August 3, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human cellular/tissue-based products 1. Human somatic cell processed product
Non-proprietary Name	Tisagenlecleucel
Brand Name	Kymriah Suspension for Intravenous Infusion
Applicant	Novartis Pharma K.K.
Date of Application	November 29, 2021 (Application for partial change approval)

Results of Deliberation

In its meeting held on August 3, 2022, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The application may be approved. The re-examination period is 10 years.

The following approval conditions must be satisfied.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. 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

July 14, 2022
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	November 29, 2021

Shape, Structure, Active 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 (3) Regenerative medical product with a new indication

Items Warranting Special Mention
Orphan regenerative medical product (Orphan Regenerative Medicinal Product 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 efficacy in the treatment of relapsed or refractory follicular 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 and dosage and administration or method of use shown below, with the following approval 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 who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy:
   - 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 diffuse large B-cell lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy and 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

3. Relapsed or refractory follicular lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy:
   - Newly diagnosed patients who failed to achieve a response to ≥2 lines of systemic therapy; newly diagnosed patients who achieved a response to ≥2 lines of systemic therapy but subsequently relapsed; patients who received ≥1 line of systemic therapy after relapse but failed to achieve a response; or patients who received ≥1 line of systemic therapy after relapse and achieved a response but subsequently relapsed again

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 or at ≤−120°C.

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 or at ≤−120°C until immediately before use.

5. Pretreatment before administration of Kymriah

Conduct the following lymphodepleting chemotherapy as pretreatment at least 2 days before administration of Kymriah. The period between pretreatment chemotherapy and administration of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition. Lymphodepleting chemotherapy may be omitted depending on the patient's condition (e.g., the peripheral white blood cell count <1,000/μL within 1 week prior to the planned administration of Kymriah).

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

1) Cyclophosphamide at 500 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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 diffuse large B-cell lymphoma and patients with relapsed or refractory follicular lymphoma

1) Cyclophosphamide at 250 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
   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) Grading is according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.03.

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. Do not re-administer Kymriah.

(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 diffuse large B-cell lymphoma and relapsed or refractory follicular 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.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. 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)

May 24, 2022

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	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	November 29, 2021

Shape, Structure, Active 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

1. Relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia. Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy:
   - 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 diffuse large B-cell lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy and 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

3. Relapsed or refractory follicular lymphoma

(Underline denotes additions.)

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 or at ≤−120°C.

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 or at ≤−120°C 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, c~~Conduct the following lymphodepleting chemotherapy as pretreatment at least 2 days before administration of Kymriah. The period between pretreatment chemotherapy and administration of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition after reading the Clinical Studies section. Lymphodepleting chemotherapy may be omitted in case of severe cytopenia (e.g., the

peripheral white blood cell count <1,000/μL within 1 week prior to the planned administration of Kymriah).

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

1) Cyclophosphamide at 500 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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 diffuse large B-cell lymphoma and patients with relapsed or refractory follicular lymphoma

1) Cyclophosphamide at 250 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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) Grading is according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.03.

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. Do not re-administer Kymriah.

(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 diffuse large B-cell lymphoma and relapsed or refractory follicular 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.

(Underline denotes additions. Strikethrough denotes deletions.)

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.

In Japan, Kymriah has been approved for the indications of "relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia" and "relapsed or refractory CD19-positive diffuse large B-cell lymphoma[1)]" in March 2019.

Kymriah was designated as an orphan regenerative medical product with the intended indication or performance of “CD19-positive follicular lymphoma” as of May 25, 2016 (Orphan Regenerative Medical Product Designation No. 3 of 2016 [*28 sai*]).

1.2 Development history etc.

The applicant initiated a global phase II study (Study E2202) in patients with relapsed or refractory follicular lymphoma (FL), which is a type of B-cell lymphoma, in November 2018.

In August 2021, a Supplemental Biologics License Application and Type II Variation were submitted in the US and EU, respectively, for an additional indication or performance of relapsed or refractory FL, based on the results from Study E2202. Kymriah was approved for the indication or performance of "adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy" in April 2022 in the EU. The US application is under review.

In Japan, the applicant initiated patient enrollment in Study E2202 in [redacted] 20[redacted].

[1)] This indication was amended to "relapsed or refractory diffuse large B-cell lymphoma" in April 2021.

The applicant has filed a partial change application for an additional indication or performance of relapsed or refractory FL based on the results from Study E2202.

2. Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication, no additional quality data have been submitted.

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

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

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

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

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

Although the present application is intended for a new indication, the biological disposition data were previously evaluated for the initial approval of Kymriah, and no new study data have been submitted.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 1 global phase II study presented in Table 1.

Table 1. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	Number of patients enrolled	Dosing regimen	Main endpoints
Evaluation	Global	E2202	II	Patients with relapsed or refractory FL	98	A single intravenous infusion of 0.6-6.0 × 10^8 anti-CD19 CAR-positive viable T cells	Efficacy Safety

The clinical study is summarized below. Main adverse events other than deaths observed in the clinical study are presented in Section "8. Adverse Events Observed in Clinical Study."

6.1 Evaluation data

6.1.1 Global study

6.1.1.1 Global phase II study (CTD 5.3.5.2-1, Study E2202 [ongoing since November 2018

(data cutoff date of March 29, 2021)])

An open-label, uncontrolled study was conducted at 30 sites in 12 countries including Japan (3 sites in Japan) to evaluate the efficacy and safety of Kymriah in patients with relapsed or refractory FL (target sample size, 113 subjects). Table 2 shows key inclusion/exclusion criteria.

Table 2. Key inclusion/exclusion criteria

Inclusion criteria ● Patients with relapsed or refractory FL (Grade 1-3A) ≥18 years of age meeting any of the following criteria. ➢ Refractory to a second or later line of systemic therapy (including anti-CD20 antibodies and alkylating agents) or relapsed within 6 months after completion of a second or later line of systemic therapy ➢ Relapsed during anti-CD20 antibody maintenance (following at least two lines of therapies as above) or within 6 months after maintenance completion ➢ Relapsed after autologous HSCT • ECOG PS 0 or 1 **Exclusion criteria** ● Evidence of histologic transformation, FL Grade 3B ● Prior allogeneic HSCT, prior gene therapy, prior adoptive T cell therapy, or prior anti-CD19 therapy ● Active CNS involvement by malignancy

The study had the following sequential phases: Screening (from screening and leukapheresis to enrollment), Pre-treatment (from enrollment to lymphodepleting [LD] chemotherapy, Kymriah manufacturing period), and Treatment/Follow-up (from Kymriah infusion through 24 months post-infusion).

