017, and the response rate at the time of the additional analysis is shown in Table 27. As of the additional analysis (data cut-off on December 8, 2017), 165 patients enrolled in Study C2201 underwent leukapheresis (145 in primary cohort, 19 in Cohort A), and 111 patients (95 in primary cohort, 16 in Cohort A)

16) In total, 43 patients (29.3%) dropped out before receiving tisagenlecleucel mainly because of deaths in 16 patients, the attending physician decision in 12 patients, and manufacturing failure in 9 patients. In addition, the median period (range) from enrollment to administration of tisagenlecleucel was 54 days (30-357 days).

17) In clinical studies of ibrutinib, etc. in patients with relapsed or refractory DLBCL, the response rate was 14% to 21.7% (*Clin Lymphoma Myeloma Leuk.* 2010;10:192-6, *Hematology.* 2008;13:261-6, *Blood.* 2012; 120: Abstract 686). The threshold of 20% was therefore used.

received tisagenlecleucel. Of the primary cohort, 93 patients who were subjected to the 3-month post-dose follow-up survey (or prematurely discontinued the study) were included in the efficacy analysis population for the additional analysis, and all of the 111 patients who had received tisagenlecleucel were included in the safety analysis population.

Table 27. Results from additional analysis of efficacy (determined by the IRC, efficacy analysis population, data cut-off on December 8, 2017)

	Number of patients (%)	
	Overall population n = 93	Japanese population n = 3
CR	37 (39.8)	1 (33.3)
PR	11 (11.8)	1 (33.3)
SD	14 (15.1)	0
PD	24 (25.8)	1 (33.3)[*1]
Unknown	7 (7.5)	0
Response (CR + PR)	48	2
(Response rate [95% CI[*2]] [%])	(51.6 [41.0, 62.1])	(66.7 [9.4, 99.2])

*1 This patient had received a diagnosis of DLBCL when enrolled in the study, but neuroendocrine tumor was diagnosed 1 month after administration of tisagenlecleucel.
*2 Clopper-Pearson method

Furthermore, an additional analysis was performed with a cut-off date of [redacted], 20[redacted] to investigate the efficacy and safety of tisagenlecleucel in Japanese patients, and the response rate is shown in Table 28.

Table 28. Results from additional analysis of response rate (determined by the IRC, efficacy analysis population, data cut-off on [redacted], 20[redacted])

	Number of patients (%)
	Japanese population n = 9
CR	5 (55.6)
PR	2 (22.2)
SD	0
PD	2 (22.2)
Response (CR + PR)	7
(Response rate [95% CI[*]] [%])	(77.8 [40.0, 97.2])

* Clopper-Pearson method

Safety results:

In total, 2.7% (3 of 111) of patients died within 30 days after administration of tisagenlecleucel. Causes of the deaths were disease progression in 3 patients, and a causal relationship to tisagenlecleucel or LD chemotherapy was ruled out in all patients. In addition, 45.0% (50 of 111) of patients died >30 days after administration of tisagenlecleucel. Causes of the deaths were disease progression in 42 patients, multiple organ dysfunction syndrome in 2 patients, and cerebral haemorrhage, duodenal ulcer haemorrhage, neuroendocrine carcinoma, pulmonary haemorrhage, chronic kidney disease, and sepsis in 1 patient each. For pulmonary haemorrhage in 1 patient,[18)] a

18) A male patient aged 6[redacted] years with a history of gastrointestinal haemorrhage. On Day 1 of administration of tisagenlecleucel, Grade 2 CRS occurred. On Day 3, CRS deteriorated to Grade 3, and pyrexia at 40.4°C occurred. On Day 5, he was admitted to the intensive care unit (ICU), but on Day 11 he was discharged from the ICU because CRS resolved. On Day 14, he experienced the second event of CRS associated with hypotension, hypoxaemia, mental status changes, etc. On Day 23, he experienced Grade 4 platelet count decreased and received platelet transfusion. On Day 30, CRS resolved. On Day 34, he experienced Grade 4 platelet count decreased again and received platelet transfusion. On Day 37, he experienced Grade 3 gastrointestinal haemorrhage, Grade 4 tumour haemorrhage and pulmonary haemorrhage. On Day 45, he experienced tumour haemorrhage and pulmonary haemorrhage again and died despite receiving transfusion, epinephrine administration, and cardiopulmonary resuscitation.

causal relationship to either or both of tisagenlecleucel and LD chemotherapy could not be ruled out. None of the Japanese patients died owing to adverse events.

7.1.2 Foreign clinical studies

7.1.2.1 Foreign phase II study (CTD 5.3.5.2-2, Study B2205J, ongoing since August 2014 [data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of tisagenlecleucel in patients with relapsed or refractory[19] B-ALL at 3 years of age (at the time of screening) to ≤21 years of age (at the initial diagnosis of B-ALL)[20] (target number of patients enrolled, 67 patients; target number of patients treated, 50 patients) at 9 study sites in 1 country.

Tisagenlecleucel was intravenously administered as a single dose. Patients weighing ≤50 kg received the target dose of 2.0×10^6 to 5.0×10^6 cells/kg (acceptable dose, 0.2×10^6-5.0×10^6 cells/kg), and patients weighing >50 kg received the target dose of 1.0×10^8 to 2.5×10^8 cells (acceptable dose, 0.1×10^8-2.5×10^8 cells). In addition, to stabilize the disease during the manufacturing period of tisagenlecleucel (from enrollment to LD chemotherapy), patients were allowed to receive bridging chemotherapy considered appropriate by the investigator. Further, patients showing a peripheral white blood cell count >1000/μL within 1 week before the planned infusion of tisagenlecleucel were required to complete the following LD chemotherapy as pretreatment until 2 days before the infusion, in order to enhance the survival and proliferation of tisagenlecleucel in the patient's body.

LD chemotherapy

- Intravenous infusion of cyclophosphamide at 500 mg/m^2 once daily for 2 days and intravenous infusion of fludarabine at 30 mg/m^2 once daily for 4 days

- For patients ineligible for treatment with cyclophosphamide and fludarabine,[21] intravenous infusion of cytarabine at 500 mg/m^2 once daily for 2 days and intravenous infusion of etoposide at 150 mg/m^2 once daily for 3 days

A total of 35 patients enrolled underwent leukapheresis, and 29 patients received tisagenlecleucel.[22] All of the patients who had received tisagenlecleucel were included in the efficacy and safety analyses.

The primary endpoint was the overall remission rate within 6 months after administration of tisagenlecleucel (percentage of patients who achieved CR or CRi) determined by the IRC according to the same efficacy criteria as those in Study B2202.

---

19) Patients meeting any of the criteria (a) to (f) were included:
(a) ≥2 relapses occurred in the bone marrow; (b) relapse occurred in the bone marrow after allogeneic HSCT, and ≥6 months have passed since the allogeneic HSCT; (c) ineligible for allogeneic HSCT; (d) newly diagnosed primary ALL that failed to achieve CR after 2 cycles of the same standard chemotherapy; (e) relapsed ALL that failed to achieve CR after 1 cycle of chemotherapy; and (f) patients positive for Philadelphia chromosome who are intolerant to, or have a contraindication to, TKIs, or who have not responded to ≥2 TKIs.

20) Patients aged 3 to 25 years were included.

21) Patients with a history of Grade 4 hemorrhagic cystitis due to cyclophosphamide or patients resistant to cyclophosphamide.

22) Six patients (17.1%) dropped out before receiving tisagenlecleucel because of deaths in 4 patients and manufacturing failure in 2 patients. In addition, the median period (range) from enrollment to administration of tisagenlecleucel was 37 days (24-86 days).

After start of the study, its protocol was revised ([redacted], 20[redacted]). The interim analysis was planned to be performed when at least 50 patients who had been enrolled in Study B2205J and had received tisagenlecleucel manufactured at Penn completed the ≥6-month follow-up period or prematurely discontinued Study B2205J. In addition, the final analysis was planned to be performed when all of the patients who had been enrolled in Study B2205J and had received tisagenlecleucel manufactured at Penn and by the applicant completed the ≥6-month follow-up period or prematurely discontinued Study B2205J. To adjust the type 1 error probability associated with the interim analysis, significance levels for the interim and final analyses were calculated according to the O'Brien-Fleming-type alpha spending function.

Efficacy results:

The interim analysis was performed with a cut-off date of [redacted], 20[redacted], and the overall remission rate determined by the IRC, the primary endpoint, is shown in Table 29. The lower limit (43.6%) of 98.95% CI of the overall remission rate exceeded the predetermined threshold of 20%.[23)]

Table 29. Results from interim analysis of overall remission rate (determined by the IRC, efficacy analysis population at the time of interim analysis, data cut-off on [redacted], 20[redacted])

	Number of patients (%)
	n = 29
CR	18 (62.1)
CRi	2 (6.9)
NR	7 (24.1)
Unknown	2 (6.9)
Remission (CR + CRi) (overall remission rate [98.95% CI*] [%])	20 (69.0 [43.6, 88.1])

* Clopper-Pearson method

Safety results:

In total, 6.9% (2 of 29) of patients died within 30 days after administration of tisagenlecleucel. Causes of the deaths were disease progression and embolic stroke in 1 patient each. A causal relationship to tisagenlecleucel was ruled out for embolic stroke in 1 patient,[24)] but that to the LD chemotherapy could not be ruled out. In addition, 27.6% (8 of 29) of patients died >30 days after administration of tisagenlecleucel. Causes of the deaths were all disease progression.

[23)] In a study of clofarabine in pediatric and AYA patients with relapsed or refractory B-ALL who had received ≥2 lines of chemotherapy, the remission rate was 20% (*J Clin Oncol.* 2006;24:1917-23). The threshold of 20% was therefore used.

[24)] A female patient aged [redacted] years. She received cyclophosphamide and fludarabine as LD chemotherapy. On Day 2 of administration of tisagenlecleucel, Grade 3 CRS and FN occurred. On Day 6, Clostridium difficile infection was found in culture stool. The infection was treated with antibacterial drugs, etc. On Day 17, FN resolved. On Day 21, Grade 3 FN occurred again. On Day 24, Grade 4 embolic stroke and Grade 2 confusional state occurred, and endotracheal intubation was performed. On the same day, computed tomography (CT) examination showed cerebral haemorrhage, and echocardiography showed a mass in the left atrium. On Day 31, she died of embolic stroke. Autopsy revealed a clot mass infected with *Mucor* in the atrium.

7.2 Reference data

7.2.1 Foreign clinical studies

7.2.1.1 Foreign phase I study (CTD 5.3.5.4-1, Study CTL019B2102J [Study B2102J], March 2010 to July 2015)

An open-label, uncontrolled study was conducted to investigate the safety of tisagenlecleucel in patients with relapsed or refractory[25)] B-cell leukemia or malignant lymphoma at ≥18 years of age (target number of patients enrolled, 30 patients) at 1 study site in 1 country.

Tisagenlecleucel was intravenously administered at the target dose of 5.0×10^9 cells (acceptable dose, 1.5×10^7-5.0×10^9 cells), divided into 3 infusions (10%, 30%, and 60% of the target number of cells administered at the first, second, and third infusions, respectively).

Safety results:
No deaths occurred within 30 days after administration of tisagenlecleucel. In addition, 40.0% (8 of 20) of the patients died >30 days after administration of tisagenlecleucel. Causes of the deaths were myocardial infarction, graft versus host disease, Pseudomonas infection, sepsis, adenocarcinoma, haemorrhage, unknown cause, and disease progression in 1 patient each. A causal relationship to tisagenlecleucel could not be ruled out for Pseudomonas infection in 1 patient.[26)]

7.2.1.2 Foreign phase I/IIa study (CTD 5.3.5.2-3, Study B2101J, ongoing since March 2012 [data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the safety of tisagenlecleucel in patients with relapsed or refractory[25)] B-cell leukemia or malignant lymphoma at 1 to 24 years of age (target number of patients enrolled, 86 patients) at 1 study site in 1 country.

Tisagenlecleucel was intravenously administered at 1.5×10^7 to 5.0×10^9 cells, divided into 3 infusions (10%, 30%, and 60% of the total number of cells administered at the first, second, and third infusions, respectively).

Safety results:
In total, 5.4% (3 of 56) of patients died within 30 days after the final administration of tisagenlecleucel. Causes of the deaths were all disease progression, and a causal relationship to tisagenlecleucel was ruled out for all deaths.

7.2.1.3 Foreign phase II study (CTD 5.3.5.4-2, Study CTL019A2201 [Study A2201], ongoing since January 2013 [data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the safety of tisagenlecleucel in patients with relapsed or refractory[27)] chronic lymphocytic leukemia (CLL) at ≥18 years of age (target number of patients enrolled, 30 patients) at 1 study site in 1 country.

---

25) The study included patients with no standard therapeutic options including HSCT.
26) A male patient aged 5[redacted] years with CLL. Death occurred 639 days after administration of tisagenlecleucel.
27) Patients with ≥2 lines of prior chemotherapy were included.

Tisagenlecleucel was intravenously administered as a single low dose ($1.0\text{-}5.0 \times 10^7$ cells) or a single high dose ($1.0\text{-}5.0 \times 10^8$ cells).

Safety results:
In total, no deaths occurred within 30 days after administration of tisagenlecleucel. In addition, 32.1% (9 of 28) of patients died >30 days after administration of tisagenlecleucel. Causes of the deaths were disease progression in 7 patients; hypoxia in 1 patient; and disease progression and post procedural infection (infection at the site of aspiration bone marrow) in 1 patient. A causal relationship to tisagenlecleucel could not be ruled out for hypoxia in 1 patient[28)] and post procedural infection in 1 patient.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA determined that, among the clinical studies included in the submitted evaluation data, the following 2 global phase II studies were important in evaluating the efficacy and safety of tisagenlecleucel in pediatric and AYA patients with B-ALL and patients with DLBCL, and data from these studies were mainly used for the evaluation.

- Study B2202 in pediatric and AYA patients with relapsed or refractory B-ALL
- Study C2201 in patients with relapsed or refractory DLBCL

Data from the Japanese cohorts in Studies B2202 and C2201 were used to evaluate the efficacy and safety of tisagenlecleucel in Japanese patients.

7.R.2 Efficacy in pediatric and AYA patients with relapsed or refractory B-ALL

As a result of the following review, PMDA has concluded that tisagenlecleucel was shown to be effective in pediatric and AYA patients with relapsed or refractory B-ALL to a certain extent.

7.R.2.1 Efficacy endpoint and evaluation results

The applicant's explanation about the primary endpoint in Study B2202 and the efficacy of tisagenlecleucel in pediatric and AYA patients with relapsed or refractory B-ALL:
Pediatric and AYA patients with relapsed or refractory B-ALL, the study population of Study B2202, are reported to have poor prognosis with the median overall survival (OS) of 3 to 6 months (*J Clin Oncol.* 2010;28:648-54, etc.). In this population, achieving complete remission has a clinical significance because there is no standard treatment that has proven to extend OS. Thus selecting remission rate as the primary endpoint in Study B2202 was appropriate.

In Study B2202, the efficacy was determined according to the original criteria established based on the guideline of the International Working Group for ALL at the time of study planning (*J Clin Oncol.* 2003;21:4642-9), and based on NCCN guidelines 2013 version prepared on the basis of a report from

[28)] A male patient aged 5[redacted] years with CLL. On Day 3 of administration of tisagenlecleucel, Grade 3 pneumonitis and Grade 2 pyrexia occurred. On Day 4, Grade 4 dyspnoea occurred, leading to admission to the ICU. The CT examination on Day 5 resulted in a diagnosis of pneumonitis associated with chemotherapy. Pneumonitis was resolving with corticosteroid, etc., and the patient was discharged (date unknown). On Day 62, hypoxaemia occurred, leading to endotracheal intubation. Bronchoscopy on Day 63 revealed bilateral pulmonary haemorrhage. Despite high-dose corticosteroid treatment, the patient died of hypoxaemia on Day 72.

the American Society of Hematology (*Blood.* 2007;109:1810-6). Table 30 shows major differences between the NCCN guidelines and the criteria of Study B2202 and reasons for the differences.

Table 30. Major differences in the efficacy criteria (excerpt) between the NCCN guidelines and Study B2202

Item	NCCN guidelines	Study B2202	Reason for the difference
Classification	5 classes of "CR," "CRi," "refractory," "disease progression," and "relapse"	4 classes of "CR," "CRi," "no-response," and "relapse"	There is no need to distinguish "refractory" from "disease progression" in evaluating the efficacy of tisagenlecleucel, and thus both are categorized as "no-response."
Definition of CR (Extramedullary lesion)	No evidence of extramedullary lesion	• No clinical findings potentially attributable to an extramedullary lesion (by physical exam and central nervous system symptom assessment) • Remission confirmed by an additional assessment, if any (lumbar puncture examination, imaging examination of the central nervous system, cerebrospinal fluid examination such as biopsy)	The NCCN guidelines do not provide a clear definition. A detailed definition was therefore established for Study B2202.
Definition of CR (Trilineage hematopoiesis)	Evidence of trilineage hematopoiesis	Peripheral blood cell counts are restored in patients who have not received platelet or neutrophil transfusion within 7 days before peripheral blood collection.	The NCCN guidelines do not provide a clear definition. A detailed definition was therefore established for Study B2202.

In consideration of a result from the efficacy interim analysis in Study B2202, which presented the overall remission rate significantly exceeding the pre-determined threshold [see Section 7.1.1.1], and the following points, tisagenlecleucel is expected to be effective in pediatric and AYA patients with relapsed or refractory B-ALL:

- Achieving minimal residual disease (MRD) negative bone marrow is expected to lead to favorable prognosis in pediatric and AYA patients with relapsed or refractory ALL (*Lancet.* 2001;358:1239-41, etc.). In Study B2202, 81.3% (61 of 75) of patients achieved remission with MRD negative bone marrow,[29] and especially, all of the patients who achieved CR or CRi within 3 months after administration of tisagenlecleucel also achieved MRD negative bone marrow.

- The median duration of remission in patients who achieved remission has not been obtained because the percentage of continued remission has not reached 50% (median follow-up period, 9.92 months), indicating that the remission state is maintained.

- The OS (median) in pediatric and AYA patients with relapsed or refractory ALL is approximately 3 to 6 months (*J Clin Oncol*. 2010;28:648-54, *J Clin Oncol*. 2010;28:2339-47, etc.). In Study B2202, on the other hand, the median OS [95% CI] (months) in 75 patients who had received tisagenlecleucel was 19.1 [15.2, not estimated] at the last analysis timepoint, and the 12-month survival rate [95% CI] (%) was 76.4 [62.7, 85.5]. The results of OS from this study, compared with those in the past reports, indicate that tisagenlecleucel is expected to be effective. Figure 3 shows a swimmer's plot on survival period.

[29] MRD negative was defined as <0.01% as determined by FCM at a central laboratory.

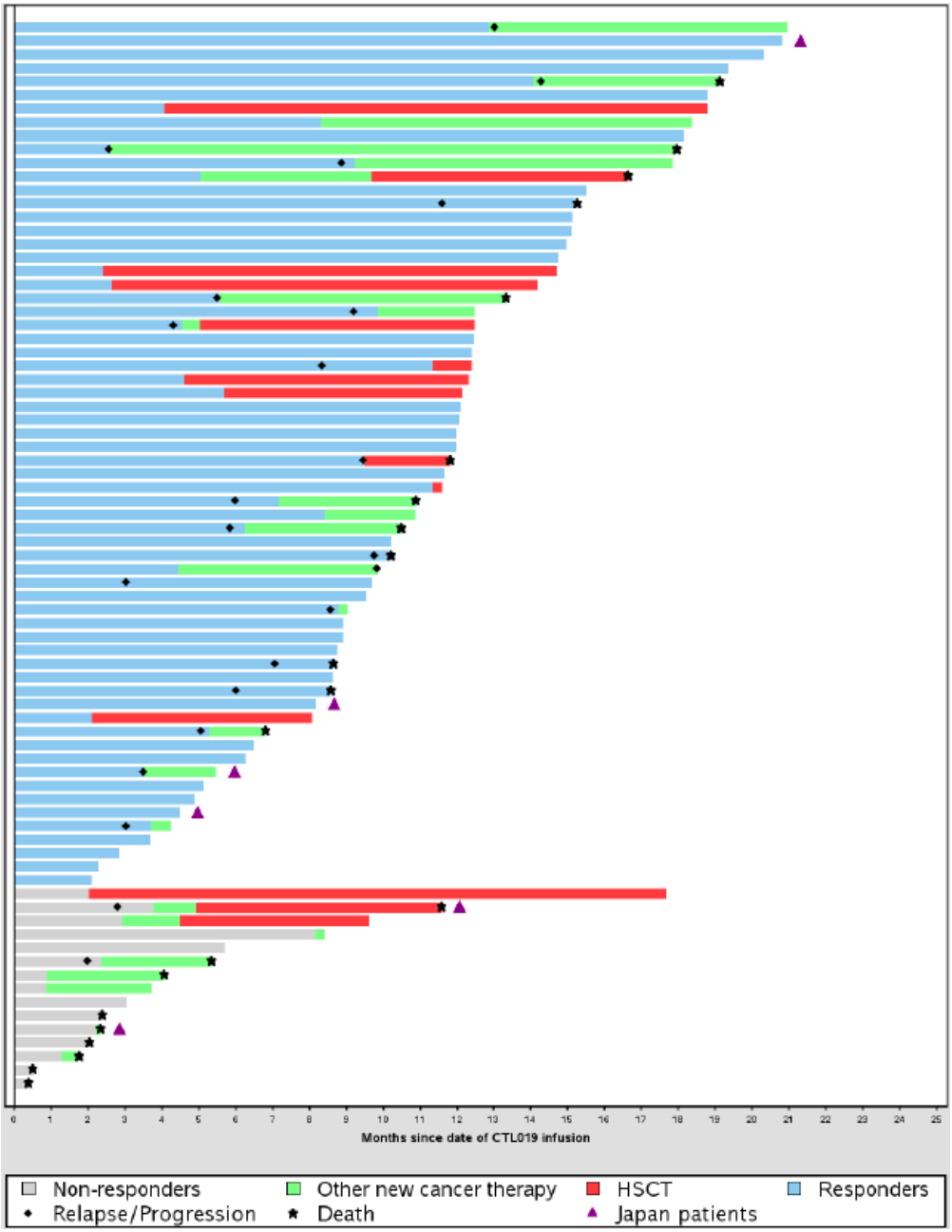

Figure 3. Swimmer's plot in Study B2202
(data cut-off on April 25, 2017 for non-Japanese patients and [redacted], 20[redacted] for Japanese patients)

- Tisagenlecleucel is effective irrespective of age category. In particular, a high response rate is obtained also in patients aged ≥10 years who are known to have poor prognosis (Practical guidelines for pediatric leukemia and lymphoma, 2016 version, issued by the Japanese Society of Pediatric Hematology/Oncology, etc.) (Table 31).

Table 31. Analysis results by age
(centrally assessed, efficacy analysis population, data cut-off on April 25, 2017)

	Number of patients (%)		
	<10 years n = 31	≥10 and <18 years n = 31	≥18 years n = 13
CR	16 (51.6)	22 (71.0)	7 (53.8)
CRi	8 (25.8)	5 (16.1)	3 (23.1)
No response	3 (9.7)	1 (3.2)	2 (15.4)
Unknown	4 (12.9)	3 (9.7)	1 (7.7)
Remission (CR + CRi)	24	27	10
(overall remission rate [95% CI*] [%])	(77.4 [58.9, 90.4])	(87.1 [70.2, 96.4])	(76.9 [46.2, 95.0])

* Clopper-Pearson method

- As described below, even the sub-groups generally considered to have poor prognosis showed favorable results indicating that tisagenlecleucel is expected to be effective:
  - Remission was achieved in 82.6% (38 of 46) of patients with a prior treatment with hematopoietic stem cell transplantation (HSCT) and 79.3% (23 of 29) of patients without a prior treatment with HSCT, indicating that tisagenlecleucel can be expected to be equally effective in both patients with a post-HSCT relapsed or refractory malignancy and patients without a prior treatment with HSCT.
  - Of 6 patients with a refractory malignancy who had not achieved CR even after ≥2 lines of chemotherapy, 5 patients (83.3%) achieved remission.
  - Of 28 patients with high-risk mutations,[30)] 22 patients (78.6%) achieved remission.
  - Of 6 patients with Down syndrome, 5 patients (83.3%) achieved remission.

- An additional analysis (data cut-off on [redacted], 20[redacted]) in Study B2202 showed that 4 of 6 Japanese patients achieved remission (3 patients with CR, 1 patient with CRi); the remission rate [95% CI] (%) was 66.7 [22.3, 95.7] [see Section 7.1.1.1]. All of the 4 patients achieved MRD negative bone marrow. In addition, 1 of 3 patients with CR experienced relapse 106 days after administration of tisagenlecleucel, but the remaining 2 patients are alive without relapse (at 120 and 169 days after administration, respectively) (Figure 3). In consideration of the above results, tisagenlecleucel is expected to be effective in Japanese patients as well.

PMDA's conclusion:
The above applicant's explanation is understandable. According to the results described above, tisagenlecleucel was shown to be effective to a certain extent in the patient population eligible for Study B2202.

30) Patients with *BCR-ABL* fusion gene or *MLL* rearrangement

7.R.2.2 LD chemotherapy in pediatric and AYA patients with relapsed or refractory B-ALL

The protocol of Study B2202 stipulated that patients must undergo LD chemotherapy when their peripheral white blood cell count exceeded 1000/μL within 1 week prior to the planned administration of tisagenlecleucel [see Section 7.1.1.1]. The applicant explained the clinical significance of LD chemotherapy, reasons for selection of antineoplastic drugs used for LD chemotherapy, and the efficacy and safety of LD chemotherapy by type.

The applicant's explanation:

Clinical significance of LD chemotherapy

Chemotherapy before administration of tisagenlecleucel is expected to enhance the survival and proliferation of CAR-expressing T cells in the body and thus to augment the antitumor effect of tisagenlecleucel by strengthening the innate immunity (*Ann Oncol.* 1996;7:827-35), increasing use of cytokines (*Nat Immunol.* 2001;2:1032-9), and decreasing the number of regulatory T cells (*J Exp Med.* 2002;195: 85-94) and bone marrow-derived suppressor cells (*J Exp Med.* 2002;195:485-94 and *Eur J Immunol.* 2001;31:2642-51).

Antineoplastic drugs used for LD chemotherapy

Based on clinical experience from non-myeloablative allogeneic HSCT practices and in clinical studies of tisagenlecleucel conducted by Penn, the applicant selected (1) cyclophosphamide + fludarabine and, for patients ineligible for these drugs, (2) cytarabine + etoposide.

Efficacy and safety of LD chemotherapy

Pooled data from Studies B2202 and B2205J were analyzed because these studies used the same LD chemotherapy regimen.

In Studies B2202 and B2205J, 99 patients received LD chemotherapy (97 receiving cyclophosphamide + fludarabine, 2 receiving cytarabine + etoposide).

Of these, 87 patients received cyclophosphamide and fludarabine at predetermined doses, but 10 patients received these drugs at reduced doses. The remaining 2 patients received cytarabine and etoposide at predetermined doses.

The efficacy of cyclophosphamide + fludarabine:

Of the 97 patients who had received cyclophosphamide + fludarabine, 79 (81.4%) were found to have a peripheral white blood cell count ≤1000/μL after the chemotherapy. In addition, tisagenlecleucel led to CR in 58 patients (59.8%) and CRi in 20 patients (20.6%); the overall remission rate [95% CI] (%) was 80.4 [71.1, 87.8].

The safety of cyclophosphamide + fludarabine:

Tables 32 and 33 show the summary of safety and incidences of adverse events that occurred within 8 weeks after the administration of tisagenlecleucel and require special attention when using tisagenlecleucel (cytokine release syndrome [CRS], tumor lysis syndrome [TLS], febrile neutropenia

[FN], infection, neuropathy, and myelosuppression [31)]) in the 97 patients who received cyclophosphamide + fludarabine. In patients who received cyclophosphamide + fludarabine, incidences of the adverse events requiring special attention when using tisagenlecleucel were not clearly increased; there were no safety concerns. No particular attention has to be paid to the safety.

Table 32. Summary of safety (Studies B2202 and B2205J)

	Number of patients (%) n = 97
All adverse events	97 (100)
Grade ≥ 3 adverse events	83 (85.6)
Adverse events leading to death	6 (6.2)
Serious adverse events	74 (76.3)

Table 33. Adverse events requiring special attention (Studies B2202 and B2205J)

	Number of patients (%) n = 97	
	All Grades	Grade 3 or 4
CRS	78 (80.4)	41 (42.3)
TLS	2 (2.1)	2 (2.1)
FN	35 (36.1)	35 (36.1)
Infection	41 (42.3)	18 (18.6)
Neuropathy	35 (36.1)	10 (10.3)
Myelosuppression	36 (37.1)	31 (32.0)

The efficacy of cytarabine + etoposide:
Two patients[32)] who had received cytarabine + etoposide showed a decreased lymphocyte count after treatment with tisagenlecleucel (peripheral white blood cell count: 140 and 600/μL, respectively). However, both patients died 10 days after receiving tisagenlecleucel due to deterioration of the underlying disease. Therefore evaluating the efficacy of cytarabine + etoposide is difficult.

The safety of cytarabine + etoposide:
Grade 3 vomiting and blood fibrinogen decreased occurred in 1 patient in Study B2202, but no serious adverse events occurred. The safety of cytarabine + etoposide cannot be fully evaluated because only a few patients received these drugs. At present, however, no particular attention has to be paid to the safety of these drugs.

PMDA's view:
Study protocols stipulated that patients must undergo LD chemotherapy when their peripheral white blood cell count exceeded 1000/μL within 1 week prior to the planned administration of tisagenlecleucel. Therefore patients receiving LD chemotherapy have not been compared with those not receiving LD chemotherapy. Thus the effects of LD chemotherapy on the efficacy and safety of tisagenlecleucel remain unclear.

In view the following points, however, LD chemotherapy (cyclophosphamide + fludarabine, or cytarabine + etoposide) should be recommended when the peripheral white blood cell count exceeds 1000/μL within 1 week prior to the planned administration of tisagenlecleucel:

31) Events that did not resolve by 28 days after administration of tisagenlecleucel are tabulated.
32) Both of them had a prior treatment with cytarabine and etoposide.

- The above applicant's explanation (i.e., LD chemotherapy before administration of tisagenlecleucel is expected to be effective) is understandable to some extent based on the published literature.

- In Studies B2202 and B2205J, cyclophosphamide + fludarabine decreased the peripheral white blood cell count. Further, the results of the studies suggested the efficacy of tisagenlecleucel.

- In Studies B2202 and B2205J, only 2 patients received cytarabine + etoposide, and both of them died 10 days after administration of tisagenlecleucel. Thus, the effects of cytarabine + etoposide on the efficacy of tisagenlecleucel remain unclear. However, cytarabine + etoposide should be kept as an LD chemotherapy option, because this regimen decreases the peripheral white blood cell count, and a certain number of patients are ineligible for cyclophosphamide + fludarabine in clinical settings.

- At present, LD chemotherapy does not require any particular attention to the safety and is tolerable.

7.R.3 Efficacy in patients with relapsed or refractory DLBCL

As a result of the following review, PMDA has concluded that tisagenlecleucel was shown to be effective to a certain extent in patients with relapsed or refractory DLBCL.

7.R.3.1 Efficacy endpoint and evaluation results

The applicant's explanation about the primary endpoint in Study C2201 and the efficacy of tisagenlecleucel in patients with relapsed or refractory DLBCL:

Among patients with relapsed or refractory DLBCL (i.e., patients eligible for Study C2201), those who responded to treatment had favorable outcome (*Bone Marrow Transplant.* 2016;51:51-7, etc.). This suggests that achieving a response has a clinical significance in this patient population, and thus the response rate was selected as the primary endpoint in Study C2201. The response rate was determined according to the internationally accepted Lugano response criteria.

In view of a result from the efficacy interim analysis in Study C2201, which presented the response rate significantly exceeding the pre-determined threshold [see Section 7.1.1.2], and the following points, tisagenlecleucel is expected to be effective in patients with relapsed or refractory DLBCL:

- The median duration of response in patients who achieved response has not been obtained because the percentage of continued response has not reached 50% (median follow-up period, 13.9 months), indicating that the response state is maintained.

- The OS (median) in patients with relapsed or refractory DLBCL is approximately 4.4 to 6.3 months (*Bone Marrow Transplant.* 2016;51:51-7, etc.). In Study C2201, on the other hand, the median OS [95% CI] (months) in 111 patients who had received tisagenlecleucel was 11.7 [6.6, not estimated] at the additional analysis timepoint (data cut-off on December 8, 2017), and the 12-month survival rate [95% CI] (%) was 49.0 [38.5, 58.7]. The results on OS from this study, compared with those in the past reports, indicate that tisagenlecleucel is expected to be effective. Figure 4 shows a swimmer's plot on survival period.

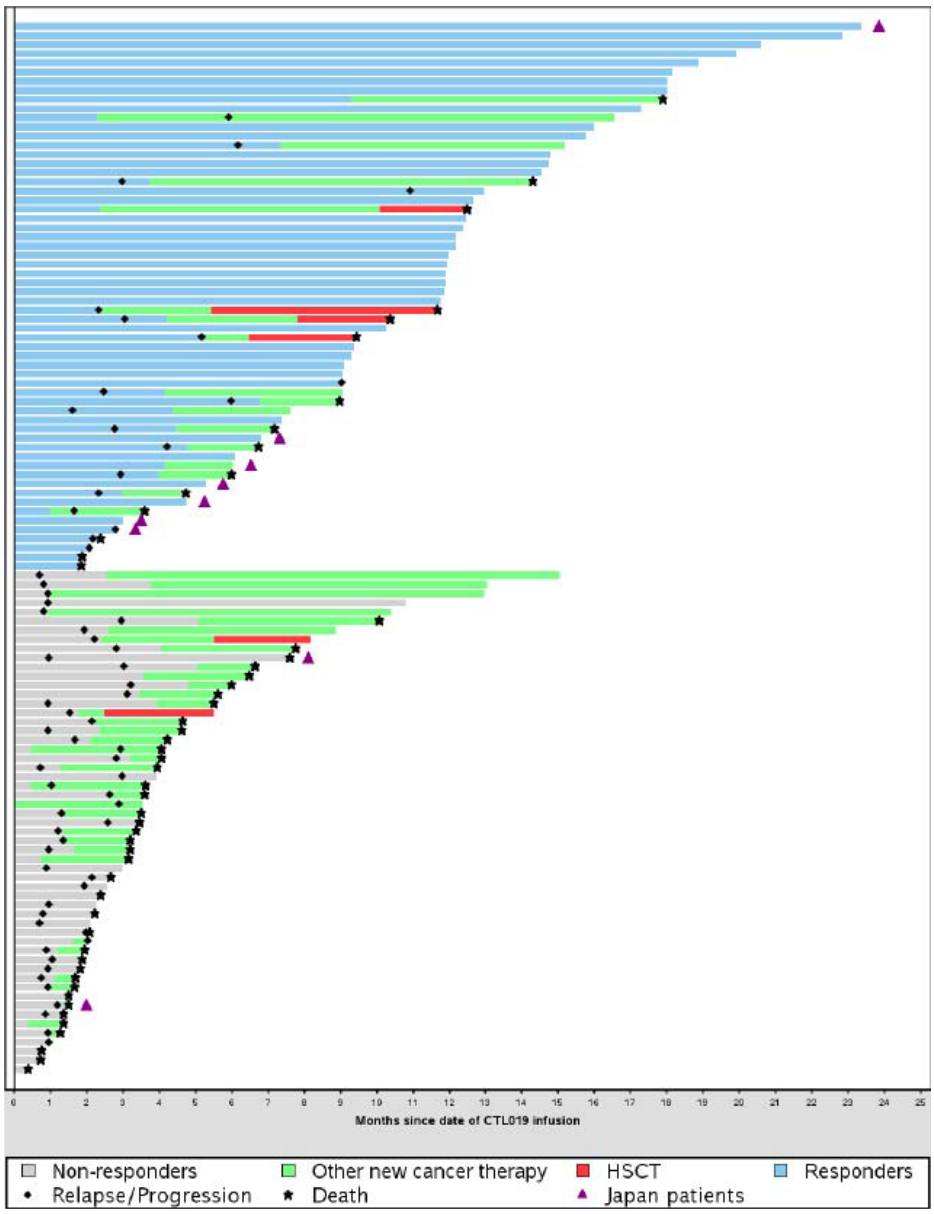

Figure 4. Swimmer's plot in Study C2201
(data cut-off on December 8, 2017 for non-Japanese patients and [redacted], 20[redacted] for Japanese patients)

- A Japanese additional analysis (data cut-off on [redacted], 20[redacted]) in Study C2201 was performed to investigate the efficacy of tisagenlecleucel in Japanese patients (n = 9). The results showed that 7 patients responded to the drug (5 with CR, 2 with PR); the response rate [95% CI] (%) was 77.8 [40.0, 97.2] [see Section 7.1.1.2]. Of the 5 patients with CR, 4 are still alive without relapse (90, 91, 78, and 550 days after administration, respectively, as of writing). These results suggest that tisagenlecleucel is expected to be effective in Japanese patients as well.

The above applicant's explanation is understandable. On the basis on the above results, PMDA has concluded that tisagenlecleucel was shown to be effective to a certain extent in the patient population eligible for Study C2201.

7.R.3.2 LD chemotherapy in patients with DLBCL

The protocol of Study C2201 stipulated that patients must undergo LD chemotherapy when their peripheral white blood cell count exceeded 1000/μL within 1 week prior to the planned administration of tisagenlecleucel [see Section 7.1.1.2]. The applicant explained reasons for selection of antineoplastic drugs used for LD chemotherapy and the efficacy and safety of LD chemotherapy by type. The clinical significance of LD therapy in patients with DLBCL is the same as that in patients with B-ALL [see Section 7.R.2.2].

The applicant's explanation:

Antineoplastic drugs used for LD chemotherapy

The applicant selected cyclophosphamide + fludarabine because this regimen was used in clinical development of CAR-T-cell therapy in patients with CD19-positive non-Hodgkin's lymphoma (*Sci Transl Med.* 2016;8:355ra116). Furthermore, for patients ineligible for cyclophosphamide + fludarabine, bendamustine alone was selected, because this drug was considered to potently reduce lymphocytes in patients with non-Hodgkin's lymphoma.

The efficacy and safety of LD chemotherapy

In Study C2201, 103 patients received LD chemotherapy (81 receiving cyclophosphamide + fludarabine,[33)] 22 receiving bendamustine alone).

Efficacy results:

Of patients who received cyclophosphamide + fludarabine, 63 received the drugs at predetermined doses and 17 at other doses. Of patients who received bendamustine alone, 20 received the drug at predetermined dose and 2 at other doses.

Table 34 shows the response rate to LD chemotherapy.

Table 34. Analysis results by LD chemotherapy type (centrally assessed, data cut-off on December 8, 2017)

	Number of patients (%)	
	Cyclophosphamide + fludarabine n = 68	Bendamustine n = 18
CR	28 (41.2)	7 (38.9)
PR	9 (13.2)	2 (11.1)
SD	10 (14.7)	3 (16.7)
PD	16 (23.5)	4 (22.2)
Unknown	5 (7.4)	2 (11.1)
Response (CR + PR)	37	9
(Response rate [95% CI*] [%])	(54.4 [41.9, 66.6])	(50.0 [26.0, 74.0])

* Clopper-Pearson method

Safety results:

Tables 35 and 36 show the summary of safety and incidences of adverse events that occurred within 8 weeks after the administration of tisagenlecleucel and require special attention when using tisagenlecleucel (i.e., CRS, TLS, FN, infection, neuropathy, and myelosuppression[34)]).

33) One patient was treated with cyclophosphamide alone at the discretion of the attending physician.

34) Events that did not resolve by 28 days after administration of tisagenlecleucel are tabulated.

Table 35. Summary of safety (Study C2201)

	Number of patients (%)	
	Cyclophosphamide + fludarabine n = 81	Bendamustine n = 22
All adverse events	81 (100)	22 (100)
Grade ≥3 adverse events	71 (87.7)	21 (95.5)
Adverse events leading to death	7 (8.6)	2 (9.1)
Serious adverse events	51 (63.0)	16 (72.7)

Table 36. Adverse events requiring special attention (Study C2201)

	Number of patients (%)			
	Cyclophosphamide + fludarabine n = 81		Bendamustine n = 22	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
CRS	44 (54.3)	15 (18.5)	15 (68.2)	6 (27.3)
TLS	0	0	0	0
FN	13 (16.0)	12 (14.8)	3 (13.6)	3 (13.6)
Infection	29 (35.8)	18 (22.2)	5 (22.7)	2 (9.1)
Neuropathy	16 (19.8)	10 (12.3)	5 (22.7)	2 (9.1)
Myelosuppression	35 (43.2)	26 (32.1)	9 (40.9)	6 (27.3)

PMDA's view:

Study protocol stipulated that patients must undergo LD chemotherapy when their peripheral white blood cell count exceeded 1000/μL within 1 week prior to the planned administration of tisagenlecleucel. Therefore patients receiving LD chemotherapy have not been compared with those not receiving LD chemotherapy. Thus the effects of LD chemotherapy on the efficacy, etc. of tisagenlecleucel remain unclear.

The results of Study C2201, however, suggested the efficacy of tisagenlecleucel in both patients receiving cyclophosphamide + fludarabine and those receiving bendamustine alone. Therefore, LD chemotherapy (cyclophosphamide + fludarabine or bendamustine alone) should be recommended when the peripheral white blood cell count exceeds 1000/μL within 1 week prior to the planned administration of tisagenlecleucel.

7.R.4 Safety [for adverse events, see Section "9. Adverse events observed in clinical studies, etc."]

As a result of the following review, PMDA has concluded that adverse events requiring special attention when using tisagenlecleucel are CRS, neuropathy, infection, myelosuppression, hypersensitivity, hypogammaglobulinaemia, and TLS; and attention should be paid to these adverse events when tisagenlecleucel is used.

In addition, PMDA has concluded that tisagenlecleucel can be tolerable if appropriate actions on adverse events such as observation and management are taken by physicians with sufficient knowledge and experience in treatment of B-ALL and DLBCL at medical institutions with adequate equipment capable of taking actions on the above adverse events.