Kymriah was to be administered via a single intravenous infusion at a target dose of 0.6×10^8 to 6.0×10^8 CAR-positive viable T cells.

The following LD chemotherapy as pre-treatment was to be completed at least 2 days prior to Kymriah infusion to facilitate engraftment and homeostatic expansion of the administered CAR-positive viable T cells. This step was to be omitted in case of any condition (e.g., peripheral white blood cell count <1,000/μL) that, in the investigator's opinion, precluded LD chemotherapy.

LD chemotherapy

- Cyclophosphamide 250 mg/m^2 and fludarabine 25 mg/m^2 infused intravenously once daily for 3 days
- If the patient had previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrated resistance to a previous cyclophosphamide-containing regimen, the patient was allowed to receive bendamustine 90 mg/m^2 infused intravenously once daily for 2 days.

During the screening and pre-treatment periods, patients were allowed to receive chemotherapy based on the investigator's choice (bridging therapy) to stabilize the disease.

Assuming the underlying complete response rate (CRR) (the primary endpoint) of 30% with a threshold ≤15%, a sample size of 90 was needed to provide at least 90% cumulative power to demonstrate statistical significance at one-sided cumulative 0.025 level of significance. Assuming 20% enrolled patients would not be infused due to reasons such as manufacturing failure and worsening of the patient's condition, it was estimated that at least 113 patients would need to be enrolled to ensure 90 patients are treated.

Although 98 patients who underwent leukapheresis and had a leukapheresis product accepted for manufacturing were enrolled, 1 patient was withdrawn from the study based on the investigator's decision due to disease response to bridging therapy prior to Kymriah infusion. All of the 97 patients infused with Kymriah were included in the safety set, and 94 patients were included in the efficacy analysis set (the remaining 3 patients were excluded because they had no measurable disease at baseline, as determined by an Independent Review Committee [IRC]). All of 9 Japanese patients enrolled in the study received Kymriah infusion, and 1 patient had no measurable disease at baseline as determined by IRC.

The primary efficacy endpoint for the study was the CR rate as assessed by IRC according to the Lugano classification (*J Clin Oncol*. 2014; 32: 3059-68).

One interim analysis for overwhelming efficacy was planned when the first approximately 50 patients received Kymriah infusion and have either completed at least 6 months of follow-up or discontinued earlier. Table 3 shows the results of the primary endpoint at the interim analysis (data cutoff date of May 26, 2020). The CR rate as assessed by IRC [99.5% CI] (%) was 65.4 [45.1, 82.4], which was greater than the pre-specified threshold of 15%,[2)] demonstrating statistical significance.

[2)] The threshold of 15% was based on the observed CR rate (14%) to idelalisib in patients with relapsed or refractory FL after ≥2 lines of therapy (*Haematologica*. 2017; 102: e156-9).

Table 3. Best overall response at interim analysis (IRC assessment, Efficacy analysis set, data cutoff date of May 26, 2020)

	n (%)
	N = 52
CR	34 (65.4)
PR	9 (17.3)
SD	1 (1.9)
PD	7 (13.5)
Unknown	1 (1.9)
CR rate [99.5% CI] (%)*1	65.4 [45.1, 82.4]
P-value (one-sided)*2	<0.0001
Response (CR or PR)	43
Overall response rate [95% CI] (%)*1	82.7 [69.7, 91.8]

*1: Clopper-Pearson method

*2: A one-sided binomial exact test (alpha = 0.25%) against a threshold of 15%. The method of Lan-DeMets with the O'Brien-Fleming α spending function was used to adjust for multiplicity of hypothesis testing due to interim analysis.

The primary analysis was to be performed when approximately 90 patients received Kymriah infusion and have either completed at least 6 months of follow-up or discontinued earlier. Table 4 shows the results of the primary endpoint at the primary analysis (data cutoff date of September 28, 2020). The CR rate as assessed by IRC [95% CI] (%) was 66.0 [55.5, 75.4].

Table 4. Best overall response at primary analysis (IRC assessment, Efficacy analysis set, data cutoff date of September 28, 2020)

	n (%)
	N = 94
CR	62 (66.0)
PR	19 (20.2)
SD	3 (3.2)
PD	9 (9.6)
Unknown	1 (1.1)
CR rate [95% CI] (%)*1	66.0 [55.5, 75.4]
Response (CR or PR)	81
Overall response rate [95% CI] (%)*1	86.2 [77.5, 92.4]

*1: Clopper-Pearson method

A follow-up analysis (data cutoff date of March 29, 2021) was performed when approximately 90 patients received Kymriah infusion and have either completed at least 12 months of follow-up or discontinued earlier. Table 5 shows the results of the primary endpoint at the follow-up analysis. The CR rate [95% CI] (%) in the Japanese subgroup was 100 [63.1, 100.0].

Table 5. Best overall response at follow-up analysis (IRC assessment, Efficacy analysis set, data cutoff date of March 29, 2021)

	n (%)
	N = 94
CR	65 (69.1)
PR	16 (17.0)
SD	3 (3.2)
PD	9 (9.6)
Unknown	1 (1.1)
CR rate [95% CI] *1	69.1 [58.8, 78.3]
Response (CR or PR)	81
Overall response rate [95% CI] (%)*1	86.2 [77.5, 92.4]

*1: Clopper-Pearson method

As for safety (data cutoff date of March 29, 2021), there were 7 deaths after Kymriah infusion, all of which occurred ≥30 days after Kymriah infusion. The causes of deaths were disease progression (5 subjects), an adverse event (1 subject) (cytokine release syndrome [CRS],[3] Japanese), and others (1 subject) (euthanasia[4]). A causal relationship to Kymriah could not be ruled out for 1 case of CRS.

6.R Outline of the Review Conducted by PMDA

6.R.1 Efficacy

Based on the following considerations, PMDA concluded that a certain level of efficacy of Kymriah was demonstrated in patients with relapsed or refractory FL.