7.R.4.1 Safety profile of tisagenlecleucel in pediatric and AYA patients with relapsed or refractory B-ALL and differences in the safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety of tisagenlecleucel in pediatric and AYA patients with relapsed or refractory B-ALL:

Table 37 shows the summary of the safety in Study B2202 (data cut-off on April 25, 2017).

Table 37. Summary of safety (Study B2202)

	Number of patients (%) n = 75
All adverse events	75 (100)
Grade 3 or 4 adverse events	66 (88.0)
Serious adverse events	58 (77.3)
Deaths within 30 days after administration of tisagenlecleucel	2 (2.7)
Deaths >30 days after administration of tisagenlecleucel	17 (22.7)

Table 38 shows adverse events with an incidence of ≥10% in Study B2202.

Table 38. Adverse events with an incidence of ≥10% (Study B2202)

System organ class Preferred term (MedDRA/J ver. 20.0)	Number of patients (%) n = 75	
	All Grades	Grade ≥3
All adverse events	75 (100)	66 (88.0)
Blood and lymphatic system disorders		
FN	27 (36.0)	27 (36.0)
Anaemia	23 (30.7)	9 (12.0)
Cardiac disorders		
Tachycardia	17 (22.7)	3 (4.0)
Gastrointestinal disorders		
Vomiting	22 (29.3)	1 (1.3)
Nausea	19 (25.3)	2 (2.7)
Diarrhoea	18 (24.0)	1 (1.3)
Constipation	14 (18.7)	0
Abdominal pain	11 (14.7)	2 (2.7)
General disorders and administration site conditions		
Pyrexia	30 (40.0)	10 (13.3)
Fatigue	16 (21.3)	0
Immune system disorders		
CRS	58 (77.3)	35 (46.7)
Hypogammaglobulinaemia	25 (33.3)	4 (5.3)
Infections and infestations		
Upper respiratory tract infection	9 (12.0)	2 (2.7)
Investigations		
Platelet count decreased	23 (30.7)	14 (18.7)
Neutrophil count decreased	22 (29.3)	20 (26.7)
White blood cell count decreased	21 (28.0)	14 (18.7)
AST increased	20 (26.7)	11 (14.7)
ALT increased	18 (24.0)	7 (9.3)
Lymphocyte count decreased	16 (21.3)	15 (20.0)
Blood bilirubin increased	13 (17.3)	9 (12.0)
International normalised ratio increased	9 (12.0)	0
Metabolism and nutrition disorders		
Decreased appetite	29 (38.7)	11 (14.7)
Hypokalaemia	20 (26.7)	11 (14.7)
Hypophosphataemia	18 (24.0)	9 (12.0)
Hypocalcaemia	16 (21.3)	5 (6.7)
Hyperuricaemia	9 (12.0)	1 (1.3)
Hyperglycaemia	8 (10.7)	4 (5.3)
Musculoskeletal and connective tissue disorders		
Pain in extremity	13 (17.3)	1 (1.3)
Back pain	10 (13.3)	3 (4.0)

System organ class Preferred term (MedDRA/J ver. 20.0)	Number of patients (%) n = 75	
	All Grades	Grade ≥3
Myalgia	10 (13.3)	0
Arthralgia	8 (10.7)	1 (1.3)
Nervous system disorders		
Headache	27 (36.0)	2 (2.7)
Encephalopathy	8 (10.7)	4 (5.3)
Psychiatric disorders		
Anxiety	12 (16.0)	2 (2.7)
Delirium	8 (10.7)	3 (4.0)
Renal and urinary disorders		
Acute kidney injury	11 (14.7)	7 (9.3)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	18 (24.0)	14 (18.7)
Cough	17 (22.7)	0
Pulmonary oedema	12 (16.0)	7 (9.3)
Nasal congestion	9 (12.0)	0
Pleural effusion	8 (10.7)	3 (4.0)
Tachypnoea	8 (10.7)	4 (5.3)
Vascular disorders		
Hypotension	22 (29.3)	15 (20.0)
Hypertension	13 (17.3)	4 (5.3)

In Study B2202, serious adverse events with an incidence of ≥5% were CRS in 47 patients (69.0%), FN in 15 patients (20.0%), hypotension in 8 patients (10.7%), pyrexia in 7 patients (9.3%), and acute kidney injury, hypoxia, and respiratory failure in 5 patients (6.7%) each. A causal relationship to tisagenlecleucel could not be ruled out for CRS in 47 patients, FN in 13 patients, hypotension in 8 patients, acute kidney injury in 4 patients, pyrexia in 3 patients, and hypoxia and respiratory failure in 2 patients each.

Within 30 days after administration of tisagenlecleucel, deaths occurred in 2 patients (owing to disease progression and cerebral haemorrhage in 1 patient each). A causal relationship to tisagenlecleucel could not be ruled out for cerebral haemorrhage in 1 patient. More than 30 days after administration of tisagenlecleucel, deaths occurred in 17 patients (owing to disease progression in 12 patients, and encephalitis, systemic mycosis, lower respiratory tract infection bacterial, hepatobiliary disease, and unknown cause in 1 patient each). A causal relationship to tisagenlecleucel could not be ruled out for encephalitis and systemic mycosis in 1 patient each.

The applicant's explanation about differences in safety profile between Japanese and non-Japanese patients:
Table 39 shows the summary of the safety in Japanese patients (data cut-off on [redacted], 20[redacted]) and non-Japanese patients (data cut-off on April 25, 2017) in Study B2202.

Table 39. Differences in safety profile between Japanese and non-Japanese patients (Study B2202)

	Number of patients (%)	
	Japanese patients n = 6	Non-Japanese patients n = 73
All adverse events	6 (100)	73 (100)
Grade ≥3 adverse events	6 (100)	64 (87.7)
Serious adverse events	4 (66.7)	57 (78.1)
Deaths within 30 days after administration of tisagenlecleucel	0	2 (2.7)

All-grade adverse events with an incidence ≥20% higher in Japanese patients than in non-Japanese patients included white blood cell count decreased (4 Japanese patients [66.7%], 20 non-Japanese patients [27.4%]), hepatic function abnormal (4 patients [66.7%], 1 patient [1.4%]), hypoxia (3 patients [50.0%], 17 patients [23.3%]), neutropenia (3 patients [50.0%], 5 patients [6.8%]), serum ferritin increased (3 patients [50.0%], 5 patients [6.8%]), pleural effusion (2 patients [33.3%], 6 patients [8.2%]), disseminated intravascular coagulation (2 patients [33.3%], 5 patients [6.8%]), blood fibrinogen decreased (2 patients [33.3%], 5 patients [6.8%]), TLS (2 patients [33.3%], 3 patients [4.1%]), pancreatitis (2 patients [33.3%], 3 patients [4.1%]), and cardiac dysfunction (2 patients [33.3%], 0 patients).

Grade ≥3 adverse events with an incidence ≥20% higher in Japanese patients than in non-Japanese patients included hepatic function abnormal (3 patients [50.0%], 0 patients), white blood cell count decreased (4 patients [66.7%], 13 patients [17.8%]), CRS (5 patients [83.3%], 33 patients [45.2%]), neutropenia (3 patients [50.0%], 3 patients [4.1%]), hypoxia (3 patients [50.0%], 13 patients [17.8%]), acute kidney injury (2 patients [33.3%], 6 patients [8.2%]), and TLS (2 patients [33.3%], 3 patients [4.1%]).

PMDA's view:
Serious adverse events such as CRS occurred at high incidences in Study B2202. When tisagenlecleucel is administered to a pediatric or AYA patient with relapsed or refractory B-ALL, the patients should be extremely carefully monitored, and if adverse events occurred, the events should be individually addressed. In addition, clinical experience with tisagenlecleucel in Japanese patients is limited, and thus strict comparison of the safety of tisagenlecleucel between Japanese and non-Japanese patients has limitations. Because some adverse events (e.g., CRS) occurred more frequently in Japanese patients than in non-Japanese patients, adverse events should be managed more carefully in Japanese patients. Furthermore, Section 7.R.4.4.1 discusses CRS, including how to handle CRS, because CRS events are often serious.

7.R.4.2 Safety profile of tisagenlecleucel in patients with relapsed or refractory DLBCL and differences in the safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety of tisagenlecleucel in patients with relapsed or refractory DLBCL:
Table 40 shows the summary of the safety in Study C2201 (data cut-off on December 8, 2017).

Table 40. Summary of safety (Study C2201)

	Number of patients (%) n = 111
All adverse events	111 (100)
Grade 3 or 4 adverse events	99 (89.2)
Serious adverse events	72 (64.9)
Deaths within 30 days after administration of tisagenlecleucel	3 (2.7)
Deaths >30 days after administration of tisagenlecleucel	50 (45.0)

Table 41 shows adverse events with an incidence of ≥10% in Study C2201.

Table 41. Adverse events with an incidence of ≥10% (Study C2201)

System organ class Preferred term (MedDRA/J ver. 20.1)	Number of patients (%) n = 111	
	All Grades	Grade ≥3
All adverse events	111 (100)	99 (89.2)
Blood and lymphatic system disorders		
Anaemia	53 (47.7)	43 (38.7)
Neutropenia	22 (19.8)	22 (19.8)
FN	18 (16.2)	17 (15.3)
Thrombocytopenia	14 (12.6)	13 (11.7)
Cardiac disorders		
Tachycardia	12 (10.8)	3 (2.7)
Gastrointestinal disorders		
Diarrhoea	35 (31.5)	1 (0.9)
Nausea	32 (28.8)	1 (0.9)
Constipation	18 (16.2)	1 (0.9)
General disorders and administration site conditions		
Pyrexia	39 (35.1)	6 (5.4)
Fatigue	28 (25.2)	7 (6.3)
Oedema peripheral	17 (15.3)	0
Chills	14 (12.6)	0
Immune system disorders		
CRS	64 (57.7)	24 (21.6)
Infections and infestations		
Upper respiratory tract infection	13 (11.7)	2 (1.8)
Investigations		
Neutrophil count decreased	38 (34.2)	37 (33.3)
White blood cell count decreased	37 (33.3)	34 (30.6)
Platelet count decreased	37 (33.3)	31 (27.9)
Blood creatinine increased	12 (10.8)	4 (3.6)
Weight decreased	12 (10.8)	3 (2.7)
Metabolism and nutrition disorders		
Hypokalaemia	25 (22.5)	9 (8.1)
Hypomagnesaemia	19 (17.1)	0
Hypophosphataemia	19 (17.1)	15 (13.5)
Decreased appetite	13 (11.7)	4 (3.6)
Nervous system disorders		
Headache	25 (22.5)	1 (0.9)
Dizziness	13 (11.7)	0
Psychiatric disorders		
Anxiety	12 (10.8)	1 (0.9)
Respiratory, thoracic and mediastinal disorders		
Cough	19 (17.1)	0
Dyspnoea	19 (17.1)	5 (4.5)
Vascular disorders		
Hypotension	29 (26.1)	10 (9.0)

In Study C2201, serious adverse events with an incidence of ≥3% were CRS in 30 patients (27.0%), FN in 9 patients (8.1%), pyrexia in 8 patients (7.2%), and acute kidney injury, encephalopathy, and fatigue in 4 patients (3.6%) each. A causal relationship to tisagenlecleucel could not be ruled out for CRS in 30 patients, FN and pyrexia in 6 patients each, encephalopathy in 4 patients, and acute kidney injury and fatigue in 2 patients each.

Within 30 days after administration of tisagenlecleucel, deaths occurred in 3 patients all owing to disease progression. All of the deaths were unrelated to tisagenlecleucel. More than 30 days after administration of tisagenlecleucel, deaths occurred in 50 patients (owing to disease progression in 42 patients, and multiple organ dysfunction syndrome in 2 patients, cerebral haemorrhage, duodenal ulcer haemorrhage, neuroendocrine carcinoma, pulmonary haemorrhage, chronic kidney disease, and sepsis in 1 patient each). A causal relationship to tisagenlecleucel could not be ruled out for pulmonary haemorrhage in 1 patient.

The applicant's explanation about differences in safety profile between Japanese and non-Japanese patients:
Table 42 shows the summary of the safety in Japanese patients (data cut-off on [redacted], 20[redacted]) and non-Japanese patients (data cut-off on December 8, 2017) in Study C2201.

Table 42. Differences in safety profile between Japanese and non-Japanese patients (Study C2201)

	Number of patients (%)	
	Japanese population n = 9	Non-Japanese population n = 106
All adverse events	9 (100)	106 (100)
Grade ≥3 adverse events	8 (88.9)	95 (89.6)
Serious adverse events	4 (44.4)	70 (66.0)
Deaths within 30 days after administration of tisagenlecleucel	0	3 (2.8)

All-grade adverse events with an incidence ≥20% higher in Japanese patients than in non-Japanese patients included decreased appetite (3 Japanese patients [33.3%], 12 non-Japanese patients [11.3%]), nasopharyngitis (3 patients [33.3%], 5 patients [4.7%]), lymphocyte count decreased (3 patients [33.3%], 2 patients [1.9%]), and pancytopenia (2 patients [22.2%], 2 patients [1.9%]).

Grade ≥3 adverse events with an incidence ≥20% higher in Japanese patients than in non-Japanese patients included lymphocyte count decreased (3 patients [33.3%], 1 patient [0.9%]) and pancytopenia (2 patients [22.2%], 1 patient [0.9%]).

PMDA's view:
Serious adverse events such as CRS occurred at high incidences in Study C2201. When tisagenlecleucel is administered to a patient with DLBCL, the patients should be extremely carefully monitored, and if adverse events occurred, the events should be individually addressed. In addition, clinical experience with tisagenlecleucel in Japanese patients is limited, and thus strict comparison of the safety of tisagenlecleucel between Japanese and non-Japanese patients has limitations. Because some adverse events (e.g., pancytopenia) occurred more frequently in Japanese patients than in non-Japanese patients, adverse events should be more carefully managed in Japanese patients.

7.R.4.3 Differences in safety profile by disease

The applicant's explanation about differences in safety profile of tisagenlecleucel between patients with DLBCL and pediatric and AYA patients with B-ALL:
Table 43 shows the summary of the safety in Study B2202 (data cut-off on April 25, 2017) and Study C2201 (data cut-off on December 8, 2017).

Table 43. Summary of safety (Studies B2202 and C2201)

	Number of patients (%)	
	Study B2202 n = 75	Study C2201 n = 111
All adverse events	75 (100)	111 (100)
Grade ≥3 adverse events	66 (88.0)	99 (89.2)
Serious adverse events	58 (77.3)	72 (64.9)
Deaths within 30 days after administration of tisagenlecleucel	2 (2.7)	3 (2.7)
Deaths >30 days after administration of tisagenlecleucel	17 (22.7)	50 (45.0)

All-grade adverse events with an incidence ≥15% higher in Study B2202 than in Study C2201 included decreased appetite (38.7% in Study B2202, 11.7% in Study C2201), hypogammaglobulinaemia (33.3%, 8.1%), alanine aminotransferase (ALT) increased (24.0%, 0%), aspartate aminotransferase (AST) increased (26.7%, 4.5%), vomiting (29.3%, 9.0%), FN (36.0%, 16.2%), CRS (77.3%, 57.7%), lymphocyte count decreased (21.3%, 2.7%), hypocalcaemia (21.3%, 5.4%), and hypoxia (24.0%, 8.1%). Grade ≥3 adverse events with an incidence ≥10% higher in Study B2202 than in Study C2201 included CRS (46.7%, 21.6%), FN (36.0%, 15.3%), lymphocyte count decreased (20.0%, 1.8%), hypoxia (18.7%, 3.6%), AST increased (14.7%, 0.9%), decreased appetite (14.7%, 3.6%), hypotension (20.0%, 9.0%), and blood bilirubin increased (12.0%, 1.8%).

All-grade adverse events with an incidence ≥15% higher in Study C2201 than in Study B2202 was anaemia (47.7% in Study C2201, 30.7% in Study B2202). Grade ≥3 adverse events with an incidence ≥10% higher in Study C2201 than in Study B2202 included anaemia (38.7%, 12.0%), neutropenia (19.8%, 4.0%), and white blood cell count decreased (30.6%, 18.7%).

PMDA's view:
There are no clear differences in profile of adverse events between Studies B2202 and C2201. Attention, however, should be paid to incidences of adverse events that differed between these 2 studies, and information about the concerned differences should be appropriately provided to healthcare professionals using materials, etc.

7.R.4.4 Safety profile of tisagenlecleucel by event

The following sections show the reviews conducted by PMDA on events occurring frequently and events that became serious in some patients, as indicated by the safety data on tisagenlecleucel mainly from Studies B2202 and C2201.

7.R.4.4.1 CRS

The applicant explained CRS in patients receiving tisagenlecleucel in terms of (a) incidence of CRS in clinical studies, (b) risk factors of onset and aggravation of CRS, (c) preventive treatment against CRS, and (d) management of CRS.

(a) Incidence of CRS in clinical studies

Adverse events coded as Medical Dictionary for Regulatory Activities Japanese version (MedDRA) PTs "Cytokine release syndrome," "Cytokine storm," "Shock," "Macrophage activation," or "Histiocytosis haematophagic" were classified as "CRS," and are listed in Table 44.

Table 44. Incidence of CRS (Studies B2202 and C2201)

PT*	Number of patients (%)			
	Study B2202 n = 75		Study C2201 n = 111	
	All Grades	Grade ≥3	All Grades	Grade ≥3
CRS (overall)	58 (77.3)	35 (46.7)	64 (57.7)	24 (21.6)
CRS	58 (77.3)	35 (46.7)	64 (57.7)	24 (21.6)
Histiocytosis haematophagic	5 (6.7)	3 (4.0)	1 (0.9)	0

* Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

Table 45 shows characteristics of the patients who experienced Grade ≥4[35)] CRS in Studies B2202 and C2201.

Table 45. List of patients with Grade ≥4 CRS (Studies B2202 and C2201)

Study	Age	Sex	Race	Dose of tisagenlecleucel ($\times 10^8$)	PT*	Grade	Seriousness	Causal relationship	Time to onset (days)	Duration (days)	Tocilizumab Number of doses/day	Outcome
		Female	Non-Japanese	0.76	CRS	4	Serious	Yes	2	21	3/3, 6, 8	Resolved
		Male	Non-Japanese	0.75	CRS	4	Serious	Yes	10	7	2/10, 11	Resolved
		Female	Non-Japanese	1.19	CRS	4	Serious	Yes	5	8	1/7	Resolved
	1	Male	Japanese	1.0	CRS	4	Serious	Yes	3	18	2/10, 11	Resolved
		Male	Non-Japanese	1.0	CRS	4	Serious	Yes	2	9	1/6	Resolved
		Male	Non-Japanese	1.0	CRS	4	Serious	Yes	3	7	1/5	Resolved
	2	Female	Non-Japanese	1.0	CRS	4	Serious	Yes	2	11	1/8	Resolved
		Male	Non-Japanese	0.50	CRS	4	Serious	Yes	4	10	2/7, 9	Resolved
	1	Female	Non-Japanese	2.0	CRS	4	Serious	Yes	2	9	1/7	Resolved
B2202	1	Male	Non-Japanese	2.0	CRS	4	Serious	Yes	1	19	1/18	Resolved
	2	Female	Non-Japanese	1.7	CRS	4	Serious	Yes	3	15	3/4, 8, 9	Resolved
	1	Female	Non-Japanese	1.8	CRS	4	Serious	Yes	1	8	2/5, 7	Resolved
	1	Female	Non-Japanese	1.7	CRS	4	Serious	Yes	2	9	2/5, 7	Resolved
	2	Female	Non-Japanese	2.2	CRS	4	Serious	Yes	2	17	2/6, 15	Resolved
	1	Male	Non-Japanese	1.22	CRS	4	Serious	Yes	1	17	2/7, 8	Resolved
	1	Male	Non-Japanese	1.74	CRS	4	Serious	Yes	2	29	2/2, 5	Resolved
	1	Female	Non-Japanese	1.3	CRS	4	Serious	Yes	2	6	1/5	Resolved
	1	Male	Non-Japanese	1.8	CRS	4	Serious	Yes	5	6	1/6	Resolved
		Male	Non-Japanese	0.66	CRS	4	Serious	Yes	2	13	3/6, 8, 8	Resolved
	3	Female	Non-Japanese	2.9	CRS	4	Non-serious	Yes	2	14	2/2, 6	Resolved
	5	Male	Non-Japanese	5	CRS	4	Serious	Yes	2	7	2/3, 5	Resolved
	4	Female	Non-Japanese	3	CRS	4	Serious	Yes	4	7	2/5, 7	Resolved
	3	Female	Non-Japanese	1.7	CRS	4	Serious	Yes	2	13	1/8	Resolved
C2201	5	Male	Non-Japanese	3.3	CRS	4	Serious	Yes	7	13	2/8, 11	Resolved
	6	Male	Non-Japanese	2.8	CRS	4	Serious	Yes	2	8	2/5, 7	Resolved
	5	Male	Non-Japanese	4.1	CRS	4	Serious	Yes	2	13	2/8, 9	Resolved
	6	Male	Non-Japanese	4.1	CRS	4	Serious	Yes	2	8	2/4, 7	Resolved
	5	Female	Non-Japanese	3	CRS	4	Serious	Yes	6	6	1/6	Resolved

* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

In Studies B2202 and C2201, no CRS leading to death occurred.

[35)] CRS was graded according to the following definition (the Penn Grading Scale for Cytokine Release Syndrome).

Grade 1	**Mild reaction**: Only requiring treatment with supportive care such as antipyretics and anti-emetics.
Grade 2	**Moderate reaction**: Requiring intravenous therapies or parenteral nutrition. Some signs of organ dysfunction (i.e. Grade 2 creatinine increased or Grade 3 hepatic function abnormal) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms including fevers with associated neutropenia.
Grade 3	**Severe reaction**: Hospitalization required for management of symptoms related to organ dysfunction including CTCAE Grade 4 hepatic function abnormal or Grade 3 creatinine increased related to CRS and not attributable to any other conditions. This excludes management of pyrexia or myalgias and includes hypotension treated with intravenous fluids (multiple fluid boluses for blood pressure support) or low dose pressor (norepinephrine at <0.2 μg/kg/min, etc.), coagulopathy requiring fresh frozen plasma or cryoprecipitate, and hypoxia requiring supplemental oxygen. Patients admitted for management of suspected infection due to pyrexia and/or neutropenia may have Grade 2 CRS.
Grade 4	**Life-threatening complications**: Hypotension requiring high dose pressor (norepinephrine at ≥0.2 μg/kg/min, etc.) or hypoxia requiring mechanical ventilation.

In Study B2202 (58 patients) and Study C2201 (64 patients), the median number of days (range) from the start of administration of tisagenlecleucel to the first onset of CRS was 3.0 days (1-22 days) and 3.0 days (1-51 days), respectively.

(b) Risk factors of onset and aggravation of CRS

CRS is defined as a systemic inflammatory reaction caused by cytokines released by activated T cells. CRS is considered to occur as a consequence of proliferation and activation of CAR-expressing T cells as well as death of tumor cells.

The relationship between CRS and tisagenlecleucel exposure or tumor burden was investigated to assess whether they are predictive factors of CRS.

The relationship between CRS and tisagenlecleucel exposure:
A pooled analysis of Studies B2202 and B2205J was performed to investigate the relationship between $AUC_{0\text{-}28d}$ or C_{max} of tisagenlecleucel and CRS of all grades, Grade ≥3, or Grade 4. The results suggested that the risk of all-grade CRS would increase with higher exposure to tisagenlecleucel ($AUC_{0\text{-}28d}$ and C_{max}).

The relationship between CRS and tumor burden:
The relationship between CRS and tumor volume of DLBCL[36)] in Study C2201 was investigated. The results showed that the median tumor volume (mL) at baseline was 29 in patients without CRS (n = 40), 60 in patients with Grade 1 or 2 CRS (n = 40), and 145 in patients with Grade 3 or 4 CRS (n = 24), suggesting that the tumor volume at baseline positively correlates with the onset and severity of CRS. In patients with B-ALL, severity of CRS was related to MRD (*Blood.* 2017;130:2317-25). These findings suggest that, in patients with either B-ALL or DLBCL, the incidence and seriousness of CRS increase with the tumor burden at baseline.

(c) Preventive treatment against CRS

At present, recommended preventive treatment against CRS associated with tisagenlecleucel has not been established, because it was not clearly stipulated in the protocols of Studies B2202 and C2201. In addition, such a preventive treatment within 72 hours after administration of tisagenlecleucel might affect the proliferation and function of the administered cells, and therefore corticosteroid was not used to prevent CRS.

(d) Measures taken on CRS

The protocols of Studies B2202 and C2201 stipulated that CRS must be managed in accordance with the procedures presented in Table 46.

36) The tumor volume was independently determined by positron emission tomography (PET) imaging at baseline.

Table 46. Outline of CRS management algorithm (Studies B2202 and C2201)

Stage	Severity of CRS (symptoms and conditions, etc.)	Management method
Several hours to several days after administration of tisagenlecleucel	Prodromal symptoms: Low-grade fever, fatigue, and anorexia	• Observation, rule out infection (by culture examination) • Antibiotics in consideration of febrile neutropenia • Symptomatic support
First line treatment	Symptom progression: High fever, hypoxia, moderate hypotension	• Oxygen, fluids, low dose vasopressor support, antipyretics
Second line treatment	If the following symptom progression is observed: • Hemodynamic instability despite intravenous fluids and moderate to high dose vasopressor support • Worsening respiratory distress, including pulmonary infiltrates • High-flow oxygen and/or need for mechanical ventilation • Rapid clinical deterioration	• First dose of tocilizumab (12 mg/kg for patients weighing <30 kg, 8 mg/kg for patients weighing ≥30 kg, but up to 800 mg/body)
Third line treatment	Lack of clinical improvement while awaiting tocilizumab response	• If no improvement is observed within 12 to 18 hours after the first dose of tocilizumab, consider using corticosteroid. • Methylprednisolone at 2 mg/kg
Fourth line treatment	Lack of clinical improvement while awaiting response to the third line treatment	• If no response to corticosteroid is observed within 24 hours, consider the second dose of tocilizumab (12 mg/kg for patients weighing <30 kg, 8 mg/kg for patients weighing ≥30 kg, but up to 800 mg/body).
Fifth line treatment	Lack of clinical improvement while awaiting response to the fourth line treatment	• If no response to corticosteroid and the second dose of tocilizumab is observed within 24 hours or further clinical deterioration occurs, consider the third dose of tocilizumab (12 mg/kg for patients weighing <30 kg, 8 mg/kg for patients weighing ≥30 kg, but up to 800 mg/body) (only for Japanese patients in Study B2202).*
Sixth line treatment	Lack of clinical improvement while awaiting response to the fifth line treatment	• Consider anti-T-cell therapy such as cyclophosphamide, antithymocyte globulin, and alemtuzumab.

* Intravenous siltuximab (unapproved in Japan) at 11 mg/kg in countries and regions where it is approved. In Study C2201, the third dose of tocilizumab was allowed at the investigator's discretion.

CRS was managed in accordance with the above algorithm. The incidences of all-grade CRS were 77.3% (58 of 75) of patients in Study B2202 and 57.7% (64 of 111) of patients in Study C2201, and the incidences of serious CRS were 62.7% (47 of 75) of patients in Study B2202 and 27.0% (30 of 111) of patients in Study C2201. No CRS leading to death occurred in either study.

Based on the above, CRS occurring after administration of tisagenlecleucel can be controlled by managing the patient in the ICU, etc. and by complying with the CRS management algorithm (e.g., treatment with tocilizumab).

PMDA's view:

Attention should be paid to CRS especially early after administration of tisagenlecleucel, because (a) the incidence of CRS associated with tisagenlecleucel was high, (b) serious CRS occurred, and (c) CRS occurs approximately 3 days after the start of tisagenlecleucel therapy. Healthcare professionals must be appropriately informed of CRS management algorithm used in clinical studies (e.g., treatment with tocilizumab) through the package insert, etc., to raise their awareness so that they can take immediate and proper actions based on the algorithm when CRS occurs after administration of tisagenlecleucel. Furthermore, information should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions, in order to ensure that tisagenlecleucel 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 ICU, etc. that can implement systemic control immediately in an emergency case.

7.R.4.4.2 Neuropathy

The applicant's explanation about neuropathy in patients receiving tisagenlecleucel:

Adverse events coded as MedDRA SMQ (broad) "Noninfectious encephalopathy/delirium" were classified as "neuropathy," and are listed in Table 47.

Table 47. Incidences of neuropathy reported by ≥2% of patients in Study B2202 or C2201

PT*	Number of patients (%)			
	Study B2202 n = 75		Study C2201 n = 111	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Neuropathy	33 (44.0)	12 (16.0)	27 (24.3)	15 (13.5)
Delirium	8 (10.7)	3 (4.0)	3 (2.7)	2 (1.8)
Encephalopathy	8 (10.7)	4 (5.3)	7 (6.3)	5 (4.5)
Confusional state	7 (9.3)	0	10 (9.0)	3 (2.7)
Agitation	6 (8.0)	0	2 (1.8)	1 (0.9)
Tremor	6 (8.0)	0	5 (4.5)	0
Mental status changes	5 (6.7)	2 (2.7)	3 (2.7)	3 (2.7)
Somnolence	5 (6.7)	2 (2.7)	2 (1.8)	2 (1.8)
Cognitive disorder	3 (4.0)	1 (1.3)	1 (0.9)	1 (0.9)
Hallucination	3 (4.0)	0	0	0
Irritability	3 (4.0)	0	1 (0.9)	0
Lethargy	3 (4.0)	0	1 (0.9)	0
Muscular weakness	2 (2.7)	1 (1.3)	0	0
Seizure	2 (2.7)	2 (2.7)	2 (1.8)	0
Dysphagia	1 (1.3)	1 (1.3)	4 (3.6)	1 (0.9)
Aphasia	1 (1.3)	0	3 (2.7)	1 (0.9)
Disturbance in attention	1 (1.3)	0	3 (2.7)	1 (0.9)

* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

Table 48 shows characteristics of the patients who experienced serious or Grade ≥3 neuropathy in Studies B2202 and C2201.

Table 48. List of patients with serious or Grade ≥3 neuropathy

Study	Age	Sex	PT*	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to tisagenlecleucel	Outcome
B2202	1[redacted]	Female	Muscular weakness	3	Non-serious	4	8+	No	Unresolved
	[redacted]	Female	Encephalopathy	3	Serious	23	7+	Yes	Unresolved
	[redacted]	Female	Encephalopathy	3	Non-serious	6	8	Yes	Resolved
	[redacted]	Male	Depressed level of consciousness	3	Non-serious	2	3	Yes	Resolved
	1[redacted]	Female	Mental status changes	2	Serious	284	15	No	Resolved
	1[redacted]	Female	Mental status changes	3	Non-serious	5	37	Yes	Resolved
			Somnolence	3	Non-serious	8	13	Yes	Resolved
			Dysphagia	3	Non-serious	18	11	Yes	Resolved
			Encephalopathy	3	Non-serious	32	6	Yes	Resolved
	1[redacted]	Male	Encephalopathy	4	Non-serious	9	34	Yes	Resolved
			Delirium	3	Non-serious	11	23	Yes	Resolved
			Somnolence	3	Non-serious	15	8	No	Resolved
	2[redacted]	Female	Cognitive disorder	3	Non-serious	5	4	Yes	Resolved
			Cognitive disorder	2	Serious	8	10	Yes	Resolved
	1[redacted]	Female	Seizure	3	Serious	489	83	No	Resolving
	1[redacted]	Male	Delirium	3	Serious	21	15+	Yes	Unresolved
			Dysarthria	3	Serious	28	8+	No	Unresolved
	[redacted]	Female	Mental status changes	3	Serious	142	21+	No	Unresolved
	2[redacted]	Female	Delirium	3	Non-serious	6	12	Yes	Resolved
	[redacted]	Female	Seizure	3	Non-serious	7	4	Yes	Resolved
C2201	4[redacted]	Female	Dysphagia	3	Non-serious	10	32+	No	Unresolved
	5[redacted]	Male	Confusional state	3	Serious	5	36	No	Resolved
			Somnolence	4	Serious	7	1	No	Resolved
	6[redacted]	Female	Confusional state	3	Serious	89	2	No	Resolved
	6[redacted]	Male	Delirium	3	Non-serious	7	1	Yes	Resolved
	5[redacted]	Male	Encephalopathy	4	Serious	12	50+	Yes	Resolving
	6[redacted]	Female	Memory impairment	3	Non-serious	27	1+	No	Unresolved
			Memory impairment	3	Non-serious	29	1+	No	Unresolved
			Delirium	3	Non-serious	32	1+	No	Unresolved
			Somnolence	3	Non-serious	32	1+	No	Unresolved
	2[redacted]	Female	Encephalopathy	3	Serious	9	4	Yes	Resolved
	7[redacted]	Female	Confusional state	3	Serious	15	7	Yes	Resolved
	6[redacted]	Male	Encephalopathy	4	Non-serious	5	18+	Yes	Unresolved
	5[redacted]	Male	Mental status changes	3	Non-serious	8	18	Yes	Resolved
			Aphasia	3	Non-serious	8	10	Yes	Resolved
	6[redacted]	Male	Agitation	3	Non-serious	6	45	Yes	Resolved
			Metabolic encephalopathy	3	Serious	6	38	Yes	Resolved
	4[redacted]	Female	Mental status changes	3	Serious	9	15+	Yes	Unresolved
	6[redacted]	Female	Mental status changes	3	Non-serious	323	17	No	Resolved
			Mental status changes	3	Non-serious	368	13+	No	Unresolved
	7[redacted]	Female	Encephalopathy	4	Serious	6	16	Yes	Resolved
			Cognitive disorder	3	Non-serious	66	7+	No	Unresolved
	3[redacted]	Female	Disturbance in attention	3	Non-serious	6	6	Yes	Resolved
			Stupor	4	Non-serious	7	5	Yes	Resolved
			Encephalopathy	4	Serious	7	5	Yes	Resolved

\+ The event has not resolved and thus is ongoing.
* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver.20.1 in Study C2201.

In Studies B2202 and C2201, no neuropathy leading to death occurred.

In Study B2202 (33 patients) and Study C2201 (27 patients), the median number of days (range) from administration of tisagenlecleucel to the first onset of neuropathy was 7.0 days (2-489 days) and 6.0 days (1-323 days), respectively.

PMDA's view:
Because the incidence of neuropathy in patients who received tisagenlecleucel was high, and serious neuropathy occurred, attention should be paid to neuropathy when tisagenlecleucel is administered. In addition, special attention should be paid to serious neuropathy such as encephalopathy and seizure,

which were observed in clinical studies, and thus the patient should be carefully monitored after administration of tisagenlecleucel. Accordingly, information about the incidence of neuropathy in clinical studies and their details should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions.

7.R.4.4.3 Infection

The applicant's explanation about infection in patients receiving tisagenlecleucel:
Adverse events coded as MedDRA SOC "Infections and infestations" were categorized as "infection," and are listed in Table 49.

Table 49. Incidences of infection reported by ≥5% of patients in Study B2202 or C2201

PT*	Number of patients (%)			
	Study B2202 n = 75		Study C2201 n = 111	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infection	50 (66.7)	34 (45.3)	60 (54.1)	36 (32.4)
Upper respiratory tract infection	9 (12.0)	2 (2.7)	13 (11.7)	2 (1.8)
Rhinovirus infection	6 (8.0)	1 (1.3)	1 (0.9)	0
Viral upper respiratory tract infection	6 (8.0)	1 (1.3)	0	0
Conjunctivitis	5 (6.7)	0	4 (3.6)	0
Staphylococcal bacteraemia	5 (6.7)	5 (6.7)	1 (0.9)	0
Staphylococcal infection	5 (6.7)	2 (2.7)	1 (0.9)	0
Clostridium difficile infection	4 (5.3)	3 (4.0)	5 (4.5)	5 (4.5)
Gastroenteritis	4 (5.3)	1 (1.3)	0	0
Otitis media	4 (5.3)	1 (1.3)	3 (2.7)	1 (0.9)
Sinusitis	4 (5.3)	2 (2.7)	4 (3.6)	0
Urinary tract infection	1 (1.3)	1 (1.3)	8 (7.2)	4 (3.6)
Pneumonia	3 (4.0)	2 (2.7)	6 (5.4)	5 (4.5)

* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

In Studies B2202 and C2201, infection leading to death occurred in 2.7% (2 of 75) of patients and 1.8% (2 of 111) of patients, respectively, and serious infection occurred in 33.3% (25 of 75) of patients and 17.1% (19 of 111) of patients, respectively.

There have been no reports of reactivation of hepatitis B or C virus or activation of human immunodeficiency virus from Japanese and foreign clinical studies or post-marketing experience in foreign countries (as of July 1, 2018).
.

PMDA's view:
Attention should be paid to infection associated with tisagenlecleucel, because patients treated with tisagenlecleucel experienced infection leading to death and serious and Grade ≥3 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.

7.R.4.4.4 Myelosuppression

The applicant's explanation about myelosuppression in patients receiving tisagenlecleucel:
Adverse events coded as MedDRA SMQ (broad) "Haematopoietic cytopenias" and did not resolve within 28 days after administration of tisagenlecleucel were classified as "myelosuppression," and are listed in Table 50.

Table 50. Incidences of myelosuppression (Studies B2202 and C2201)

PT*	Number of patients (%)			
	Study B2202 n = 75		Study C2201 n = 111	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression	28 (37.3)	24 (32.0)	49 (44.1)	36 (32.4)
White blood cell count decreased	11 (14.7)	8 (10.7)	12 (10.8)	7 (6.3)
Platelet count decreased	9 (12.0)	7 (9.3)	26 (23.4)	21 (18.9)
Neutrophil count decreased	8 (10.7)	6 (8.0)	7 (6.3)	7 (6.3)
Lymphocyte count decreased	7 (9.3)	5 (6.7)	1 (0.9)	1 (0.9)
Anaemia	6 (8.0)	4 (5.3)	22 (19.8)	6 (5.4)
Thrombocytopenia	6 (8.0)	6 (8.0)	7 (6.3)	7 (6.3)
Neutropenia	3 (4.0)	2 (2.7)	5 (4.5)	4 (3.6)
Pancytopenia	2 (2.7)	2 (2.7)	1 (0.9)	1 (0.9)
FN	1 (1.3)	1 (1.3)	2 (1.8)	2 (1.8)
Lymphopenia	1 (1.3)	1 (1.3)	1 (0.9)	1 (0.9)
Haemoglobin decreased	1 (1.3)	0	0	0
Bone marrow failure	0	0	1 (0.9)	1 (0.9)

* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

In Studies B2202 and C2201, no myelosuppression leading to death occurred, but serious myelosuppression occurred in 4.0% (3 of 75) of patients and 2.7% (3 of 111) of patients, respectively.

In Studies B2202 (28 patients) and C2201 (49 patients), time to recovery from myelosuppression (time taken to alleviate myelosuppression from Grade ≥3 to Grade ≤2) was 61 and 60 days for leukocytes, 70 and 90 days for lymphocytes, 60 and 57 days for neutrophils, 44 and 60 days for hemoglobin, and 59 and 83 days for platelets, respectively.

In Study B2202, all-grade FN occurred in 36.0% (27 of 75) of patients and Grade ≥3 FN in 36.0% (27 of 75) of patients. In Study C2201, all-grade FN occurred in 16.2% (18 of 111) of patients and Grade ≥3 FN in 15.3% (17 of 111) of patients.

In Studies B2202 and C2201, preventive treatment against myelosuppression was not stipulated by the study protocols and therefore was not given to study patients. However, myelosuppression was considered manageable with appropriate actions such as transfusion and antibiotics provided at the investigator's discretion.

PMDA's view:
Attention should be paid to myelosuppression associated with tisagenlecleucel because clinical study patients experienced FN, Grade ≥3 myelosuppression that did not resolve within 28 days after administration of tisagenlecleucel, and serious myelosuppression. Accordingly, information about the incidence of myelosuppression and time to recovery in clinical studies should be appropriately provided to healthcare professionals using the package insert, etc. In addition, the applicant should appropriately provide information to healthcare professionals through the package insert, etc. and raise their awareness, to ensure that they perform blood tests periodically after administration of tisagenlecleucel and take proper actions when myelosuppression occurs.

7.R.4.4.5 Hypersensitivity

The applicant's explanation about hypersensitivity in patients receiving tisagenlecleucel:

Adverse events coded as MedDRA SMQ (narrow) “Hypersensitivity” are listed in Table 51. The protocols of Studies B2202 and C2201 stipulated that subjects must receive premedication with acetaminophen and diphenhydramine hydrochloride to prevent hypersensitivity.

Table 51. Incidences of hypersensitivity reported by ≥2 patients in Study B2202 or C2201

PT*	Number of patients (%)			
	Study B2202 n = 75		Study C2201 n = 111	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypersensitivity	28 (37.3)	5 (6.7)	25 (22.5)	1 (0.9)
Rash	7 (9.3)	0	5 (4.5)	0
Face oedema	7 (9.3)	1 (1.3)	2 (1.8)	0
Drug hypersensitivity	2 (2.7)	1 (1.3)	0	0
Rash maculo-papular	2 (2.7)	1 (1.3)	1 (0.9)	0
Dermatitis atopic	2 (2.7)	0	0	0
Eczema	2 (2.7)	0	1 (0.9)	0
Eyelid oedema	2 (2.7)	0	0	0
Rhinitis allergic	2 (2.7)	0	2 (1.8)	0
Infusion related reaction	0	0	3 (2.7)	0
Dermatitis contact	0	0	2 (1.8)	0
Urticaria	1 (1.3)	0	2 (1.8)	0

* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

Table 52 shows characteristics of the patients who experienced serious or Grade ≥3 hypersensitivity in Studies B2202 and C2201.