6.R.1.1 Efficacy endpoint and evaluation results

The applicant's explanation about the efficacy of Kymriah in patients with relapsed or refractory FL:

Patients with relapsed or refractory FL (the patient population of Study E2202) achieving a CR had good outcomes (*Haematologica*. 2017; 102: e156-9, etc.). This means that achieving CR in this patient population is considered clinically meaningful. Thus, the CR rate was chosen as the

3) A 7[redacted]-year-old man experienced CRS (Grade 1) on Day 7, which resolved on Day 30. The patient had stomatitis, pneumonia, anaemia, platelet count decreased, and neutropenia. On Day 345, these events were persisting and encephalopathy (Grade 3), hypercytokinaemia, sepsis, and hypotension occurred. The patient received antibiotics, dexamethasone, noradrenaline, and mechanical ventilation, but the general condition worsened. The investigator diagnosed that the patient had CRS symptoms related to Kymriah. The patient received tocilizumab, high-dose corticosteroids, vasopressin and, on Day 374, adalimumab and antithymocyte immunoglobulin. The patient died on Day 375. The blood CAR transgene levels were 96 copies/μg at Month 3 and below the lower limit of quantification at Month 6 and Month 9. Blood samples were not collected at Month 12 (2 weeks before the death) or at the time of death; therefore there were no laboratory data supporting the causal relationship between CRS and Kymriah. An autopsy revealed macrophage activation syndrome. There were no findings suggestive of FL relapse. CD19 immunohistochemical staining of the macrophage aggregation sites including the brain showed no CD19 expressing cells, and the causal relationship between CRS and Kymriah could not be determined.

4) A 5[redacted]-year-old woman experienced CRS (Grade 1) on Day 4, which worsened to Grade 2 on the following day. The patient received tocilizumab. On Day 9, the patient recovered from CRS but experienced immune effector cell-associated neurotoxicity syndrome (ICANS) (Grade 1), which worsened to Grade 4 on Day 11 but resolved on Day 16 following treatment. The patient experienced encephalitis due to human herpesvirus 6 on Day 12, which resolved on Day 21. Approximately 8 months after the infusion of Kymriah, the patient experienced non-fluent aphasia and mild left paresis. The investigator considered that the patiend had progressive multifocal leukoencephalophathy (PML) (Grade 2) related to Kymriah. PML worsened to Grade 3 on Day 265. The patient chose euthanasia due to progressive neurological symptoms and died on Day 302. No definitive diagnosis of PML was made.

primary endpoint for Study E2202. The Lugano classification, which is used internationally, was employed as the response criteria.

At the interim analysis of Study E2202 (data cutoff date of May 26, 2020), the CR rate as assessed by IRC [99.5% CI] (%) was 65.4 [45.1, 82.4], which was greater than the pre-specified threshold of 15%. Moreover, at the primary analysis (data cutoff date of September 28, 2020) and at the follow-up analysis (data cutoff date of March 29, 2021), the CR rates as assessed by IRC [95% CI] (%) were 66.0 [55.5, 75.4] and 69.1 [58.8, 78.3], respectively.

As to secondary endpoints, at the follow-up analysis (data cutoff date of March 29, 2021), the median duration of response (DOR) [95% CI] (months) was not estimable [15.6, NE], and the median progression free survival (PFS) [95% CI] (months) was 18.4 [12.3, NE]. At the follow-up analysis (data cutoff date of March 29, 2021), the median overall survival (OS) was not estimable, and the OS rates [95% CI] (%) were 95.3 [88.0, 98.2] at Month 12 and 91.6 [81.7, 96.2] at Month 18.

According to reports on clinical studies in patients with relapsed or refractory FL (*Lancet Oncol*. 2020; 21:1433-42, *Lancet Oncol*. 2016; 17:1081-93, etc.), the CR rates were 4% to 46%, the median PFS ranged from 10.9 to 39.4 months, the median OS ranged from 49.1 to 109.7 months, and the OS rates at 2 years were 86% to 93%. Treatment efficacy such as the CR rate in patients with FL has been reported to decline with every successive line of therapy (*Ann Hematol*. 2020; 99: 2133-9). Given these findings, Study E2202 demonstrated the efficacy of Kymriah.

In Japanese patients (N = 8), the CR rate [95% CI] (%) was 100 [63.1, 100.0], the median DOR [95% CI] (months) was not estimable [6.5, NE], the median PFS [95% CI] (months) was not estimable [9.5, NE], the median OS [95% CI] (months) was not estimable [12.3, NE], and the OS rate at Month 12 [95% CI] (%) was 100 [100.0, 100.0] (data cutoff date of March 29, 2021). Thus, based on the obtained results, Kymriah is expected to have efficacy of in Japanese patients.

PMDA concluded that the above explanation by the applicant is understandable, and that Study E2202 demonstrated a certain level of efficacy of Kymriah in patients with relapsed or refractory FL.

6.R.2 Safety (for adverse events, see Section "8. Adverse Events Observed in Clinical Study")

PMDA's conclusion:

Based on the following considerations, adverse events that require particular attention following administration of Kymriah in patients with relapsed or refractory FL are similar to those events

that were considered to require attention at the time of the previous approval of Kymriah (for the previously approved indications or performance).[5)] Attention should be paid to the possible occurrence of these adverse events following administration of Kymriah also in patients with relapsed or refractory FL.

Kymriah is tolerable as long as physicians with adequate knowledge of and experience in the treatment of FL take appropriate actions (e.g., monitoring and management of adverse events) at medical institutions with adequate facilities for the management of the above adverse events.

6.R.2.1 Safety profile of Kymriah

The applicant's explanation about the safety of Kymriah:
Safety data from Study E2202 (data cutoff date of March 29, 2021) are summarized in Table 6.

Table 6. Summary of safety data
(Study E2202, Safety set, data cutoff date of March 29, 2021)

	n (%)
	All subjects N = 97
All adverse events	96 (99.0)
Grade ≥3 adverse events	76 (78.4)
Serious adverse events	42 (43.3)
Death within 30 days after Kymriah infusion	0
Death >30 days after Kymriah infusion	7 (7.2)

The incidences of serious adverse events in Study E2202 are shown in Section "8.1 Global phase II study (Study E2202)."