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

Study	Age	Sex	PT*	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to tisagenlecleucel	Outcome
B2202	[redacted]	Female	Skin necrosis	3	Non-serious	9	45	Yes	Unresolved
			Vaginal ulceration	3	Non-serious	20	3	No	Resolved
	1[redacted]	Male	Face oedema	3	Non-serious	7	4	Yes	Resolved
	1[redacted]	Male	Red man syndrome	3	Non-serious	2	1	Yes	Resolved
	2[redacted]	Female	Drug hypersensitivity	3	Serious	99	6	No	Resolved
	[redacted]	Female	Rash maculo-papular	3	Non-serious	22	1	No	Resolved
B2205J	[redacted]	Male	Face oedema	3	Non-serious	1	25	Yes	Resolved
	1[redacted]	Female	Anaphylactic reaction	4	Serious	18	1	No	Resolved
	2[redacted]	Male	Rash maculo-papular	3	Non-serious	11	6	Yes	Resolved
C2201	2[redacted]	Male	Face oedema	2	Serious	7	46	No	Resolved
	5[redacted]	Male	Allergic transfusion reaction	3	Non-serious	24	1	No	Resolved
	2[redacted]	Male	Infusion related reaction	2	Serious	1	1	Yes	Resolved
	5[redacted]	Female	Allergic bronchitis	2	Serious	263	19	No	Resolved

* MedDRA/J ver. 20.0 was applied in Study B2202; MedDRA/J ver. 19.0 in Study B2205J; and MedDRA/J ver. 20.1 in Study C2201.

In Studies B2202 and C2201, no hypersensitivity leading to death occurred.

In Study B2202 (28 patients) and Study C2201 (25 patients), the median number of days (range) from administration of tisagenlecleucel to the first onset of hypersensitivity was 19.5 days (2-263 days) and 14 days (1-366 days), respectively.

PMDA's view:
Attention should be paid to hypersensitivity associated with tisagenlecleucel because patients treated with tisagenlecleucel experienced serious or Grade ≥3 hypersensitivity. Accordingly, information about the incidence of hypersensitivity in clinical studies and premedication stipulated in the protocols should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions.

7.R.4.4.6 Hypogammaglobulinaemia

The applicant's explanation about hypogammaglobulinaemia in patients receiving tisagenlecleucel:
Adverse events coded as MedDRA PTs "B-lymphocyte abnormalities," "B lymphocyte count decreased," "hypogammaglobulinaemia," or "pure white cell aplasia" were classified as "hypogammaglobulinaemia," and are listed in Table 53.

Table 53. Incidence of hypogammaglobulinaemia (Studies B2202 and C2201)

PT*	Number of patients (%)			
	Study B2202 n = 75		Study C2201 n = 111	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypogammaglobulinaemia	25 (33.3)	4 (5.3)	9 (8.1)	2 (1.8)

* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

Table 54 shows characteristics of the patients who experienced Grade ≥3 hypogammaglobulinaemia following administration of tisagenlecleucel in Studies B2202 and C2201.

Table 54. List of patients with Grade ≥3 hypogammaglobulinaemia

Study	Age	Sex	PT*	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to tisagenlecleucel	Outcome
B2202	1[redacted]	Male	Hypogammaglobulinaemia	3	Non-serious	16	390	Yes	Unresolved
	[redacted]	Male	Hypogammaglobulinaemia	3	Non-serious	28	142	No	Unresolved
	1[redacted]	Female	Hypogammaglobulinaemia	3	Non-serious	17	286	No	Unresolved
	1[redacted]	Female	Hypogammaglobulinaemia	3	Non-serious	29	145	Yes	Unknown
C2201	5[redacted]	Female	Hypogammaglobulinaemia	3	Non-serious	77	382	Yes	Unresolved
	5[redacted]	Male	Hypogammaglobulinaemia	3	Non-serious	15	87	Yes	Unresolved

* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

In Studies B2202 and C2201, neither fatal nor serious hypogammaglobulinaemia occurred.

In Study B2202 (25 patients) and Study C2201 (9 patients), the median number of days (range) from administration of tisagenlecleucel to the first onset of hypogammaglobulinaemia was 28.0 days (1-374 days) and 93.0 days (15-366 days), respectively.

Furthermore, protocols of Studies B2202 and C2201 stipulated that a serum γ-globulin level should be periodically determined, and intravenous immunoglobulin should be administered in accordance with

the national standard in participating countries in case of hypogammaglobulinaemia. Information on the concerned stipulations will be provided to healthcare professionals using the package insert, etc.

PMDA's view:
Patients receiving tisagenlecleucel experienced Grade ≥3 hypogammaglobulinaemia, and therefore attention should be paid to hypogammaglobulinaemia associated with tisagenlecleucel. Accordingly, the following information should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions: Incidences of hypogammaglobulinaemia in clinical studies; a serum γ-globulin level should be periodically determined after administration of tisagenlecleucel; appropriate actions such as intravenous immunoglobulin should be taken in case of hypogammaglobulinaemia.

7.R.4.4.7 TLS

The applicant's explanation about TLS in patients receiving tisagenlecleucel:
Adverse events coded as MedDRA SMQ (narrow) "Tumour lysis syndrome" were classified as TLS. TLS events occurred in 5.3% (4 of 75) of patients and 0.9% (1 of 111) of patients in Studies B2202 and C2201, respectively, and all were Grade ≥3. Table 55 shows characteristics of the patients who experienced TLS in Studies B2202 and C2201.

Table 55. List of patients with TLS

Study	Age	Sex	Primary disease	Dose of tisagenlecleucel	PT*	Grade	Seriousness	Time to onset (days)	Causal relationship to tisagenlecleucel	Outcome
B2202	1[redacted]	Male	B-ALL	4.4×10^6 cells/kg	TLS	3	Non-serious	11	Yes	Resolved
	1[redacted]	Female	B-ALL	2.0×10^6 cells/kg	TLS	4	Serious	284	No	Resolved
	1[redacted]	Male	B-ALL	2.8×10^6 cells/kg	TLS	3	Non-serious	13	Yes	Resolved
	1[redacted]	Male	B-ALL	3.0×10^6 cells/kg	TLS	3	Serious	8	Yes	Resolved
C2201	5[redacted]	Male	DLBCL	3.3×10^8 cells/body	TLS	3	Non-serious	8	Yes	Resolved

* MedDRA/J ver. 20.0 was applied in Study B2202, and MedDRA/J ver. 20.1 in Study C2201.

PMDA's view:
Serious TLS occurred in patients who received tisagenlecleucel, and therefore attention should be paid to TLS associated with tisagenlecleucel. Accordingly, information about the incidence of TLS in clinical studies and the others should be appropriately provided to healthcare professionals using the package insert, etc. to raise cautions so that adequate actions can be taken in case of TLS.

7.R.4.4.8 Others

7.R.4.4.8.1 Secondary malignant tumor

The applicant's explanation about secondary malignant tumor:
Using the database (data cut-off on July 1, 2018) consisting of the safety information from clinical studies of tisagenlecleucel and post-marketing experience in foreign countries, adverse events coded as MedDRA SMQ "Malignant or unspecified tumours" and MedDRA PT "Myelodysplastic syndrome"

were classified as secondary malignant tumor. Table 56 shows characteristics of the patients who experienced secondary malignant tumor.

Table 56. List of patients with secondary malignant tumor

Study	Age	Sex	Primary disease	PT*	Grade	Serious/ Non-serious	Time to onset (days)	Causal relationship to tisagenlecleucel	Outcome
B2202	[redacted]	Female	B-ALL	Myelodysplastic syndrome	Unreported	Serious	261	No	Unresolved
C2201	6[redacted]	Male	DLBCL	Prostate cancer	Unreported	Serious	72	No	Unresolved
	7[redacted]	Male		Prostate cancer	3	Serious	573	No	Unknown
	6[redacted]	Male		Acute myeloid leukemia	Unreported	Serious	363	No	Unresolved
	6[redacted]	Male		Myelodysplastic syndrome	Unreported	Serious	413	No	Unresolved
	7[redacted]	Female		Myelodysplastic syndrome	Unreported	Serious	355	No	Unresolved
A2201	5[redacted]	Male	CLL	Lung adenocarcinoma	3	Serious	52	No	Unresolved
A2101J	5[redacted]	Female	DLBCL	Second primary malignancy	3	Serious	51	Yes	Deterioration
A2208J	6[redacted]	Male	CLL	Adenocarcinoma	5	Serious	1024	No	Death
	7[redacted]	Male	CLL	Lung adenocarcinoma	3	Serious	870	No	Resolved
A2205B	[redacted]	Male	ALL	Acute myeloid leukemia	Unreported	Serious	731	No	Unresolved
	6[redacted]	Male	CLL	Thymoma	3	Serious	1702	No	Resolved
	6[redacted]	Male	ALL	Prostate cancer	3	Serious	Unknown	Yes	Resolved
B2205J	[redacted]	Male	ALL	Glioblastoma multiforme	Unreported	Serious	964	No	Death
Spontaneous report	2[redacted]	Male	ALL	Histiocytic sarcoma	Unreported	Serious	72	Unreported	Unreported
Post-marketing	Unknown	Male	ALL	Acute myeloid leukemia	Unreported	Serious	Unknown	Unreported	Death

*: MedDRA ver. 21.0

PMDA's view:

For secondary malignant tumor, a relationship to the primary disease or age cannot be ruled out, and at present, the relationship to tisagenlecleucel remains unclear. For some of the events, however, a causal relationship to tisagenlecleucel 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 tisagenlecleucel.

7.R.4.4.8.2 Complications associated with leukapheresis

The applicant explained complications associated with leukapheresis before manufacture of tisagenlecleucel based on results from the interim analysis (data cut-off on [redacted], 20[redacted]) in a global phase II study (Study B2206) in patients with ALL or DLBCL, which is currently ongoing to collect information about the complications.

The applicant's explanation:

The safety evaluation period was defined as the period from the day of leukapheresis procedure to the following day, and the safety of leukapheresis was evaluated. As of the cut-off date, 304 patients (135 patients with ALL, 169 patients with DLBCL) underwent leukapheresis. Table 57 shows adverse events with an incidence of ≥3% of patients with either ALL or DLBCL.

Table 57. Adverse events with an incidence of ≥3% of patients with either ALL or DLBCL

Preferred term (MedDRA ver. 21.0)	Number of patients (%)			
	ALL n = 135		DLBCL n = 169	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	68 (50.4)	28 (20.7)	68 (40.2)	11 (6.5)
Platelet count decreased	16 (11.9)	11 (8.1)	6 (3.6)	1 (0.6)
Anaemia	12 (8.9)	2 (1.5)	9 (5.3)	1 (0.6)
Hypocalcaemia	11 (8.1)	1 (0.7)	1 (0.6)	0
Catheter site pain	8 (5.9)	0	2 (1.2)	0
Hypokalaemia	7 (5.2)	3 (2.2)	4 (2.4)	1 (0.6)
Hypertension	6 (4.4)	4 (3.0)	3 (1.8)	1 (0.6)
Pyrexia	6 (4.4)	0	4 (2.4)	0
Nausea	4 (3.0)	0	5 (3.0)	0
Hypomagnesaemia	3 (2.2)	0	5 (3.0)	0
Hypotension	3 (2.2)	1 (0.7)	5 (3.0)	1 (0.6)
Paraesthesia	2 (1.5)	0	7 (4.1)	0
Dyspnoea	1 (0.7)	0	5 (3.0)	1 (0.6)
Diarrhoea	0	0	5 (3.0)	0
Fatigue	0	0	6 (3.6)	0
Lymphocyte count decreased	0	0	5 (3.0)	3 (1.8)

Serious adverse events occurred in 5 patients with ALL (3.7%, chills, FN, hypotension, neutropenia, paraesthesia, pneumonia, pneumothorax, and pyrexia in 1 patient each [including duplicate counting]) and in 5 patients with DLBCL (3.0%, hypotension, blood calcium increased, bronchial obstruction, depressed level of consciousness, dyspnoea, muscular weakness, sepsis, and supraventricular tachycardia in 1 patient each [including duplicate counting]). A causal relationship to leukapheresis could not be ruled out for hypotension, blood calcium increased, and supraventricular tachycardia in 1 patient with DLBCL each. In addition, no death occurred during the period for leukapheresis.

Based on the above results including the low incidence of serious events for which a causal relationship to leukapheresis could not be ruled out, the complications associated with leukapheresis are considered manageable.

PMDA accepted the applicant's explanation.

7.R.4.4.8.3 Risk of contamination of leukemia cells in the T cell-modification process

There is a report that CAR gene was unintentionally introduced into a leukemic cell contained in the peripheral mononuclear fraction collected from the patient by apheresis, and the CAR-transduced leukemic cell was administered and proliferated in the patient body without being recognized by CAR-T cells (*Nature Medicine.* 2018;24:1499-1503). PMDA asked the applicant about the risk of contamination of leukemic cells in the peripheral mononuclear fraction.

The applicant's response:

The above report was from the phase I/II study in patients with B-ALL conducted at Penn at an early development stage. Tisagenlecleucel cells obtained from the manufacturing process at Penn contained residual B cells at 0.01% to 0.03%, indicating the potential contamination of leukemic cells. The proposed process, on the other hand, uses the FAST process, which selects only T cells using Dynabeads CD3/CD28CTS, to reduce contamination of B cells in the cell culture process. In fact, all

the final product batches of tisagenlecleucel were demonstrated to be free from residual B cells. Thus, tisagenlecleucel is not presumed to have the risk of leukemic cell contamination.

PMDA accepted the applicant's explanation.

7.R.5 Clinical positioning and indication or performance of tisagenlecleucel in pediatric and AYA patients with relapsed or refractory B-ALL

The proposed "Indication or Performance" of Kymriah in treatment of B-ALL was "Relapsed or refractory CD19-positive disease below: B-cell acute lymphoblastic leukemia." In addition, the "Precautions for Indication or Performance" section included the following statements:

- Kymriah should be used in patients aged ≤25 years.
- Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining.

PMDA's conclusion:

Based on reviews in sections "7.R.2 Efficacy in pediatric and AYA patients with relapsed or refractory B-ALL" and "7.R.4.1 Safety profile of tisagenlecleucel in pediatric and AYA patients with relapsed or refractory B-ALL and differences in the safety profile between Japanese and non-Japanese patients" as well as the review presented below, PMDA has concluded that the "Indication or Performance" of Kymriah should be follows:

> Treatment of relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. For patients with ≥2 lines of prior chemotherapy, Kymriah should be used only in those who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.

Further, details of the prior treatment and age of the patients included in Study B2202 [see Section 7.1.1.1] should be provided in the Clinical Studies section of the package insert, and that the following cautionary statements should be included in the "Precautions for Indication or Performance" section.

- Kymriah should be used in patients aged ≤25 years.
- Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining.
- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the "Clinical Studies" section regarding prior treatment received by the clinical study patients.

7.R.5.1 Clinical positioning and target population of tisagenlecleucel

The foreign practical guidelines include the following description about use of tisagenlecleucel in pediatric and AYA patients with relapsed or refractory B-ALL. At present, no other description about use of tisagenlecleucel is found in Japanese practical guidelines or representative textbooks of clinical oncology available in Japan or foreign countries.

Practical guidelines

- NCCN guidelines (Acute Lymphoblastic leukemia, ver. 1.2018): Tisagenlecleucel is one of the treatment options for patients with relapsed or refractory ALL (<26 years of age and with refractory

disease or ≥2 relapses, and with a prior treatment with ≥2 tyrosine kinase inhibitors [TKIs] if ALL is positive for Philadelphia chromosome), and allogeneic HSCT may be considered after tisagenlecleucel therapy (Category 2A[37]). Significance of allogeneic HSCT after administration of tisagenlecleucel remains unknown.

The applicant's explanation about clinical positioning and "Indication or Performance" of Kymriah:
Based on results from Study B2202, tisagenlecleucel is positioned as one of the treatment options for patients with CD19-positive relapsed or refractory B-ALL.

Although Study B2202 included the patients under the definite inclusion criteria in terms of the prior treatment and prior allogeneic HSCT, it is not necessary to limit the target population of tisagenlecleucel by the prior treatment or prior allogeneic HSCT, provided that the "Indication or Performance" section states that Kymriah is indicated for patients with relapsed or refractory disease.

Prior treatment

Most of the patients (n = 68) included in Study B2202 had received ≥2 lines of prior chemotherapy, but the study also included 7 patients with only 1 line of prior chemotherapy (3 patients who had received ≥2 cycles of chemotherapy to treat ALL but failed to achieve CR; 3 patients who had achieved remission after the first chemotherapy, then underwent allogeneic HSCT, but experienced a bone marrow relapse; 1 patient who had achieved CR after the first chemotherapy, then experienced a relapse in the bone marrow, but was not eligible for allogeneic HSCT).

The efficacy and safety results in the overall population (n = 75) and the subpopulation of patients with only 1 line of prior chemotherapy (n = 7) in Study B2202, are shown below.

In Study B2202, the overall remission rate was 81.3% (61 of 75) of patients in the overall population and 100% (7 of 7) of patients with only 1 line of prior chemotherapy. This suggests that tisagenlecleucel is effective in both populations.

Table 58 shows the safety profile, revealing no clear differences between the 2 populations.

Table 58. Summary of safety (Study B2202)

	Number of patients (%)	
	Overall population n = 75	Patients with only 1 line of prior chemotherapy n = 7
All adverse events	75 (100)	7 (100)
Grade 3 or 4 adverse events	66 (88.0)	4 (57.1)
Serious adverse events	58 (77.3)	4 (57.1)
Adverse events leading to death	19 (25.3)	0

The above results indicate that tisagenlecleucel is clinically useful in patients with B-ALL irrespective of the number of lines of prior chemotherapy.

[37] Based upon lower-level evidence, there is a uniform NCCN consensus that the intervention is appropriate.

Prior allogeneic HSCT

Study B2202 included 29 patients without prior allogeneic HSCT, 16 of whom were eligible for but had not undergone allogeneic HSCT (no donors found, or patient's refusal of allogeneic HSCT[38)]).

The efficacy and safety results in the overall population (n = 75), the subpopulation of patients without prior allogeneic HSCT (n = 29), and the other subpopulation of patients without prior allogeneic HSCT despite being eligible for allogeneic HSCT (n = 16) in Study B2202, are shown below.

In Study B2202, the overall remission rate was 81.3% (61 of 75) of patients in the overall population, 79.3% (23 of 29) of patients without prior allogeneic HSCT, and 81.3% (13 of 16) of patients without prior allogeneic HSCT despite being eligible for allogeneic HSCT. This suggests that tisagenlecleucel is effective in all of the populations.

Table 59 shows the safety profile, revealing no clear differences between the 3 populations.

Table 59. Summary of safety (Study B2202)

	Number of patients (%)		
	Overall population n = 75	Patients without prior allogeneic HSCT n = 29	Patients without prior allogeneic HSCT despite being eligible for allogeneic HSCT n = 16
All adverse events	75 (100)	29 (100)	16 (100)
Grade 3 or 4 adverse events	66 (88.0)	25 (86.2)	15 (93.8)
Serious adverse events	58 (77.3)	25 (86.2)	14 (87.5)
Adverse events leading to death	19 (25.3)	9 (31.0)	6 (37.5)

The above results indicate that tisagenlecleucel is clinically useful in patients with B-ALL irrespective of prior allogeneic HSCT.

Study B2202 enrolled patients aged 3 years (at the time of screening for Study B2202) to ≤21 years (at the initial diagnosis of B-ALL) for the following reasons:

- The lower age limit was ≥3 years to increase the success rate of manufacturing of tisagenlecleucel, because the manufacturing of tisagenlecleucel did not succeed in 71% of patients aged ≤3 years in a foreign phase I study (Study B2101J).

- The upper age limit was ≤21 years because, according to a survey of treatments of ALL provided by pediatric oncologists in clinical practice (the applicant reviewed this survey at the time of planning of Study B2202), many pediatric oncologists provided treatment to patients aged up to 21 years (*Ped Blood Cancer.* 2008;50:1090-3).

For the lower age limit, however, the manufacturing process of tisagenlecleucel was improved after start of Study B2202, making it possible to manufacture tisagenlecleucel from a patient aged <3 years. During the period between the launch in the US and June 27, 2018, tisagenlecleucel was successfully

38) The protocol of Study B2202 stipulated that the physician not participating in the study must explain allogeneic HSCT to the patient, to ensure that the patient can determine whether to undergo allogeneic HSCT by themselves. Thereby the intention of the patient was confirmed.

manufactured from 3 patients aged <3 years, 1 of whom achieved CR. The applicant therefore considers it unnecessary to specify a lower age limit for the target population of tisagenlecleucel.

For the upper age limit, administration of tisagenlecleucel to patients aged >25 years is not recommended at present, because Study B2202 enrolled no patients who would be >25 years old when receiving tisagenlecleucel. However, a global phase III study (Study I2301) is being planned to investigate the efficacy of tisagenlecleucel in adult patients with relapsed or refractory B-ALL.

Furthermore, there are a small number of patients with CD19-negative ALL. The inclusion criteria of Study B2202 therefore required subjects to have documented CD19 expression. Also in the post-marketing settings, patients should test positive for CD19 antigen before receiving tisagenlecleucel.

Based on the above, the applicant has proposed the following "Indication or Performance" and the "Precautions for Indication or Performance" of Kymriah:

Indication or Performance:
Relapsed or refractory CD19-positive disease below: B-cell acute lymphoblastic leukemia

Precautions for Indication or Performance:
- Kymriah should be used in patients aged ≤25 years.
- Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining.

PMDA's view:
For the reasons described below, at present, the target population of tisagenlecleucel should be the same as that included in Study B2202, and thus the prior treatment and prior allogeneic HSCT in the patients in Study B2202 should be described clearly in the "Indication or Performance" of Kymriah.
- Allogeneic HSCT is the only curative treatment for B-ALL. However, there are no study data comparing the efficacy and safety of allogeneic HSCT and tisagenlecleucel, and the clinical position of tisagenlecleucel in relation to allogeneic HSCT is unclear. Therefore, treatment with tisagenlecleucel is not recommended for patients for whom allogeneic HSCT is available.

- Administration of tisagenlecleucel is highly likely to cause serious adverse events such as CRS, and treatment with tisagenlecleucel is not recommended for patients who have received prior treatments not allowed by the protocol of Study B2202.

In addition, the Study B2202 inclusion criteria for the prior treatment differed depending on Philadelphia chromosome because of the different treatment strategy of relapsed or refractory B-ALL according to the chromosome status; and Study B2202 included patients who had failed to achieve CR with ≥2 cycles of chemotherapy. In view of this fact, details of the prior treatment received by the clinical study patients should be described in the Clinical Studies section in the package insert, and the

following cautionary statement should be included in the “Precautions for Indication or Performance” section.

- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the “Clinical Studies” section regarding prior treatment received by the clinical study patients.

In addition, the age range of the target patient population does not have to be clearly specified in the “Indication or Performance,” because the above applicant’s explanation is understandable; and there is no general consensus about the upper age limit of pediatric and AYA patients with B-ALL. However, the “Precaution for Indication or Performance” section should include a cautionary statement that the efficacy and safety of tisagenlecleucel remain unclear in patients aged >25 years.

In addition, the following statement may be included as proposed by the applicant.

- Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining.

Based on the above, PMDA has concluded that the “Indication or Performance” and “Precautions for Indication or Performance” of Kymriah should be as follows:

Indication or Performance

Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. For patients with ≥2 lines of prior chemotherapy, Kymriah should be used only in those who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.

Precautions for Indication or Performance

- Kymriah should be used in patients aged ≤25 years.
- Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining.
- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the “Clinical Studies” section regarding prior treatment received by the clinical study patients.

7.R.5.2 Allogeneic HSCT after administration of tisagenlecleucel

The applicant’s explanation about allogeneic HSCT after administration of tisagenlecleucel:

In Study B2202, 13 patients underwent allogeneic HSCT after administration of tisagenlecleucel. Of these, 8 patients underwent allogeneic HSCT while in remission, all of whom were alive at the cut-off date (follow-up period, 245-571 days). Five patients underwent allogeneic HSCT after tisagenlecleucel therapy because of a relapse or failure to achieve remission. Of these, 2 patients died from disease progression within 100 days after allogeneic HSCT, but a causal relationship between the death and tisagenlecleucel was ruled out in both patients.

Based on the above, allogeneic HSCT after administration of tisagenlecleucel is considered to raise no particular safety concerns.

PMDA's view:

PMDA largely accepted the applicant's explanation. At present, however, information about patients with B-ALL who underwent allogeneic HSCT after administration of tisagenlecleucel is very limited, and thus the concerned information should be continuously collected in post-marketing settings of tisagenlecleucel.

7.R.6 Dosage and administration or method of use for pediatric and AYA patients with relapsed or refractory B-ALL

The proposed "Dosage and Administration or Method of Use" of Kymriah for pediatric and AYA patients with relapsed or refractory B-ALL is shown below.

Process from leukapheresis at medical institution to transportation to manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells including sufficient T-lymphocytes are collected.

2. Cryopreservation of leukapheresis material
   The leukapheresis material is prepared immediately after collection, and cryopreserved in the vapor phase of liquid nitrogen.

3. Transportation of leukapheresis material
   The cryopreserved leukapheresis material is packed and transported to the manufacturing facility of Kymriah.

Process from acceptance at medical institution to infusion of Kymriah

4. Receipt and storage of Kymriah
   Kymriah is received in a frozen condition, and cryopreserved in the vapor phase of liquid nitrogen until immediately before use.

5. Pretreatment before infusion of Kymriah
   The period between pretreatment chemotherapy and infusion of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition.

6. Infusion of Kymriah
   Kymriah is thawed immediately before infusion, and administered intravenously as a single dose as described below according to the patient's disease.

The usual dosage for patients aged ≤25 years (at the time of infusion) is selected from the following doses according to body weight and infused as a single intravenous dose:

- Body weight ≤50 kg: CAR-positive viable T cells at 0.2 to 5.0 × 10^6/kg.
- Body weight >50 kg: CAR-positive viable T cells at 0.1 to 2.5 × 10^8 (irrespective of body weight).

The proposed "Precautions for Dosage and Administration or Method of Use" section included the following information:

Pretreatment

- Implementation of chemotherapy to enhance survival of transplanted cells in the case of white blood cell count >1000/μL

Infusion

- Confirmation of the identity of Kymriah (infusion bag)
- Examination of the patient's general condition before infusion of Kymriah, and postponement of the administration where necessary
- Premedication with an antihistamine or antipyretic analgesic to alleviate the infusion reaction. In addition, ensuring that emergency care is ready for possible severe adverse events associated with the administration such as anaphylaxis.
- Ensuring that a stock of the intravenous anti-IL-6 receptor preparation is available to prepare for CRS
- Thawing of Kymriah (infusion bag)
- Actions taken when any damage is found in Kymriah (infusion bag)
- Infusion rate of Kymriah
- Priming before and after infusion of Kymriah

PMDA's conclusion:

Based on reviews in sections "7.R.2 Efficacy in pediatric and AYA patients with relapsed or refractory B-ALL" and "7.R.4.1 Safety profile of tisagenlecleucel in pediatric and AYA patients with relapsed or refractory B-ALL and differences in the safety profile between Japanese and non-Japanese patients" as well as the review presented below, PMDA has concluded that the following modifications (see underlined words below) should be made to "Dosage and Administration or Method of Use" and "Precautions for Dosage and Administration or Method of Use" of Kymriah for pediatric and AYA patients with relapsed or refractory B-ALL.

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 including sufficient T-lymphocytes are collected.

2. Cryopreservation of leukapheresis material
   The leukapheresis material is prepared immediately after collection, and cryopreserved in the vapor phase of liquid nitrogen.

3. Transportation of leukapheresis material
   The cryopreserved leukapheresis material is packed and transported to the manufacturing facility of Kymriah.

Process from acceptance at medical institution to infusion of Kymriah

4. Receipt and storage of Kymriah
   Kymriah is received in a frozen condition, and cryopreserved in the vapor phase of liquid nitrogen until immediately before use.

5. Pretreatment before infusion of Kymriah
   The period between pretreatment chemotherapy and infusion of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition.

6. Infusion of Kymriah
   Kymriah is thawed immediately before infusion, and administered intravenously as a single dose as described below according to the patient's disease.

The usual dosage for patients aged ≤25 years (at the time of infusion) is determined according to body weight (see below) and infused as a single intravenous dose.

- Body weight ≤50 kg: CAR-positive viable T cells at 0.2×10^6 to 5.0×10^6/kg.
- Body weight >50 kg: CAR-positive viable T cells at 0.1×10^8 to 2.5×10^8 (irrespective of body weight).

Precautions for Dosage and Administration or Method of Use (excerpt) (underline denotes additions or corrections)

Pre-treatment

- Implementation of chemotherapy to enhance survival of transplanted cells in the case of peripheral white blood cell count >1000/μL

Infusion

- Confirmation of the identity of Kymriah (infusion bag)
- Examination of the patient's general condition before infusion of Kymriah, and postponement of the administration where necessary
- Premedication with an antihistamine, antipyretic analgesic, etc. to alleviate the infusion reaction. In addition, ensuring that emergency care is ready for possible severe adverse events associated with the administration such as anaphylaxis.
- Ensuring that a stock of tocilizumab is available to prepare for CRS
- Thawing of Kymriah (infusion bag)
- Actions taken when any damage is found in Kymriah (infusion bag)
- Infusion rate of Kymriah
- Priming before and after infusion of Kymriah

7.R.6.1 Dosage and administration or method of use of tisagenlecleucel

The applicant's explanation about the rationale for establishing "Dosage and Administration or Method of Use" for patients with relapsed or refractory B-ALL:

In a foreign phase I/IIa study (Study B2101J), tisagenlecleucel at 0.15×10^8 to 50×10^8 cells was intravenously infused in 3 divided-doses (10%, 30%, and 60% of the total number of cells

administered at the first, second, and third infusions, respectively), and when an adverse event (e.g., pyrexia) occurred after the first or second infusion, the subsequent infusion(s) were omitted. The results showed that 21 of 56 patients received only 1 infusion owing to pyrexia, but CR was achieved irrespective of the number of infusions. In Study B2202, therefore, tisagenlecleucel was administered as a single dose.

Furthermore, the following target doses of tisagenlecleucel were used in Study B2202:
Patients weighing ≤50 kg: 2.0×10^6 to 5.0×10^6 cells/kg (acceptable dose, 0.2×10^6-5.0×10^6 cells/kg)
Patients weighing >50 kg: 1.0×10^8 to 2.5×10^8 cells (acceptable dose, 0.1×10^8-2.5×10^8 cells)
These target doses were selected for the following reasons: (a) clinical experience with tisagenlecleucel at the time of planning of Study B2202 suggested that tisagenlecleucel at $<2 \times 10^6$ cells/kg would result in a failure to achieve CR; (b) only a small number of patients had received tisagenlecleucel at $>5 \times 10^8$ cells; and (c) the manufacturing of tisagenlecleucel had some limitations to be considered.

The results of Study B2202 showed the clinical usefulness of tisagenlecleucel, and thus based on the acceptable doses, etc. in Study B2202, the "Dosage and Administration or Method of Use" of Kymriah was established.

PMDA accepted the applicant's explanation.

7.R.7 Clinical positioning and indication or performance in patients with relapsed or refractory DLBCL

The proposed "Indication or Performance" of Kymriah is "Relapsed or refractory CD19-positive disease below: Diffuse large B-cell lymphoma." In addition, the "Precautions for Indication or Performance" section included the following statement:

- Kymriah should be used only in patients who are ineligible for, or relapsed after, autologous HSCT.

PMDA's conclusion:
Based on reviews in Sections "7.R.3 Efficacy in patients with relapsed or refractory DLBCL" and "7.R.4.2 Safety profile of tisagenlecleucel in patients with relapsed or refractory DLBCL and differences in the safety profile between Japanese and non-Japanese patients" as well as the review below, PMDA has concluded that the "Indication or Performance" for Kymriah should be as follows:

> Treatment of relapsed or refractory CD19-positive diffuse large B-cell lymphoma. Kymriah should be used only in patients with ≥2 lines of prior chemotherapy who are ineligible for, or relapsed after, allogeneic HSCT.

The "Clinical Studies" section of the package insert should provide details of prior treatment of the patients included in Study C2201, and the "Precautions for Indication or Performance" section should include the following cautionary statements:

- Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining.

- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the "Clinical Studies" section regarding the tissue type and prior treatment of the clinical study patients.

7.R.7.1 Clinical positioning and target population of tisagenlecleucel

The foreign practical guidelines include the following description about use of tisagenlecleucel in patients with relapsed or refractory DLBCL. At present, no other description about use of tisagenlecleucel is found in Japanese practical guidelines or representative textbooks of clinical oncology available in Japan or foreign countries.

Practical guidelines

- NCCN guidelines (B-Cell Lymphomas, ver. 1.2019): Tisagenlecleucel is one of the treatment options for patients with DLBCL who have received ≥2 lines of prior chemotherapy (including patients with DLBCL histologically transformed from follicular lymphoma [FL]) (Category 2A).

The applicant's explanation about clinical positioning and "Indication or Performance" of Kymriah:
Based on results from Study C2201, tisagenlecleucel is positioned as one of the treatment options for patients with relapsed or refractory DLBCL who are ineligible for, or relapsed after, autologous HSCT.

Study C2201 included patients with ≥2 lines of prior chemotherapy, but the proposed "Indication or Performance" would allow patients with only 1 line of prior chemotherapy to receive tisagenlecleucel. PMDA asked the applicant to explain the efficacy of tisagenlecleucel in patients with only 1 line of prior chemotherapy.

The applicant's response:
Of 93 patients included in the efficacy analysis in Study C2201, 5 patients (5.4%) had only 1 line of prior chemotherapy, and their details are shown below.

- Three (3) patients who had received chemotherapy to treat FL initially and then 1 line of chemotherapy to treat DLBCL histologically transformed from FL

- One (1) patient who had received 1 line of chemotherapy and undergone autologous HSCT to treat DLBCL, but experienced relapse leading to inclusion in Study C2201, and then received the bridging chemotherapy before administration of tisagenlecleucel

- One (1) patient who had received 2 regimens of chemotherapy (combination of rituximab [genetical recombination], cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone [R-CHOP regimen]; and combination of rituximab [genetical recombination], etoposide, prednisolone, vincristine sulfate, cyclophosphamide hydrate, and doxorubicin hydrochloride [R-EPOCH regimen]), to treat DLBCL histologically transformed from chemotherapy-naive FL. These 2 regimens were later analyzed as 1 line of chemotherapy because of absence of disease progression between the regimens. The patient then received the bridging chemotherapy before administration of tisagenlecleucel.

Of the above 5 patients, 4 patients (80.0%) responded to tisagenlecleucel (3 patients with CR, 1 patient with PR). The remaining 1 patient resulted in stable disease (SD) (i.e., the patient who had received 1 line of chemotherapy and undergone autologous HSCT to treat DLBCL, but experienced relapse, and then received bridging chemotherapy before administration of tisagenlecleucel). As described above, tisagenlecleucel is expected to be effective even in patients with DLBCL who have received only 1 line of chemotherapy.

Based on the above, the applicant has proposed the following "Indication or Performance" and "Precautions for Indication or Performance" of Kymriah:

Indication or Performance:
Relapsed or refractory CD19-positive disease below: Diffuse large B-cell lymphoma

Precautions for Indication or Performance:
- Kymriah should be used only in patients who are ineligible for, or relapsed after, autologous HSCT.

PMDA's view:
Patients who have received tisagenlecleucel are extremely likely to experience serious adverse events such as CRS and administration of tisagenlecleucel is recommended only for the population eligible for Study C2201. Thus, the "Indication or Performance" section should describe the prior treatment and prior autologous HSCT received by the patients in Study C2201.

The applicant explained that Study C2201 included 5 patients who had received only 1 line of chemotherapy. However, all of them had actually received ≥2 lines of chemotherapy including treatment for FL and bridging therapy for DLBCL. Accordingly, there are no clinical study data showing the efficacy of tisagenlecleucel in patients with DLBCL who have received only 1 line of chemotherapy, and thus tisagenlecleucel therapy should not be recommended to such patients.

Data from patients with DLBCL histologically transformed from FL (n = 3) show that tisagenlecleucel is expected to be effective in treatment of such histologically transformed DLBCL. Therefore, the Clinical Studies section of the package insert should include the following information:

> Study C2201 included (a) patients who had received only 1 line of chemotherapy after diagnosis of DLBCL but actually had received ≥2 lines of chemotherapy in total and (b) patients with DLBCL histologically transformed from FL.

Further, the following cautionary statement should be included in the "Precautions for Indication or Performance" section.
- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the "Clinical Studies" section regarding the tissue type and prior treatment of the clinical study patients.

The “Precautions for Indication or Performance” section should also provide a cautionary statement that patients with DLBCL should test positive for CD19 by FCM, etc. before receiving tisagenlecleucel.

Based on the above, PMDA has concluded that “Indication or Performance” and “Precautions for Indication or Performance” of Kymriah in patients with DLBCL should be as follows.

Indication or Performance
Relapsed or refractory CD19-positive diffuse large B-cell lymphoma. Kymriah should be used only in patients with ≥2 lines of prior chemotherapy who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.

Precautions for Indication or Performance
- Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining.

- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the “Clinical Studies” section regarding the tissue type and prior treatment of the clinical study patients.

7.R.7.2 Autologous HSCT after administration of tisagenlecleucel

The applicant’s explanation about autologous HSCT after administration of tisagenlecleucel:
In Study C2201, only 1 patient underwent autologous HSCT after administration of tisagenlecleucel. This patient achieved CR after administration of tisagenlecleucel, but relapsed on Day 157 of administration, and underwent autologous HSCT on Day 199. The autologous HSCT resulted in SD, and allogeneic HSCT was performed on Day 242. The allogeneic HSCT resulted in PR, but the patient died of cerebral haemorrhage on Day 287.

Based on the above, experience with autologous HSCT after administration of tisagenlecleucel is very limited, and thus a conclusion on the safety and efficacy remains to be reached at present.

PMDA’s view:
At present, only very limited information is available about patients with DLBCL who underwent autologous HSCT after receiving tisagenlecleucel, and thus relevant information should be continuously collected in post-marketing settings.

7.R.8 Dosage and administration or method of use for patients with relapsed or refractory DLBCL

The proposed “Dosage and Administration or Method of Use” and “Precautions for Dosage and Administration or Method of Use” of Kymriah for patients with DLBCL were the same as that for patients with B-ALL except for the following point:
- The usual adult dosage is 0.6 to 6.0 × 10^8 (irrespective of body weight) of CAR-positive viable T cells infused as a single intravenous dose.

PMDA's conclusion:
Based on reviews in Sections "7.R.3 Efficacy in patients with relapsed or refractory DLBCL" and "7.R.4.2 Safety profile of tisagenlecleucel in patients with relapsed or refractory DLBCL and differences in the safety profile between Japanese and non-Japanese patients" as well as the review below, PMDA has concluded that the following modifications (see underlined words below) should be made to the "Dosage and Administration or Method of Use" for patients with DLBCL. In addition, the "Precautions for Dosage and Administration or Method of Use" section requires the same modification as that for patients with B-ALL [see Section 7.R.5.1].

Dosage and Administration or Method of Use (statements about DLBCL are excerpted, and underline denotes addition)

- The usual adult dosage is 0.6×10^8 to 6.0×10^8 (irrespective of body weight) of CAR-positive viable T cells infused as a single intravenous dose.

7.R.8.1 Dosage and administration or method of use of tisagenlecleucel

The applicant's explanation about the rationale for "Dosage and Administration or Method of Use" for patients with relapsed or refractory DLBCL:
In Study C2201, the target dose was 5.0×10^8 cells and acceptable doses were 1.0×10^8 to 5.0×10^8 cells, because results from a foreign phase I study (Study B2102J) and a foreign phase II study (Study A2201) available at the time of planning of Study C2201 showed that a single intravenous dose of tisagenlecleucel at 1.0×10^8 to 5.0×10^8 cells was safe and expected to be effective in patients with DLBCL.

Since no established treatment is available for the population eligible for Study C2201, the patients included in the study were allowed to receive tisagenlecleucel at a dose outside the above dose range. Table 60 shows details of the patients who received tisagenlecleucel at a dose outside the dose range; these results show the efficacy and safety of tisagenlecleucel at doses ranging from 0.6×10^8 to 6.0×10^8 cells.

Table 60. List of patients who received tisagenlecleucel at a dose outside of the specified dose range

	Age	Sex	Dose of tisagenlecleucel ($\times 10^8$ cells)	Best overall response	Major adverse events (Grade)
$<1.0 \times 10^8$ cells	4[redacted]	Female	0.83	CR	CRS (Grade 1), platelet count decreased (Grade 3), bacteraemia (Grade 2), conjunctivitis (Grade 2), periodontitis (Grade 2)
	6[redacted]	Male	0.99	PD	Thrombocytopenia (Grade 3), herpes simplex (Grade 3), infection (Grade 3)
	5[redacted]	Male	0.089	PD	No
	7[redacted]	Female	0.65	PD	Confusional state (Grade 3)
	6[redacted]	Female	0.59	CR	Bronchitis (Grade 2), otitis media (Grade 2)
$>5.0 \times 10^8$ cells	5[redacted]	Female	6.00	CR	CRS (Grade 2), white blood cell count decreased (Grade 1), FN (Grade 3), disturbance in attention (Grade 1)
	3[redacted]	Female	5.25	PD	CRS (Grade 3), platelet count decreased (Grade 3), neutropenia (Grade 3), mucosal infection (Grade 2), delirium (Grade 1)
	6[redacted]	Male	5.24	Unknown	CRS (Grade 3), platelet count decreased (Grade 3)
	6[redacted]	Male	5.51	CR	CRS (Grade 3), fungal infection (Grade 2)
	4[redacted]	Male	5.70	SD	No

As described above, Study C2201 showed the clinical usefulness of tisagenlecleucel at doses ranging from 0.6×10^8 to 6.0×10^8 cells in patients with relapsed or refractory DLBCL. Based on this, "Dosage and Administration or Method of Use" of Kymriah was determined.

PMDA accepted the applicant's explanation.

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

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

To investigate the safety of Kymriah in clinical use, etc., the applicant plans a post-marketing surveillance covering all patients with B-ALL or DLBCL treated with Kymriah.

The safety specification of this surveillance includes the following:

(1) Events expected to occur in post-marketing settings based on incidences of the adverse events reported in Studies B2202, B2205J, and C2201:
"CRS," "infection," "early onset of neuropsychiatric event," "hypersensitivity," "TLS," "FN," "continuous depletion of normal B cells and hypogammaglobulinaemia" and "cytopenia persisting for ≥28 days after infusion"

(2) Events expected to occur based on the mechanism of action of tisagenlecleucel
"Brain oedema," "development of replication competent lentivirus," "secondary malignant tumor," "onset or deterioration of autoimmune disease," "onset of hematological disease," "onset or deterioration of a neuropsychiatric event," and "graft versus host disease"

(3) "Long-term safety" (because the long-term safety of Kymriah is currently unknown)

The surveillance will cover 100 patients with B-ALL and 280 patients with DLBCL based on (a) the number of patients expected to receive Kymriah in post-marketing settings (for 3 years after the market launch of Kymriah) and (b) the incidences of the above events (i.e., those included in the safety specification) in Studies B2202, B2205J, and C2201.