The applicant's explanation about differences in the safety of Kymriah between Japanese and non-Japanese populations:

Safety data from the Japanese and non-Japanese subgroups in Study E2202 are summarized in Table 7.

[5)] CRS, neurologic disorder, infection, myelosuppression, hypersensitivity, hypogammaglobulinaemia, and tumor lysis syndrome (TLS) (Review Report on Kymriah Suspension for Intravenous Infusion as of February 4, 2019)

Table 7. Summary of differences in safety between Japanese and non-Japanese populations (Study E2202, Safety set, data cutoff date of March 29, 2021)

	n (%)	
	Japanese subgroup N = 9	Non-Japanese subgroup N = 88
All adverse events	9 (100)	87 (98.9)
Grade ≥3 adverse events	9 (100)	67 (76.1)
Serious adverse events	2 (22.2)	40 (45.5)
Death within 30 days after Kymriah infusion	0	0
Death >30 days after Kymriah infusion	1 (11.1)	6 (6.8)

Table 8 shows adverse events of any Grade or Grade ≥3 adverse events reported at a ≥20% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

Table 8. Adverse events reported at a ≥20% higher incidence in Japanese subgroup than in non-Japanese subgroup (Study E2202, Safety set, data cutoff date of March 29, 2021)

PT (MedDRA/J ver.24.0)	n (%)	
	Japanese subgroup N = 9	Non-Japanese subgroup N = 88
Hypogammaglobulinaemia	5 (55.6)	9 (10.2)
Stomatitis	3 (33.3)	0
Lymphopenia	3 (33.3)	5 (5.7)
Thrombocytopenia	4 (44.4)	15 (17.0)
Neutropenia	6 (66.7)	35 (39.8)
Hypophosphataemia	3 (33.3)	6 (6.8)
FN	3 (33.3)	9 (10.2)
Grade ≥3 adverse events		
Hypophosphataemia	3 (33.3)	2 (2.3)
Lymphopenia	3 (33.3)	5 (5.7)
Neutropenia	6 (66.7)	35 (39.8)
FN	3 (33.3)	9 (10.2)

The number of Japanese subjects was limited, and there are limitations to comparison of the safety of Kymriah between Japanese and non-Japanese populations. However, there were no clear differences in the safety profile of Kymriah between the Japanese and non-Japanese subgroups.

The dosing regimen of Kymriah used in Study E2202 in FL was similar to that used in Study C2201, which enrolled patients with diffuse large B-cell lymphoma (DLBCL), the approved indication or performance. The applicant provided the following explanation about differences in the safety of Kymriah between patients with FL and those with DLBCL, the approved indication or performance:

Safety data from Study E2202 (FL) and Study C2201 (DLBCL)[6)] are summarized in Table 9.

6) An open-label, uncontrolled study to evaluate the efficacy and safety of Kymriah in adult patients with relapsed or refractory DLBCL. Kymriah was to be administered via a single intravenous infusion at a target dose of 5.0×10^8 CAR-positive viable T cells (acceptable dose range, 1.0-5.0 × 10^8 cells). (Review Report on Kymriah Suspension for Intravenous Infusion as of February 4, 2019)

Table 9. Comparison of safety between clinical studies in patients with FL and those with DLBCL (the approved indication) (Study E2202 [data cutoff date of March 29, 2021] and Study C2201 [data cutoff date of December 8, 2017], Safety set)

	n (%)	
	Study E2202 N = 97	Study C2201 N = 111
All adverse events	96 (99.0)	111 (100)
Grade ≥3 adverse events	76 (78.4)	99 (89.2)
Serious adverse events	42 (43.3)	72 (64.9)
Adverse events leading to death	2 (2.1)	9 (8.1)
CRS	48 (49.5)	64 (57.7)
Neurologic disorder (SOC "nervous system disorders" or SOC "psychiatric disorders")	42 (43.3)	68 (61.3)
Infection	48 (49.5)	60 (54.1)
Cytopenia	76 (78.4)	85 (76.6)

Table 10 shows adverse events reported at a ≥5% higher incidence in Study E2202 than in Study C2201.

Table 10. Adverse events reported at a ≥5% higher incidence in Study E2202 than in Study C2201 (Study E2202 [data cutoff date of March 29, 2021] and Study C2201 [data cutoff date of December 8, 2017], Safety set)

PT (MedDRA/J ver.24.0)	n (%)	
	Study E2202 N = 97	Study C2201 N = 111
Neutropenia	41 (42.3)	22 (19.8)
Lymphopenia	8 (8.2)	1 (0.9)
Thrombocytopenia	19 (19.6)	14 (12.6)
Lymphocyte count decreased	9 (9.3)	3 (2.7)
Hypogammaglobulinaemia	14 (14.4)	9 (8.1)
SARS-Cov-2 test negative	6 (6.2)	0
Leukopenia	8 (8.2)	3 (2.7)
Muscle spasms	7 (7.2)	2 (1.8)
Grade ≥3 adverse events		
Neutropenia	41 (42.3)	22 (19.8)
Lymphopenia	8 (8.2)	0
Leukopenia	8 (8.2)	1 (0.9)
Lymphocyte count decreased	8 (8.2)	2 (1.8)

Serious adverse events reported at a ≥2% higher incidence in Study E2202 than in Study C2201 were pneumonia (8 of 97 subjects [8.2%] in Study E2202, 4 of 111 subjects [3.6%] in Study C2201), squamous cell carcinoma (2 of 97 subjects [2.1%], 0%), and pleural effusion (2 of 97 subjects [2.1%], 0%). Adverse events leading to death reported at a higher incidence in Study E2202 than in Study C2201 were acute respiratory failure (1 of 97 subjects [1.0%], 0%) and CRS (1 of 97 subjects [1.0%], 0%).

As described above, the safety profile of Kymriah observed in Study E2202 was similar to that observed in the approved indication or performance.

PMDA's discussion:
Serious adverse events such as CRS occurred frequently in Study E2202. Following administration of Kymriah, the patient's condition should be monitored very closely, and if adverse events occur, multidisciplinary actions should be taken to manage adverse events individually. There are limitations to rigorous comparison of the safety of Kymriah between Japanese and non-Japanese populations due to limited clinical experience with Kymriah in Japanese patients. However, since the incidences of hypogammaglobulinaemia etc. were higher in the Japanese subgroup than in the non-Japanese subgroup, adverse events should be managed more carefully in Japanese patients.