The follow-up period of up to 8 years was established in view of a possibility that Kymriah survives in the patient's body for an extended period.

PMDA's view:
PMDA accepted the above applicant's explanation. The details of the post-marketing use-results survey will be finalized taking account of comments on the safety evaluation of Kymriah raised in the Expert Discussion.

9. Adverse Events Observed in Clinical Studies

Data on death reported in clinical studies submitted for safety evaluation are presented in Sections "7.1 Evaluation data" and "7.2 Reference data." Main adverse events other than death are shown below.

9.1 Global phase II study (Study B2202)

Adverse events occurred in all patients, and 94.7% (71 of 75) of patients experienced events for which a causal relationship to tisagenlecleucel could not be ruled out. Table 61 shows all-grade adverse events with an incidence of ≥20%.

Table 61. Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA/J ver. 20.0)	Number of patients (%) n = 75	
	All Grades	Grade ≥3
All adverse events	75 (100)	66 (88.0)
Blood and lymphatic system disorders		
FN	27 (36.0)	27 (36.0)
Anaemia	23 (30.7)	9 (12.0)
Cardiac disorders		
Tachycardia	17 (22.7)	3 (4.0)
Gastrointestinal disorders		
Vomiting	22 (29.3)	1 (1.3)
Nausea	19 (25.3)	2 (2.7)
Diarrhoea	18 (24.0)	1 (1.3)
General disorders and administration site conditions		
Pyrexia	30 (40.0)	10 (13.3)
Fatigue	16 (21.3)	0
Immune system disorders		
CRS	58 (77.3)	35 (46.7)
Hypogammaglobulinaemia	25 (33.3)	4 (5.3)
Investigations		
Platelet count decreased	23 (30.7)	14 (18.7)
Neutrophil count decreased	22 (29.3)	20 (26.7)
White blood cell count decreased	21 (28.0)	14 (18.7)
AST increased	20 (26.7)	11 (14.7)
ALT increased	18 (24.0)	7 (9.3)
Lymphocyte count decreased	16 (21.3)	15 (20.0)
Metabolism and nutrition disorders		
Decreased appetite	29 (38.7)	11 (14.7)
Hypokalaemia	20 (26.7)	11 (14.7)
Hypophosphataemia	18 (24.0)	9 (12.0)
Hypocalcaemia	16 (21.3)	5 (6.7)
Nervous system disorders		
Headache	27 (36.0)	2 (2.7)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	18 (24.0)	14 (18.7)
Cough	17 (22.7)	0
Vascular disorders		
Hypotension	22 (29.3)	15 (20.0)

Serious adverse events occurred in 77.3% (58 of 75) of patients. Serious adverse events reported by ≥3 patients included CRS in 47 patients (62.7%), FN in 15 patients (20.0%), hypotension in 8 patients (10.7%), pyrexia in 7 patients (9.3%), acute kidney injury, hypoxia and respiratory failure in 5 patients (6.7%) each, and back pain and cardiac arrest in 3 patients (4.0%) each. A causal relationship to tisagenlecleucel could not be ruled out for CRS in 47 patients, FN in 13 patients, hypotension in 8 patients, acute kidney injury in 4 patients, pyrexia in 3 patients, and hypoxia and respiratory failure in 2 patients each.

9.2. Global phase II study (Study C2201)

Adverse events occurred in all patients, and 89.2% (99 of 111) of patients experienced events for which a causal relationship to tisagenlecleucel could not be ruled out. Table 62 shows all-grade adverse events with an incidence of ≥20%.

Table 62. Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA/J ver. 20.1)	Number of patients (%) n = 111	
	All Grades	Grade ≥3
All adverse events	111 (100)	99 (89.2)
Blood and lymphatic system disorders		
Anaemia	53 (47.7)	43 (38.7)
Gastrointestinal disorders		
Diarrhoea	35 (31.5)	1 (0.9)
Nausea	32 (28.8)	1 (0.9)
General disorders and administration site conditions		
Pyrexia	39 (35.1)	6 (5.4)
Fatigue	28 (25.2)	7 (6.3)
Immune system disorders		
CRS	64 (57.7)	24 (21.6)
Investigations		
Neutrophil count decreased	38 (34.2)	37 (33.3)
Platelet count decreased	37 (33.3)	31 (27.9)
White blood cell count decreased	37 (33.3)	34 (30.6)
Metabolism and nutrition disorders		
Hypokalaemia	25 (22.5)	9 (8.1)
Nervous system disorders		
Headache	25 (22.5)	1 (0.9)
Vascular disorders		
Hypotension	29 (26.1)	10 (9.0)

Serious adverse events occurred in 64.9% (72 of 111) of patients. Serious adverse events reported by ≥3 patients included CRS in 30 patients (27.0%), FN in 9 patients (8.1%), pyrexia in 8 patients (7.2%), acute kidney injury, encephalopathy, and fatigue in 4 patients (3.6%) each, and Clostridium difficile infection, confusional state, dyspnoea, multiple organ dysfunction syndrome, neutrophil count decreased, and pneumonia in 3 patients (2.7%) each. A causal relationship to tisagenlecleucel could not be ruled out for CRS in 30 patients, FN and pyrexia in 6 patients each, encephalopathy in 4 patients, acute kidney injury, fatigue, and neutrophil count decreased in 2 patients each, and pneumonia, confusional state, and dyspnoea in 1 patient each.

9.3. Foreign phase II study (Study B2205J)

Adverse events occurred in all patients, and 96.6% (28 of 29) of patients experienced events for which a causal relationship to tisagenlecleucel could not be ruled out. Table 63 shows all-grade adverse events with an incidence of ≥20%.

Table 63. Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA/J ver. 19.0)	Number of patients (%) n = 29	
	All Grades	Grade ≥3
All adverse events	29 (100)	24 (82.8)
Blood and lymphatic system disorders		
Anaemia	11 (37.9)	7 (24.1)
FN	10 (34.5)	10 (34.5)
Thrombocytopenia	7 (24.1)	7 (24.1)
Neutropenia	6 (20.7)	6 (20.7)
Cardiac disorders		
Tachycardia	8 (27.6)	2 (6.9)
Gastrointestinal disorders		
Vomiting	15 (51.7)	2 (6.9)
Nausea	13 (44.8)	5 (17.2)
Diarrhoea	11 (37.9)	1 (3.4)
Abdominal pain	9 (31.0)	1 (3.4)
General disorders and administration site conditions		
Pyrexia	13 (44.8)	3 (10.3)
Fatigue	9 (31.0)	1 (3.4)
Chills	7 (24.1)	0
Immune system disorders		
CRS	26 (89.7)	11 (37.9)
Hypogammaglobulinaemia	13 (44.8)	1 (3.4)
Investigations		
ALT increased	11 (37.9)	7 (24.1)
AST increased	11 (37.9)	7 (24.1)
White blood cell count decreased	10 (34.5)	8 (27.6)
Platelet count decreased	9 (31.0)	6 (20.7)
Blood creatinine increased	8 (27.6)	2 (6.9)
Neutrophil count decreased	8 (27.6)	7 (24.1)
Prothrombin time prolonged	8 (27.6)	1 (3.4)
International normalised ratio increased	7 (24.1)	1 (3.4)
Metabolism and nutrition disorders		
Decreased appetite	13 (44.8)	10 (34.5)
Hypokalaemia	11 (37.9)	4 (13.8)
Hyperphosphataemia	6 (20.7)	0
Nervous system disorders		
Headache	8 (27.6)	0
Respiratory, thoracic and mediastinal disorders		
Cough	7 (24.1)	0
Epistaxis	7 (24.1)	3 (10.3)
Hypoxia	7 (24.1)	6 (20.7)
Vascular disorders		
Hypotension	10 (34.5)	9 (31.0)
Hypertension	6 (20.7)	1 (3.4)

Serious adverse events occurred in 79.3% (23 of 29) of patients. Serious adverse events reported by ≥3 patients included CRS in 20 patients (69.0%), FN in 10 patients (34.5%), and hypotension in 4 patients (13.8%). A causal relationship to tisagenlecleucel could not be ruled out for CRS in 20 patients, FN in 9 patients, and hypotension in 4 patients.

9.4 Foreign phase I study (Study B2102J)

Adverse events occurred in all patients with CLL and all patients with ALL, and 92.9% (13 of 14) of patients with CLL and 100% (6 of 6) of patients with ALL experienced events for which a causal relationship to tisagenlecleucel could not be ruled out. Table 64 shows all-grade adverse events with an incidence of ≥40% in either patient population.

Table 64. Adverse events with an incidence of ≥40% in either patient population

System organ class Preferred term (MedDRA/J ver. 18.0)	CLL Number of patients (%) n = 14		ALL Number of patients (%) n = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	14 (100)	13 (92.9)	6 (100)	6 (100)
Blood and lymphatic system disorders				
Neutropenia	7 (50.0)	7 (50.0)	3 (50.0)	3 (50.0)
Anaemia	6 (42.9)	5 (35.7)	4 (66.7)	4 (66.7)
Thrombocytopenia	6 (42.9)	5 (35.7)	2 (33.3)	2 (33.3)
Gastrointestinal disorders				
Nausea	8 (57.1)	0	1 (16.7)	0
Diarrhoea	7 (50.0)	0	4 (66.7)	0
General disorders and administration site conditions				
Fatigue	11 (78.6)	2 (14.3)	2 (33.3)	0
Pyrexia	10 (71.4)	1 (7.1)	2 (33.3)	0
Chills	8 (57.1)	0	1 (16.7)	0
Oedema peripheral	7 (50.0)	0	2 (33.3)	0
Immune system disorders				
CRS	8 (57.1)	6 (42.9)	6 (100)	5 (83.3)
Investigations				
Blood albumin decreased	8 (57.1)	0	1 (16.7)	0
White blood cell count decreased	8 (57.1)	7 (50.0)	2 (33.3)	2 (33.3)
Blood calcium decreased	6 (42.9)	0	1 (16.7)	1 (16.7)
Blood sodium decreased	6 (42.9)	2 (14.3)	1 (16.7)	0
Blood phosphorus decreased	3 (21.4)	1 (7.1)	3 (50.0)	3 (50.0)
Metabolism and nutrition disorders				
Hypokalaemia	7 (50.0)	0	3 (50.0)	0
Decreased appetite	6 (42.9)	0	0	0
Mental disorder				
Insomnia	6 (42.9)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	6 (42.9)	1 (7.1)	0	0

Serious adverse events occurred in 85.7% (12 of 14) of patients with CLL and 100% (6 of 6) of patients with ALL. The following are serious adverse events reported by ≥3 patients:

CLL: CRS in 6 patients (42.9%), pyrexia in 4 patients (28.6%), and FN in 3 patients (21.4%)

ALL: CRS in 5 patients (83.3%)

A causal relationship to tisagenlecleucel could not be ruled out for the following events:

CLL: CRS in 6 patients, pyrexia in 4 patients, and FN in 2 patients

ALL: CRS in 5 patients

9.5. Foreign phase I/IIa study (Study B2101J)

Adverse events occurred in all patients. All patients experienced events for which a causal relationship to tisagenlecleucel could not be ruled out. Table 65 shows all-grade adverse events with an incidence of ≥30%.

Table 65. Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver. 19.1)	Number of patients (%) n = 56	
	All Grades	Grade ≥3
All adverse events	56 (100)	54 (96.4)
Blood and lymphatic system disorders		
Lymphopenia	46 (82.1)	38 (67.9)
FN	44 (78.6)	44 (78.6)
Cardiac disorders		
Tachycardia	26 (46.4)	1 (1.8)
Gastrointestinal disorders		
Vomiting	44 (78.6)	4 (7.1)
Nausea	42 (75.0)	8 (14.3)
Diarrhoea	32 (57.1)	1 (1.8)
Abdominal pain	18 (32.1)	2 (3.6)
General disorders and administration site conditions		
Pain	27 (48.2)	7 (12.5)
Fatigue	25 (44.6)	0
Chills	22 (39.3)	0
Pyrexia	20 (35.7)	1 (1.8)
Immune system disorders		
CRS	50 (89.3)	26 (46.4)
Hypogammaglobulinaemia	37 (66.1)	0
Investigations		
White blood cell count decreased	53 (94.6)	35 (62.5)
Haemoglobin decreased	52 (92.9)	17 (30.4)
Neutrophil count decreased	51 (91.1)	39 (69.6)
Platelet count decreased	49 (87.5)	27 (48.2)
AST increased	42 (75.0)	16 (28.6)
ALT increased	40 (71.4)	17 (30.4)
Blood creatinine increased	20 (35.7)	1 (1.8)
Activated partial thromboplastin time prolonged	19 (33.9)	5 (8.9)
Metabolism and nutrition disorders		
Decreased appetite	39 (69.6)	20 (35.7)
Hyperphosphataemia	19 (33.9)	0
Nervous system disorders		
Headache	42 (75.0)	7 (12.5)
Respiratory, thoracic and mediastinal disorders		
Cough	31 (55.4)	0
Vascular disorders		
Hypotension	29 (51.8)	18 (32.1)

Serious adverse events occurred in 89.3% (50 of 56) of patients. Serious adverse events reported by ≥5 patients included CRS in 46 patients (82.1%), FN in 40 patients (71.4%), hypotension in 22 patients (39.3%), encephalopathy in 15 patients (26.8%), pyrexia in 13 patients (23.2%), capillary leak syndrome in 10 patients (17.9%), hypoxia in 8 patients (14.3%), and disseminated intravascular coagulation in 5 patients (8.9%). A causal relationship to tisagenlecleucel could not be ruled out for CRS in 46 patients, FN in 40 patients, hypotension in 21 patients, encephalopathy in 15 patients, pyrexia in 11 patients, capillary leak syndrome in 10 patients, hypoxia in 7 patients, and disseminated intravascular coagulation in 5 patients.

9.6 Foreign phase II study (Study A2201)

Adverse events occurred in all patients in both low-dose and high-dose groups. All patients in both groups experienced events for which a causal relationship to tisagenlecleucel could not be ruled out. Table 66 shows all-grade adverse events with an incidence of ≥30% in either group.

Table 66. Adverse events with an incidence of ≥30% in either group

System organ class Preferred term (MedDRA/J ver. 18.0)	Number of patients (%)			
	Low-dose (1×10^7-5×10^7 cells) n = 17		High-dose (1×10^8-5×10^8 cells) n = 11	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	17 (100)	16 (94.1)	11 (100)	11 (100)
Blood and lymphatic system disorders				
Anaemia	7 (41.2)	6 (35.3)	5 (45.5)	2 (18.2)
Gastrointestinal disorders				
Diarrhoea	7 (41.2)	0	1 (9.1)	0
Nausea	7 (41.2)	0	3 (27.3)	0
General disorders and administration site conditions				
Pyrexia	8 (47.1)	0	4 (36.4)	0
Fatigue	6 (35.3)	0	5 (45.5)	1 (9.1)
Immune system disorders				
CRS	6 (35.3)	1 (5.9)	4 (36.4)	3 (27.3)
Investigations				
CD4 lymphocyte count decreased	11 (64.7)	11 (64.7)	4 (36.4)	4 (36.4)
White blood cell count decreased	9 (52.9)	7 (64.7)	5 (45.5)	3 (27.3)
Neutrophil count decreased	6 (35.3)	6 (35.3)	2 (18.2)	2 (18.2)
Lymphocyte count decreased	4 (23.5)	4 (23.5)	4 (36.4)	4 (36.4)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	0	0	4 (36.4)	1 (9.1)

Serious adverse events occurred in 64.7% (11 of 17) of patients in the low-dose group and 100% (11 of 11) of patients in the high-dose group. Serious adverse events reported by ≥3 patients included CRS in 6 patients (35.3%), pyrexia in 5 patients (29.4%), and FN in 4 patients (23.5%) in the low-dose group; and pyrexia and CRS in 4 patients (36.4%) each and FN in 3 patients (27.3%) in the high-dose group. A causal relationship to tisagenlecleucel could not be ruled out for CRS in 6 patients, pyrexia in 5 patients, and FN in 4 patients in the low-dose group as well as pyrexia and CRS in 4 patients each and FN in 3 patients in the high-dose group.

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

10.1. 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted

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

The new regenerative medical product application data (CTD 5.3.5.2-1, CTD 5.3.5.2-4) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that Kymriah has efficacy to a certain extent in the treatment of "relapsed or refractory CD19-positive B-ALL (For patients with ≥2 lines of prior chemotherapy, Kymriah should be used only in those who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.)" and "relapsed or refractory CD19-positive DLBCL (only for patients with ≥2 lines of prior chemotherapy who are ineligible for, or relapsed after, autologous hematopoietic stem cell transplantation)," and that the product has acceptable safety in view of its benefits. Accordingly, PMDA considers that making Kymriah available in clinical practice is meaningful because it offers a new treatment option for patients with B-ALL and patients with DLBCL.

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

Review Report (2)

February 1, 2019

Product Submitted for Approval

Brand Name	Kymriah Suspension for Intravenous Infusion
Non-proprietary Name	Tisagenlecleucel
Applicant	Novartis Pharma K.K.
Date of Application	April 23, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

Based on reviews in Sections "7.R.2 Efficacy in pediatric and AYA patients with relapsed or refractory B-ALL" and "7.R.3 Efficacy in patients with relapsed or refractory DLBCL" of the Review Report (1), PMDA has reached the following conclusions on (a) the efficacy in pediatric and AYA patients with relapsed or refractory B-ALL, (b) the efficacy in patients with relapsed or refractory DLBCL, and (c) LD chemotherapy implemented before administration of tisagenlecleucel.

PMDA's conclusions:

(a) In a global phase II study (Study B2202) in pediatric and AYA patients with relapsed or refractory B-ALL, the results of IRC-assessed overall remission rate, the primary endpoint, have demonstrated that tisagenlecleucel is effective to a certain extent in the population eligible for the study.

(b) In a global phase II study (Study C2201) in patients with relapsed or refractory DLBCL, the results of IRC-assessed response rate, the primary endpoint, have demonstrated that tisagenlecleucel is effective to a certain extent in the population eligible for the study.

(c) Based on results from Study B2202, a foreign phase II study (Study B2205J), and Study C2201, LD chemotherapy should be recommended to patients who have a peripheral white blood cell count of >1000/μL within 1 week prior to the planned administration of tisagenlecleucel.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. In addition, the following comments were raised from the expert advisors:

- The applicant should investigate the efficacy and safety of tisagenlecleucel in patients who did not receive LD chemotherapy and provide the obtained information to healthcare professionals together with information about the patients who received LD chemotherapy at predetermined doses and patients who received LD chemotherapy at reduced doses.

PMDA asked the applicant to explain the efficacy and safety of tisagenlecleucel in patients who did not receive LD chemotherapy in Study B2202, B2205J, or C2201.

The applicant's response:

In Studies B2202 and B2205J, 5 patients did not receive LD chemotherapy. Of these, 3 patients (60.0%) achieved CR with tisagenlecleucel, and none achieved CRi. The overall remission rate [95% CI] (%) was 60.0 [14.7, 94.7]. Tables 69 and 70 show the summary of the safety and incidences of adverse events that occurred within 8 weeks after the administration and require special attention when using tisagenlecleucel (CRS, TLS, FN, infection, neuropathy, and myelosuppression[39]) in patients who did not receive LD chemotherapy (n = 5). No safety concerns were identified in these patients because there was no clear trend toward increased incidences of the adverse events requiring special attention when using tisagenlecleucel. No particular attention has to be paid to the safety in these patients.

Table 69. Summary of safety (Studies B2202 and B2205J)

	Number of patients (%) n = 5
All adverse events	5 (100)
Grade ≥3 adverse events	5 (100)
Adverse events leading to death	1 (20.0)
Serious adverse events	5 (100)

Table 70. Adverse events requiring special attention (Studies B2202 and B2205J)

	Number of patients (%) n = 5	
	All Grades	Grade 3 or 4
CRS	5 (100)	4 (80.0)
TLS	1 (20.0)	1 (20.0)
FN	1 (20.0)	1 (20.0)
Infection	4 (80.0)	2 (40.0)
Neuropathy	2 (40.0)	0
Myelosuppression	1 (20.0)	0

In the efficacy analysis population in Study C2201, 7 patients did not receive LD chemotherapy. Of these, 2 patients (28.6%) achieved CR with tisagenlecleucel, and none achieved PR. The response rate [95% CI] (%) was 28.6 [3.7, 71.0].

Tables 71 and 72 show the summary of the safety and incidences of adverse events that occurred within 8 weeks after the administration and require special attention when using tisagenlecleucel (CRS,

[39] Events that did not resolve by 28 days after administration of Kymriah are tabulated.

TLS, FN, infection, neuropathy, and myelosuppression[39]) in patients who did not receive LD chemotherapy (n = 8) in the safety analysis population in Study C2201. No safety concerns were identified in these patients because there was no clear trend toward increased incidences of the adverse events requiring special attention when using tisagenlecleucel. No particular attention has to be paid to the safety in these patients.

Table 71. Summary of safety (Study C2201)

	Number of patients (%) n = 8
All adverse events	8 (100)
Grade ≥3 adverse events	7 (87.5)
Adverse events leading to death	0
Serious adverse events	5 (62.5)

Table 72. Adverse events requiring special attention (Study C2201)

	Number of patients (%) n = 8	
	All Grades	Grade 3 or 4
CRS	5 (62.5)	3 (37.5)
TLS	1 (12.5)	1 (12.5)
FN	1 (12.5)	1 (12.5)
Infection	4 (50.0)	2 (25.0)
Neuropathy	2 (25.0)	2 (25.0)
Myelosuppression	5 (62.5)	4 (50.0)

PMDA's view:
PMDA accepted the above applicant's explanation. Using materials etc., the applicant should appropriately inform healthcare professionals about the efficacy and safety in patients who received LD chemotherapy at predetermined doses, who received LD chemotherapy at reduced doses, and who did not receive LD chemotherapy.

1.2 Safety

As a result of the review in Section "7.R.4 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring special attention when using tisagenlecleucel are CRS, neuropathy, infection, myelosuppression, hypersensitivity, hypogammaglobulinaemia, and TLS.

In addition, PMDA has concluded that, although attention should be paid to these adverse events when tisagenlecleucel is used, tisagenlecleucel can be tolerable if appropriate actions on adverse events such as observation and management are taken by physicians with sufficient knowledge and experience in treatment of B-ALL and DLBCL at medical institutions with adequate equipment capable of taking actions on the above adverse events.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication or performance

As a result of the reviews in Sections "7.R.5 Clinical positioning and indication or performance in pediatric and AYA patients with relapsed or refractory B-ALL" and "7.R.7 Clinical positioning and indication or performance in patients with relapsed or refractory DLBCL" of the Review Report (1),

PMDA has concluded that "Indication or Performance" and "Precautions for Indication or Performance" for patients with B-ALL and patients with DLBCL should be as follows (see Table 73).

Table 73. "Indication or Performance" and "Precautions for Indication or Performance"

Cancer type	Indication or Performance	Precautions for Indication or Performance
B-ALL	Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. For patients with ≥2 lines of prior chemotherapy, Kymriah should be used only in those who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.	• Kymriah should be used in patients aged ≤25 years. • Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining. • Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the "Clinical Studies" section regarding prior treatment received by the clinical study patients.
DLBCL	Relapsed or refractory CD19-positive diffuse large B-cell lymphoma. Kymriah should be used only in patients with ≥2 lines of prior chemotherapy who are ineligible for, or relapsed after, autologous hematopoietic stem cell transplantation.	• Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining. • Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the "Clinical Studies" section regarding the tissue type and prior treatment of the clinical study patients.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion, but at the same time, the following comment was raised:

- The phrase "≥2 lines of prior chemotherapy" is likely to be interpreted differently by different physicians, potentially leading to wrong selection of patients for tisagenlecleucel therapy. Accordingly, the wording of Indication or Performance should be modified; for example, the prior treatment of patients with relapsed disease should be presented separately from that of patients with refractory disease.

PMDA's view:

In view of the discussion at the Expert Discussion, PMDA has concluded that "Indication or Performance" and "Precautions for Indication or Performance" of tisagenlecleucel should be modified as shown in Table 74.

Table 74. "Indication or Performance" and "Precautions for Indication or Performance"

Cancer type	Indication or Performance	Precautions for Indication or Performance
B-ALL	Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. Kymriah should be used only in patients meeting any of the following criteria: • Newly diagnosed patients who failed to achieve remission with ≥2 lines of standard chemotherapy. • Patients with relapsed disease who failed to achieve remission with ≥1 line of chemotherapy. • Patients who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.	• Kymriah should be used in patients aged ≤25 years (at the time of administration). • Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining. • Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the "Clinical Studies" section regarding prior treatment received by the clinical study patients.
DLBCL	Relapsed or refractory CD19-positive diffuse large B-cell lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are ineligible for, or relapsed after, autologous hematopoietic stem cell transplantation: • Newly diagnosed patients who failed to achieve a complete response to ≥2 lines of chemotherapy; newly diagnosed patients who achieved a complete response to ≥2 lines of chemotherapy but subsequently relapsed; patients who received ≥1 line of chemotherapy after relapse but failed to achieve a complete response; or patients who received ≥1 line of chemotherapy after relapse and achieved a complete response but subsequently relapsed again. • Patients with diffuse large B-cell lymphoma transformed from follicular lymphoma who failed to achieve a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation, or who achieved a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation but subsequently relapsed.	• Kymriah should be used in patients with malignancy confirmed to be positive for CD19 antigen by flow cytometry or immunohistochemical staining. • Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Kymriah and of the information in the "Clinical Studies" section regarding the tissue type and prior treatment of the clinical study patients.

Accordingly, PMDA requested the applicant to modify the "Indication or Performance" and "Precautions for Indication 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 reviews in Sections "7.R.6 Dosage and administration or method of use for pediatric and AYA patients with relapsed or refractory B-ALL" and "7.R.8 Dosage and administration or method of use for patients with relapsed or refractory DLBCL" of the Review Report (1), PMDA has concluded that it is appropriate to establish the "Dosage and Administration or Method of Use" and "Precautions for Dosage and Administration or Method of Use" 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.

In addition, the protocols of Studies B2202 and C2201 clearly specified the dosage regimens of the antineoplastic drugs used for LD chemotherapy (fludarabine phosphate, cyclophosphamide hydrate, etoposide, cytarabine, and bendamustine hydrochloride). PMDA has concluded that physicians should refer to the dosage regimens before administering LD chemotherapy to patients to be treated with tisagenlecleucel. To ensure this, the following actions should be taken:

(a) Expand the indications of the antineoplastic drugs to include “pretreatment for tumor-specific T-cell infusion therapy”;
(b) Include the following statement in the Dosage and Administration of the antineoplastic drugs: “This drug should be used in accordance with the dosage and administration or method of use of the regenerative medical product” (when this drug is used as pretreatment for tumor-specific T-cell infusion therapy);
(c) Specify the dosage regimens of the antineoplastic drugs for LD chemotherapy (i.e., the same regimens as those used in Studies B2202 and C2201) in the Dosage and Administration or Method of Use of Kymriah.

Accordingly, PMDA requested the applicant to modify the Dosage and Administration or Method of Use as described below. As the applicant appropriately responded to the request, PMDA accepted.

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 including sufficient T-lymphocytes are collected.

2. Cryopreservation of leukapheresis material
   The leukapheresis material is prepared immediately after collection, and cryopreserved in the vapor phase of liquid nitrogen.

3. Transportation of leukapheresis material
   The cryopreserved leukapheresis material is packed and transported to the manufacturing facility of Kymriah.

Process from acceptance at the medical institution to administration of Kymriah

4. Receipt and storage of Kymriah
   Kymriah is received in a frozen condition, and cryopreserved in the vapor phase of liquid nitrogen until immediately before use.

5. Pretreatment before administration of Kymriah
   If the peripheral white blood cell count exceeds 1000/μL within 1 week prior to the planned administration of Kymriah, conduct the following lymphodepleting chemotherapy as pretreatment at least 2 days before the administration. The period between pretreatment chemotherapy and administration of Kymriah is determined based on the characteristics of the chemotherapy and the patient’s condition.
   (1) Lymphodepleting chemotherapy for patients with relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia
      1) Cyclophosphamide hydrate at 500 mg/m^2 is infused intravenously once daily for 2 days and fludarabine phosphate at 30 mg/m^2 is infused intravenously once daily for 4 days. The dose may be reduced according to the patient’s condition.

2) For patients with a history of Grade 4[Note)] hemorrhagic cystitis due to cyclophosphamide hydrate or patients resistant to cyclophosphamide hydrate:
Cytarabine at 500 mg/m^2 is infused intravenously once daily for 2 days and etoposide at 150 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.

(2) Lymphodepleting chemotherapy for patients with relapsed or refractory CD19-positive diffuse large B-cell lymphoma

1) Cyclophosphamide hydrate at 250 mg/m^2 is infused intravenously once daily for 3 days and fludarabine phosphate at 25 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.

2) For patients with a history of Grade 4[Note)] hemorrhagic cystitis due to cyclophosphamide hydrate or patients resistant to cyclophosphamide hydrate:
Bendamustine hydrochloride at 90 mg/m^2 is infused intravenously once daily for 2 days. The dose may be reduced according to the patient's condition.

Note) The Grade is according to CTCAE v4.03.

6. Administration of Kymriah

Kymriah is thawed immediately before administration, and intravenously administered as a single dose as described below according to the patient's disease.

(1) Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia
The usual dosage for patients aged ≤25 years (at the time of administration) is determined according to body weight (see below) and administered as a single intravenous dose.
- Body weight ≤50 kg: CAR-positive viable T cells at 0.2×10^6 to 5.0×10^6/kg.
- Body weight >50 kg: CAR-positive viable T cells at 0.1×10^8 to 2.5×10^8 (irrespective of body weight).

(2) Relapsed or refractory CD19-positive diffuse large B-cell lymphoma
The usual adult dosage is 0.6×10^8 to 6.0×10^8 (irrespective of body weight) of CAR-positive viable T cells administered as a single intravenous dose.

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 tisagenlecleucel. The planned sample size was 380 (100 patients with B-ALL, 280 patients with DLBCL). The planned observation period was up to 8 years.

As a result of the review in Section "8 Data Relating to Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), PMDA has concluded that the proposed plan of post-marketing surveillance is appropriate.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

In view of the above discussion and the following corrections presented by the applicant, PMDA has concluded that the post-marketing surveillance provided in Table 75 should be conducted.

Major corrections

The planned sample size is changed to 400 patients (130 patients with B-ALL, 270 patients with DLBCL) based on the latest estimated number of patients to be collected during the registration period (3 years).

The following changes are made to the safety specification:

- Events coded as "early onset of neuropsychiatric event" and "onset or deterioration of neuropsychiatric event" are integrated into a single category of "serious nervous system event" and collected accordingly.

- Events coded as "hypersensitivity" are handled as "CRS" and collected accordingly, because serious hypersensitivity is recognized as CRS.

- Events coded as "FN" are handled as "infection" and collected accordingly.

- "Transmission of an infectious agent" is added to the safety specification because viruses such as HBV may possibly be reactivated in the manufacturing process of Kymriah.

- "Use in pregnant and breast feeding women," "use in patients with HBV/HCV/HIV" and "use in patients with active central nervous system infiltration" are added to the safety specification. There is no clinical experience with Kymriah in these patients, because they patients were excluded from the clinical studies of Kymriah; thus their safety information should be collected.

- "Development of replication competent lentivirus" is removed from the safety specification, because it has to be detected by quantitative PCR, and thus information on this event is difficult to collect in clinical settings. The concerned information, however, will be continuously collected in the currently ongoing clinical studies.

Table 75. Post-marketing surveillance plan (draft)

Objective	Evaluation of safety and efficacy of Kymriah
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.
Observation period	Up to 8 years
Target population	Patients with relapsed or refractory CD19-positive B-ALL or DLBCL
Planned sample size	400 patients (130 patients with B-ALL, 270 patients with DLBCL)
Main survey items	Safety specification CRS, infection, serious nervous system event, TLS, continuous depletion of normal B cells and hypogammaglobulinaemia, cytopenia persisting for ≥28 days after infusion, brain oedema, secondary malignant tumor, onset or deterioration of autoimmune disease, hematological disease (including aplastic anaemia and bone marrow failure), deterioration of graft versus host disease, transmission of an infectious agent, use in pregnant and breast feeding women, use in patients with HBV/HCV/HIV, use in patients with active central nervous system infiltration, and long-term safety Efficacy Remission rate, response rate, OS, etc.

1.6 Others

1.6.1 Quality

1.6.1.1 Ensuring viral safety of human serum albumin and human transferrin

The applicant submitted results from evaluation of viral inactivation/removal in manufacturing processes for human serum albumin (1) and human transferrin used in manufacture of Kymriah (Table 7), and explained that these raw materials conformed to the Standard for Biological Ingredients.

PMDA accepted the applicant's response.

1.6.1.2 Control strategy of the quality of Kymriah

The applicant's explanation about the pCQAs covered by the verification:
In Section 2.R.2 of the Review Report (1), the applicant explained that the pCQAs [redacted]. However, the applicant requests a change from [redacted] to [redacted] in order to confirm the consistency of the manufacturing process. In addition, [redacted] will be specified in the verification master plan.

PMDA decided to confirm the appropriateness of [redacted] of the pCQAs at the GCTP inspection and accepted the applicant's response.

1.6.2 Designation of specified regenerative medical product

Based on "Principles for designation of biological products, specified biological products, and specified regenerative medical products" (PFSB/ELD Notification 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 Kymriah need not be designated as a specified regenerative medical product for the following reasons:

- Raw materials in use are derived from the patient.

- Biological materials in use are all manufactured through a process capable of inactivating or removing pathogens, the probability of onset of infections is low, and the risk level of adventitious agents is acceptable.

- For human-derived biological materials:
  - 293T cells have been subjected to extensive virus tests, the probability of onset of infections is low, and the risk level of adventitious agents is acceptable.
  - The blood-derived ingredients are confirmed to have the quality equivalent to that of the corresponding drug product or are derived from a qualified donor and manufactured through a process expected to inactivate or remove pathogens. Contents or residual amounts of these ingredients in Kymriah are extremely limited compared with their typical contents or cumulative amounts when they are used in drug products.

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 of approval. However, 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

1. Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. Kymriah should be used only in patients meeting any of the following criteria:
   - Newly diagnosed patients who failed to achieve remission with ≥2 lines of standard chemotherapy.
   - Patients with relapsed disease who failed to achieve remission with ≥1 line of chemotherapy.
   - Patients who are ineligible for, or relapsed after, allogeneic hematopoietic stem cell transplantation.

2. Relapsed or refractory CD19-positive diffuse large B-cell lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are ineligible for, or relapsed after, autologous hematopoietic stem cell transplantation:
   - Newly diagnosed patients who failed to achieve a complete response to ≥2 lines of chemotherapy; newly diagnosed patients who achieved a complete response to ≥2 lines of chemotherapy but subsequently relapsed; patients who received ≥1 line of chemotherapy after relapse but failed to achieve a complete response; or patients who received ≥1 line of chemotherapy after relapse and achieved a complete response but subsequently relapsed again.
   - Patients with diffuse large B-cell lymphoma transformed from follicular lymphoma who failed to achieve a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation, or who achieved a complete response to ≥2 lines of chemotherapy including ≥1 line after the transformation but subsequently relapsed.

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 including sufficient T-lymphocytes are collected.

2. Cryopreservation of leukapheresis material
   The leukapheresis material is prepared immediately after collection, and cryopreserved in the vapor phase of liquid nitrogen.

3. Transportation of leukapheresis material
   The cryopreserved leukapheresis material is packed and transported to the manufacturing facility of Kymriah.

Process from acceptance at the medical institution to administration of Kymriah

4. Receipt and storage of Kymriah

Kymriah is received in a frozen condition, and cryopreserved in the vapor phase of liquid nitrogen until immediately before use.

5. Pretreatment before administration of Kymriah

If the peripheral white blood cell count exceeds 1000/μL within 1 week prior to the planned administration of Kymriah, conduct the following lymphodepleting chemotherapy as pretreatment at least 2 days before the administration. The period between pretreatment chemotherapy and administration of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition.

(1) Lymphodepleting chemotherapy for patients with relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia

1) Cyclophosphamide hydrate at 500 mg/m^2 is infused intravenously once daily for 2 days and fludarabine phosphate at 30 mg/m^2 is infused intravenously once daily for 4 days. The dose may be reduced according to the patient's condition.

2) For patients with a history of Grade 4[Note)] hemorrhagic cystitis due to cyclophosphamide hydrate or patients resistant to cyclophosphamide hydrate:
Cytarabine at 500 mg/m^2 is infused intravenously once daily for 2 days and etoposide at 150 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.

(2) Lymphodepleting chemotherapy for patients with relapsed or refractory CD19-positive diffuse large B-cell lymphoma

1) Cyclophosphamide hydrate at 250 mg/m^2 is infused intravenously once daily for 3 days and fludarabine phosphate at 25 mg/m^2 is infused intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.

2) For patients with a history of Grade 4[Note)] hemorrhagic cystitis due to cyclophosphamide hydrate or patients resistant to cyclophosphamide hydrate:
Bendamustine hydrochloride at 90 mg/m^2 is infused intravenously once daily for 2 days. The dose may be reduced according to the patient's condition.

Note) The Grade is according to CTCAE v4.03.

6. Administration of Kymriah

Kymriah is thawed immediately before administration, and intravenously administered as a single dose as described below according to the patient's disease.

(1) Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia

The usual dosage for patients aged ≤25 years (at the time of administration) is determined according to body weight (see below) and administered as a single intravenous dose.

- Body weight ≤50 kg: CAR-positive viable T cells at 0.2×10^6 to 5.0×10^6/kg.
- Body weight >50 kg: CAR-positive viable T cells at 0.1×10^8 to 2.5×10^8 (irrespective of body weight).

(2) Relapsed or refractory CD19-positive diffuse large B-cell lymphoma
The usual adult dosage is 0.6×10^8 to 6.0×10^8 (irrespective of body weight) of CAR-positive viable T cells administered as a single intravenous dose.

Conditions of Approval

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. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Appendix

List of Abbreviations

293T cells	HEK293 cells expressing SV40 large T antigen
αCD19CAR	Anti-CD19 chimeric antigen receptor
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
Application	Application for marketing approval
AST	Aspartate aminotransferase
ATCC	American Type Culture Collection
AYA	Adolescent and Young Adult
B-ALL	Acute B cell lymphoblastic leukemia
BAV	Bovine adenovirus
Bendamustine	Bendamustine hydrochloride
BKV	BK virus
BPV	Bovine Polyoma Virus
BSA	Bovine serum albumin
BT cells	Bovine turbinate cells
BVDV	Bovine viral diarrhea virus
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
Component cells	Cells serving as a component of the product
CPE	Cytopathic effect
CQA	Critical quality attribute
CR	Complete remission
	Complete response
CRi	Complete remission with incomplete hematologic recovery
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
Cyclophosphamide	Cyclophosphamide hydrate
DLBCL	diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
EdU	5-ethynyl-2'-deoxyuridine
EoPC	End of production cell bank
[redacted]	[redacted]
FBS	Fetal bovine serum
FCM	Flow cytometry
FL	Follicular lymphoma
Fludarabine	Fludarabine phosphate
FN	Febrile neutropenia
HAD	Haemadsorption
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBoV	Human boca virus
HCV	Hepatitis C virus
HEK293 cells	Human embryonic kidney 293
HeLa cells	Human cervical cancer cells
[redacted]	[redacted]
HHV	Human herpes virus

HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
HTLV	Human T-cell leukemia virus
IBR	Infectious bovine rhinotracheitis
IRC	Independent Review Committee
JCV	JC virus
KIPyV	KI polyomavirus
Kwt	CD19-untransduced K562 cells derived from human chronic myeloid leukemic cells
K562-CD19	CD19-transduced K562 cells derived from human chronic myeloid leukemic cells
LD chemotherapy	Lymphodepleting chemotherapy
LTR	Long terminal repeat
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MRC-5 cells	Human fetal lung fibroblasts
MRD	Minimal residual disease
[redacted]	[redacted]
Naive/T_{SCM} cells	Naïve T cell/stem T cells
NCCN	National Comprehensive Cancer Network
NCCN guidelines	• National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia • National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas
NK cells	Natural killer cells
NHL	Non-Hodgkin lymphoma
NOG	NOD/SCID IL-2Rγc^{null}
NR	No response
OS	Overall survival
pCQA	Potential critical quality attribute
PD	Progressive disease
Penn	University of Pennsylvania
PI3	Parainfluenza-3
PMDA	Pharmaceuticals and Medical Devices Agency
PPV	Porcine parvovirus
PR	Partial response
PVB19	Parvovirus B19
R-CHOP	Combination regimen of rituximab (genetical recombination), cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone
RCL	Replication competent lentivirus
R-EPOCH	Combination regimen of rituximab (genetical recombination), etoposide, prednisolone, vincristine sulfate, cyclophosphamide hydrate, and doxorubicin hydrochloride
scFv	Single-chain variable fragment
SD	Stable disease
SIN	Self-inactivating
Study A2101J	Study CTL019A2101J
Study A2208J	Study CTL019A2208J
Study A2205B	Study CTL019A2205B
Study A2201	Study CTL019A2201
Study B2101J	Study CTL019B2101J

Study B2102J	Study CTL019B2102J
Study B2202	Study CTL019B2202
Study B2205J	Study CTL019B2205J
Study C2201	Study CTL019C2201
SV40	Simian Virus 40
T_{CM} cells	Central memory T cells
T_E cells	Effector T cells
T_{EM} cells	Effector memory T cells
Th2	T-helper cell 2
TKI	Tyrosine kinase inhibitor
TLS	Tumor lysis syndrome
Tocilizumab	Tocilizumab (genetical recombination)
VSV-G	Vesicular stomatitis virus G protein
Vero cells	African green monkey kidney epithelial cells
WCB	Working cell bank
WUPyV	WU polyomavirus