Attention should be paid also to the possible occurrence of neutropenia etc. because they occurred more frequently in Study E2202 than in Study C2201, which enrolled patients with DLBCL, the approved indication or performance.

Nevertheless, all of the above adverse events are known adverse events associated with Kymriah, and the package insert has already advised that blood tests should be performed regularly, etc. This means that Kymriah is tolerable as long as physicians with adequate knowledge of and experience in the treatment of FL take appropriate actions (e.g., monitoring and management of adverse events) at medical institutions with adequate facilities for the management of adverse events.

6.R.3 Clinical positioning and indication or performance

The proposed indication or performance in the present partial change application was "relapsed or refractory follicular lymphoma."

The proposed Precautions Concerning Indications or Performance section included the following statement: "Administer Kymriah to patients who failed or relapsed after ≥2 lines of therapy."

Based on Sections "6.R.1 Efficacy" and "6.R.2 Safety" and the following considerations, PMDA concluded that the following statements should be included in the Indications or Performance and Precautions Concerning Indications or Performance sections.

Indications or Performance (The underlined words are added to the proposed text in the present partial change application.)
Relapsed or refractory follicular lymphoma<u>. Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy:</u>

- <u>Newly diagnosed patients who failed to achieve a response to ≥2 lines of systemic therapy;</u>

newly diagnosed patients who achieved a response to ≥2 lines of systemic therapy but subsequently relapsed; patients who received ≥1 line of systemic therapy after relapse but failed to achieve a response; or patients who received ≥1 line of systemic therapy after relapse and achieved a response but subsequently relapsed again

Precautions Concerning Indications or Performance (The underlined words are added to, and the strikethrough words are deleted from, the proposed text in the present partial change application.)

~~Administer Kymriah to patients who failed or relapsed after ≥2 lines of therapy.~~ 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 histological type and prior treatment of the clinical study patients.

6.R.3.1 Clinical positioning and target population

With respect to the clinical positioning of Kymriah, there is no mention of Kymriah for FL in the Japanese or foreign clinical practice guidelines.

The applicant's explanation about the clinical positioning and indication or performance of Kymriah:

Since Study E2202 demonstrated the efficacy and safety of Kymriah in patients with relapsed or refractory FL after ≥2 lines of therapy, Kymriah will offer a new treatment option for these patients. Thus, "relapsed or refractory follicular lymphoma" will be included in the Indications or Performance section. Since Study E2202 enrolled patients with relapsed or refractory FL after ≥2 lines of therapy, the following statement will be included in the Precautions Concerning Indications or Performance section.

• Administer Kymriah to patients who failed or relapsed after ≥2 lines of therapy.

PMDA asked the applicant to explain whether the use of Kymriah is recommended in patients with FL Grade 3B because these patients were excluded from Study E2202.

The applicant's response:

There is limited clinical experience with Kymriah in patients with FL Grade 3B as shown below, and no data are available to recommend the use of Kymriah. Thus, the Clinical Studies section of the package insert will state that patients with FL Grade 1, 2, or 3A were enrolled in Study E2202.

- Study H2301 compared Kymriah with standard of care, both as a second line therapy, in patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. In the study, 5 patients with FL Grade 3B received Kymriah, 2 of whom achieved a response (PR and CR

in 1 patient each), and the safety profile of Kymriah was similar to that observed in the approved indications or performance.

- According to the post-marketing data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry (data cutoff date of [redacted], 20[redacted]), 1 patient with Grade 3B FL received Kymriah outside Japan. The patient had a PR. As for the safety, CRS (Grade 1) was reported.

PMDA's discussion:

The proposed indication or performance of Kymriah based on Study E2202 is largely acceptable. However, since serious adverse events such as CRS are very likely to occur following administration of Kymriah, the use of Kymriah is not recommended in patients with FL other than those enrolled in Study E2202, and the prior treatment of patients enrolled in Study E2202 should be stated in the Indications or Performance section. As to the histological type, there are no data recommending the use of Kymriah in patients with FL Grade 3B. Therefore, the details of the histological type and prior treatment of patients enrolled in Study E2202 should be presented in the Clinical Studies section of the package insert, and the following statement should be included in the Precautions Concerning Indications 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 histological type and prior treatment of the clinical study patients.

6.R.3.2 Use of Kymriah in patients previously treated with CD19-targeted CAR T-cell therapy

The applicant's explanation about the use of Kymriah in patients with relapsed or refractory FL previously treated with CD19-targeted CAR T-cell therapy:

There is no clinical experience with Kymriah in these patients in the clinical studies or post-marketing experience of Kymriah, and the efficacy and safety of Kymriah in these patients have not been established. Thus, the use of Kymriah is not recommended in these patients.

PMDA's discussion:

The explanation by the applicant (the use of Kymriah is not recommended in these patients) is acceptable. As this is very important information for selecting treatment with Kymriah, this information should be clearly included in the Indications or Performance section.

6.R.4 Dosage and administration or method of use

In the present partial change application for Kymriah, the applicant made the following changes to the approved dosage and administration or method of use:

(1) The following criteria for LD chemotherapy, etc., are described in "5. Pretreatment before

administration of Kymriah." (The underlined words are added to, and the strikethrough words are deleted from, the approved text).

~~If the peripheral white blood cell count exceeds 1000/μL within 1 week prior to the planned administration of Kymriah, c~~Conduct the following lymphodepleting chemotherapy as pretreatment at least 2 days before administration of Kymriah. The period between pretreatment chemotherapy and administration of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition after reading the Clinical Studies section. Lymphodepleting chemotherapy may be omitted in case of severe cytopenia (e.g., the peripheral white blood cell count ≤1,000/μL within 1 week prior to the planned administration of Kymriah).

(2) The following LD chemotherapy regimens for FL are provided in "5. Pretreatment before administration of Kymriah."

- Cyclophosphamide at 250 mg/m^2 (on the anhydrous basis) 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.
- For patients with a history of Grade 4[Note)] hemorrhagic cystitis due to cyclophosphamide or patients resistant to cyclophosphamide:
  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) Grading is according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.03.

(3) The following dosing regimen of Kymriah for FL is provided in "6. Administration of Kymriah."

- 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.

Based on Sections "6.R.1 Efficacy" and " 6.R.2 Safety" and the following considerations, PMDA concluded that the proposed text for Dosage and Administration or Method of Use should be modified as follows.

Dosage and Administration or Method of Use (The underlined words are added to, and the strikethrough words are deleted from, the proposed text in the present partial change application.)

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 or at ≤−120°C.

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 or at ≤−120°C until immediately before use.

5. Pretreatment before administration of Kymriah

Conduct the following lymphodepleting chemotherapy as pretreatment at least 2 days before administration of Kymriah. The period between pretreatment chemotherapy and administration of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition~~, after reading the Clinical Studies section~~. Lymphodepleting chemotherapy may be omitted depending on the patient's condition ~~in case of severe cytopenia~~ (e.g., the peripheral white blood cell count <1,000/μL within 1 week prior to the planned administration of Kymriah).

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

1) Cyclophosphamide at 500 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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 diffuse large B-cell lymphoma and patients with relapsed or refractory follicular lymphoma

1) Cyclophosphamide at 250 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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) Grading is according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.03.

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. Do not re-administer Kymriah.

(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 diffuse large B-cell lymphoma and relapsed or refractory follicular 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.

6.R.4.1 Dosing regimen of Kymriah and LD chemotherapy regimen

The applicant's explanation about the rationale for the proposed dosage and administration or method of use of Kymriah:

The dosing regimen of Kymriah and LD chemotherapy regimen for Study E2202 were selected based on Study C2201, which demonstrated the efficacy and safety of Kymriah in patients with relapsed or refractory DLBCL.

In Study E2202, patients with relapsed or refractory FL including Japanese patients received LD chemotherapy[7)] 2 to 6 days prior to Kymriah infusion and then received 0.6 to 6.0×10^8 CAR-positive viable T cells (irrespective of body weight). The study demonstrated the efficacy and

[7)] The following LD chemotherapy was completed. This step was to be omitted in case of peripheral white blood cell count <1,000/μL, etc., or any condition that, in the investigator's opinion, precluded LD chemotherapy.
- Cyclophosphamide 250 mg/m^2 and fludarabine 25 mg/m^2 infused intravenously once daily for 3 days
- If there was previous Grade 4 hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated resistance to a previous cyclophosphamide-containing regimen, the patient was allowed to receive bendamustine 90 mg/m^2 infused intravenously once daily for 2 days.

safety of Kymriah. Thus, dosage and administration or method of use of Kymriah was selected based on the dosing regimen used in Study E2202.

The criteria for LD chemotherapy and the period between the completion of LD chemotherapy and Kymriah infusion differed between Study E2202 and Study C2201.[8)] Therefore the package insert will describe the details of LD chemotherapy performed in the clinical study (in the Clinical Studies section) and include statements to the effect that "read the Clinical Studies section" and "LD chemotherapy may be omitted in case of severe cytopenia" (in the Dosage and Administration or Method of Use section).

PMDA's discussion:
The above explanation by the applicant is understandable. However, LD chemotherapy could be omitted depending on the patient's condition in Study E2202, and the use of LD chemotherapy was determined according to the patient's condition. Thus, the Dosage and Administration or Method of Use section should state that LD chemotherapy may be omitted depending on the patient's condition, and then the relevant statement should be modified.

The statement "read the Clinical Studies section for LD chemotherapy" should not be included in the Dosage and Administration or Method of Use section. Instead, the following statement regarding pretreatment should be included in the PRECAUTIONS CONCERNING Dosage and Administration or Method of Use section.

Precautions Concerning Dosage and Administration or Method of Use (excerpt) (The underlined words are added to, and the strikethrough words are deleted from, the proposed text in the present partial change application.)
• Pretreatment
~~If the peripheral white blood cell count exceeds 1,000/μL, a~~Administer cytotoxic agents that inhibit DNA synthesis etc., or chemotherapeutic agents that induce immunosuppression associated with lymphocytopenia in order to facilitate engraftment of the administered CAR T cells, prior to Kymriah infusion. Read the Clinical Studies section for ~~chemotherapeutic agents used as~~ pretreatment performed in the clinical study.

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

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

8) Patients received LD chemotherapy if they had a peripheral white blood cell count >1,000/μL within 1 week prior to the scheduled infusion of Kymriah. The period between the completion of LD chemotherapy and Kymriah infusion was 2 to 14 days.

The applicant plans to conduct post-marketing surveillance covering all patients with relapsed or refractory FL treated with Kymriah to evaluate the safety, etc. of Kymriah in clinical use.

Since the safety profile of Kymriah observed in Study E2202 was similar to that observed in the approved indication or performance [see Section 6.R.2.1], the safety specification of this surveillance includes the same events included in the safety specification[9)] for the post-marketing surveillance for the approved indications or performance.

A planned sample size of 200 patients was chosen, taking account of the importance of a long-term follow-up and considering the number of patients expected to use Kymriah in the post-marketing setting (during 3 years after the market launch) and the incidences of the events included in the safety specification in Study E2202.

An observation period of up to 8 years was chosen in order to assess each survey item.

PMDA's discussion:
Since the safety information from Japanese patients with FL treated with Kymriah is very limited etc., the applicant should conduct post-marketing surveillance covering all patients with FL treated with Kymriah, collect information, and promptly provide the obtained safety information to healthcare professionals in clinical practice.

The applicant's proposal (i.e., safety specification, planned sample size, and observation period) for the all-case surveillance is acceptable.

The details of post-marketing surveillance will be finalized, taking also account of comments from the Expert Discussion concerning safety assessment of Kymriah.

8. Adverse Events Observed in Clinical Study

Among clinical study data submitted for safety evaluation, deaths are described in Section "6.1 Evaluation data." Main adverse events other than deaths are described below.

8.1 Global phase II study (Study E2202)

Adverse events occurred in 96 of 97 subjects (99.0%), and those for which a causal relationship to Kymriah could not be ruled out occurred in 76 of 97 subjects (78.4%). Adverse events reported by ≥10% of subjects are shown in Table 11.

9) CRS, infection, serious neurological event, TLS, continuous depletion of normal B cells/hypogammaglobulinaemia, hematological disease including cytopenia, secondary malignant tumor, deterioration of graft versus host disease, brain oedema, onset or deterioration of autoimmune disease, transmission of an infectious agent, use in pregnant or breast feeding women, use in patients with HBV/HCV/HIV, use in patients with active central nervous system infiltration, and long-term safety

Table 11. Adverse events reported by ≥10% of all subjects (Safety set)

PT (MedDRA/J ver.24.0)	n (%)			
	Japanese subgroup N = 9		All subjects N = 97	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	9 (100)	9 (100)	96 (99.0)	76 (78.4)
Blood and lymphatic system disorders				
Neutropenia	6 (66.7)	6 (66.7)	41 (42.3)	41 (42.3)
Anaemia	1 (11.1)	1 (11.1)	25 (25.8)	16 (16.5)
Thrombocytopenia	4 (44.4)	2 (22.2)	19 (19.6)	11 (11.3)
FN	3 (33.3)	3 (33.3)	12 (12.4)	12 (12.4)
Gastrointestinal disorders				
Diarrhoea	2 (22.2)	1 (11.1)	21 (21.6)	1 (1.0)
Nausea	0	0	15 (15.5)	2 (2.1)
Constipation	1 (11.1)	0	14 (14.4)	0
General disorders and administration site conditions				
Pyrexia	1 (11.1)	0	19 (19.6)	1 (1.0)
Fatigue	0	0	16 (16.5)	3 (3.1)
Immune system disorders				
CRS	6 (66.7)	1 (11.1)	48 (49.5)	1 (1.0)
Hypogammaglobulinaemia	5 (55.6)	0	14 (14.4)	1 (1.0)
Investigations				
White blood cell count decreased	0	0	21 (21.6)	17 (17.5)
Neutrophil count decreased	1 (11.1)	1 (11.1)	17 (17.5)	17 (17.5)
Platelet count decreased	1 (11.1)	1 (11.1)	10 (10.3)	6 (6.2)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (11.1)	0	10 (10.3)	0
Nervous system disorders				
Headache	2 (22.2)	0	24 (24.7)	1 (1.0)
Respiratory, thoracic and mediastinal disorders				
Cough	0	0	12 (12.4)	0

Serious adverse events occurred in 42 of 97 subjects (43.3%). Those reported by ≥2 subjects were CRS (19 subjects [19.6%]); pneumonia (8 subjects [8.2%]); FN (6 subjects [6.2%]); pyrexia (3 subjects [3.1%]); and encephalopathy, infusion related reaction, neutropenia, pleural effusion, and squamous cell carcinoma (2 subjects each [2.1%]). A causal relationship to Kymriah could not be ruled out for CRS (18 subjects); pneumonia (3 subjects); FN and encephalopathy (2 subjects each); and acute kidney injury, bacteraemia, gastrointestinal ulcer, glossitis, ICANS, infusion related reaction, malignant melanoma, muscle spasms, nausea, neutropenia, perirectal abscess, haemophilus pneumonia, PML, pyrexia, sepsis, squamous cell carcinoma, stomatitis, and vomiting (1 subject each).

In the Japanese subgroup, serious adverse events occurred in 2 of 9 subjects (22.2%). The observed serious adverse events were gastrointestinal ulcer, stomatitis, CRS, pneumonia, bacteraemia, sepsis, encephalopathy, acute kidney injury, and pneumothorax (1 subject each [11.1%]). A causal relationship to Kymriah could not be ruled out for CRS, pneumonia, sepsis, bacteraemia, encephalopathy, stomatitis, gastrointestinal ulcer, and acute kidney injury (1 subject

each).

9. Results of Compliance Assessment Concerning the Application Data and Conclusion Reached by PMDA

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

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

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

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

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

On the basis of the data submitted, PMDA has concluded that Kymriah has a certain level of efficacy in the treatment of relapsed or refractory follicular lymphoma, and that Kymriah has acceptable safety in view of its benefits. Thus, offering Kymriah as a new treatment option for patients with FL in clinical practice is meaningful.

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

Review Report (2)

July 13, 2022

Product Submitted for Approval

Brand Name	Kymriah Suspension for Intravenous Infusion
Non-proprietary Name	Tisagenlecleucel
Applicant	Novartis Pharma K.K.
Date of Application	November 29, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

PMDA's conclusion:

Based on the considerations in Section "6.R.1 Efficacy" in the Review Report (1), a certain level of efficacy of Kymriah was demonstrated in patients with relapsed or refractory FL because the primary endpoint of the CR rate was greater than the pre-specific threshold in Study E2202 in patients with relapsed or refractory FL.

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

1.2 Safety

PMDA's conclusion:

Based on the considerations in Section "6.R.2 Safety" in the Review Report (1), adverse events that require particular attention following administration of Kymriah in patients with relapsed or refractory FL are similar to the events that were considered to require attention[10)] at the time of the previous approval of Kymriah (for the previously approved indications or performance).

[10)] CRS, neurologic disorder, infection, myelosuppression, hypersensitivity, hypogammaglobulinaemia, and TLS (Review Report on Kymriah Suspension for Intravenous Infusion as of February 4, 2019)

Attention should be paid to the possible occurrence of these adverse events following administration of Kymriah also in patients with relapsed or refractory FL.

Kymriah is tolerable as long as physicians with adequate knowledge of and experience in the treatment of FL take appropriate actions (e.g., monitoring for and management of adverse events) at medical institutions with adequate facilities for the management of the above adverse events.

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

1.3 Clinical positioning and indication or performance

PMDA's conclusion:

Based on the considerations in Section "6.R.3 Clinical positioning and indication or performance" in the Review Report (1), the details of the histological type and prior treatment of patients enrolled in Study E2202, should be presented in the Clinical Studies section of the package insert, and the following statements should be included in the Indications or Performance and Precautions Concerning Indications or Performance sections concerning the present application, as shown in the above section in the Review Report (1).

Indications or Performance

Relapsed or refractory follicular lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy:

- Newly diagnosed patients who failed to achieve a response to ≥2 lines of systemic therapy; newly diagnosed patients who achieved a response to ≥2 lines of systemic therapy but subsequently relapsed; patients who received ≥1 line of systemic therapy after relapse but failed to achieve a response; or patients who received ≥1 line of systemic therapy after relapse and achieved a response but subsequently relapsed again

Precautions Concerning Indications or Performance

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 histological type and prior treatment of the clinical study patients.

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

PMDA requested that the applicant include the above statements in the Indications or Performance and Precautions Concerning Indications or Performance sections concerning the

present application. As the applicant appropriately responded to the request, PMDA accepted the applicant's response.

1.4 Dosage and administration or method of use

Based on the considerations in Section "6.R.4 Dosage and administration or method of use" in the Review Report (1), PMDA concluded that the following statements should be included in the Dosage and Administration or Method of Use section, as shown in the above section in the Review Report (1).

Dosage and Administration or Method of Use (The underlined words are added to, and the strikethrough words are deleted from, the approved text.)

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 or at ≤−120°C.

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 or at ≤−120°C 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, c~~Conduct the following lymphodepleting chemotherapy as pretreatment at least 2 days before administration of Kymriah. The period between pretreatment chemotherapy and administration of Kymriah is determined based on the characteristics of the chemotherapy and the patient's condition. <u>Lymphodepleting chemotherapy may be omitted depending on the patient's condition (e.g., the peripheral white blood cell count <1,000/μL within 1 week prior to the planned administration of Kymriah).</u>

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

1) Cyclophosphamide at 500 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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 diffuse large B-cell lymphoma and patients with relapsed or refractory follicular lymphoma

1) Cyclophosphamide at 250 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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) Grading is according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.03.

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. Do not re-administer Kymriah.

(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 diffuse large B-cell lymphoma and relapsed or refractory follicular 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.

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

PMDA requested that the applicant include the above statements in the Dosage and Administration or Method of Use section. As the applicant appropriately responded to the request, PMDA accepted the applicant's response.

1.5 Post-marketing surveillance plan (draft)

At the time of application, the applicant proposed a plan of post-marketing surveillance (draft) covering all patients with FL treated with Kymriah to evaluate the safety, etc. of Kymriah in clinical use. The planned sample size was 200 patients. The planned observation period was up to 8 years.

Based on the considerations in Section "7. Risk Analysis and Outline of the Review Conducted by PMDA" in the Review Report (1), PMDA concluded that the plan of post-marketing surveillance proposed by the applicant was acceptable.

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

PMDA requested that the applicant modify the post-marketing surveillance plan in view of the comments from the Expert Discussion and the following point:

- In Study E2202, Kymriah was not administered to patients who received prior allogeneic HSCT or patients with active CNS involvement by malignancy. Therefore, the use of Kymriah is not recommended in these patients, and "deterioration of graft versus host disease" and "use in patients with active central nervous system infiltration" should be deleted from the safety specification for patients with FL.

The applicant then submitted an outline of post-marketing surveillance plan (draft) (see Table 12), and PMDA accepted it.

Table 12. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the safety and efficacy of Kymriah.
Survey method	All-case surveillance The applicant will obtain data in the target population from the data accumulated in the registry database (FormsNet) owned by the Center for International Blood and Marrow Transplant Research (CIBMTR) via the Japanese Data Center for Hematopoietic Cell Transplantation.
Population	Patients with relapsed or refractory FL
Observation period	Up to 8 years
Planned sample size	200 patients
Main survey items	Safety specification CRS, infection, serious neurological events, TLS, continuous depletion of normal B cells/hypogammaglobulinaemia, hematological disease including cytopenia, secondary malignant tumor, brain oedema, onset or deterioration of autoimmune disease, transmission of an infectious agent, use in pregnant and breast feeding women, use in patients with HBV/HCV/HIV, long-term safety

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication or performance and dosage and administration or method of use as shown below, with the following approval conditions, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch. Since the product received an orphan regenerative medical product designation with the intended indication or performance of "CD19-positive follicular lymphoma," the re-examination period for the additional indication or performance is 10 years.

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 who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy:
   - 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 diffuse large B-cell lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy and 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

3. Relapsed or refractory follicular lymphoma. Kymriah should be used only in patients meeting any of the following criteria who are naïve to CD19-targeted chimeric antigen receptor T-cell infusion therapy:
   - Newly diagnosed patients who failed to achieve a response to ≥2 lines of systemic therapy; newly diagnosed patients who achieved a response to ≥2 lines of systemic therapy but subsequently relapsed; patients who received ≥1 line of systemic therapy after relapse but failed to achieve a response; or patients who received ≥1 line of systemic therapy after relapse and achieved a response but subsequently relapsed again

(Underline denotes additions.)

Dosage and Administration or Method of Use

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4. Receipt and storage of Kymriah

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

1) Cyclophosphamide at 500 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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 diffuse large B-cell lymphoma and patients with relapsed or refractory follicular lymphoma

1) Cyclophosphamide at 250 mg/m^2 (on the anhydrous basis) 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 or patients resistant to cyclophosphamide:
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) Grading is according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.03.

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. Do not re-administer Kymriah.

(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 diffuse large B-cell lymphoma and relapsed or refractory follicular 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.

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. 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

adalimumab	adalimumab (genetical recombination)
application	marketing application
partial change application	application for partial change approval
bendamustine	bendamustine hydrochloride
CAR	chimeric antigen receptor
CD	cluster of differentiation
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CNS	central nervous system
CR	complete response
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
cyclophosphamide	cyclophosphamide hydrate
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
ESMO Clinical Practice Guidelines	European Society for Medical Oncology Clinical Practice Guidelines
FL	follicular lymphoma
fludarabine	fludarabine phosphate
FN	febrile neutropenia
foreign clinical practice guidelines	NCCN guidelines and ESMO clinical practice guidelines
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
ICANS	immune effector cell-associated neurotoxicity syndrome
IRC	Independent Review Committee
Japanese clinical practice guidelines	Practical Guidelines for Hematological Malignancies by Japanese Society of Hematology
Kymriah	Kymriah Suspension for Intravenous Infusion
LD chemotherapy	lymphodepleting chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology
NHL	non-Hodgkin lymphoma
OS	overall survival
PD	progressive disease
PFS	progression free survival
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukoencephalopathy
PR	partial response
PS	performance status
PT	preferred term
scFv	single-chain variable fragment
SD	stable disease
SOC	system organ class
Study C2201	Study CCTL019C2201
Study E2202	Study CCTL019E2202
Study H2301	Study CCTL019H2301

TLS	tumor lysis syndrome
tocilizumab	tocilizumab (genetical recombination)
vasopressin	synthetic vasopressin