PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrKYMRIAH®

Tisagenlecleucel

Cell suspension in infusion bag, 1.2 x 10^6 to 6.0 x 10^8 CAR-positive viable T cells, for intravenous use

Novartis Standard

Antineoplastic and immunomodulating agents

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KYMRIAH is a registered trademark

RECENT MAJOR LABEL CHANGES

INDICATIONS, (1)	08/2020
DOSAGE AND ADMINISTRATION, Dosing Considerations (4.1)	08/2020
DOSAGE AND ADMINISTRATION, Administration (4.3)	08/2020
WARNINGS AND PRECAUTIONS, (8)	08/2020

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KYMRIAH® (tisagenlecleucel) is a CD19-directed genetically modified autologous T-cell immunocellular therapy indicated for the treatment of:

- pediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia (ALL) who are refractory, have relapsed after allogeneic stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse.

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

1.1 Pediatrics

B-cell ALL: No formal studies have been performed in relapsed or refractory B-cell ALL pediatric patients below 3 years of age.

DLBCL: No formal studies in DLBCL have included patients younger than 18 years of age.

1.2 Geriatrics (≥65 years of age)

B-cell ALL: The safety and efficacy of KYMRIAH in this population has not been established (see **11 ACTION AND CLINICAL PHARMACOLOGY**).

DLBCL: No dose adjustment is required in patients 65 years of age or older (see **11 ACTION AND CLINICAL PHARMACOLOGY**).

2 CONTRAINDICATIONS

KYMRIAH is contraindicated in patients with known hypersensitivity to tisagenlecleucel or to any component of the product formulation, including dimethyl sulfoxide (DMSO) or dextran 40. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Cytokine release syndrome (CRS) is a commonly life-threatening adverse event, occurring in patients receiving tisagenlecleucel infusion. Monitor for CRS after treatment with tisagenlecleucel. Provide supportive care as needed. (see Description of selected adverse drug reactions and section Warnings and Precautions, Immune, Cytokine release syndrome).

Neurological toxicities, which may be severe or life-threatening, can occur following treatment with tisagenlecleucel, including concurrently with CRS. Monitor for neurological events after treatment with tisagenlecleucel. Provide supportive care as needed.

Tisagenlecleucel should be administered by experienced healthcare professionals at specialized treatment centres.

4 DOSAGE AND ADMINISTRATION

KYMRIAH must be administered in a treatment centre that has been qualified by Novartis Pharmaceuticals Canada Inc. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for KYMRIAH administration and management of patients treated with KYMRIAH.

- Manufacture and release of Kymriah usually takes 3 – 4 weeks
- Leukapheresis material from patients who test positive for HIV, active HBV or active HCV will not be accepted for manufacturing of Kymriah. Screening for active HBV, active HCV and HIV must be performed in accordance with clinical guidelines *before* collection of cells for manufacturing.

4.1 Dosing Considerations

- For autologous use only – immediately prior to infusion, verify that the patient's identity matches the information on the patient specific infusion bag(s).
- For intravenous use only. Do NOT use a leukocyte depleting filter.
- Kymriah is intended for a single treatment

- Ensure the availability of a minimum of 2 doses of tocilizumab per patient and emergency equipment prior to infusion. Treatment centers should ensure that additional doses of tocilizumab can be accessed within 8 hours of the previous dose (see Table 8-1)**.**

Active central nervous system (CNS) leukemia or lymphoma

- There is limited experience with the use of KYMRIAH in patients with active CNS leukemia and active CNS lymphoma. The risk/benefit of KYMRIAH has not been established for these populations.

Concomitant diseases

- Patients with active central nervous system (CNS) disorder or inadequate renal, hepatic, pulmonary or cardiac function were excluded from the studies. These patients are likely to be more vulnerable to the consequences of the adverse reactions described after KYMRIAH infusion and will require additional monitoring and management.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

KYMRIAH is provided as a single-dose, one-time treatment, in a patient specific infusion bag(s).

Pediatric and Young Adult B-cell ALL:

- For patients 50 kg and below: 0.2 to 5.0 x 10^6 chimeric antigen receptor (CAR)-positive viable T-cells/kg body weight.
- For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T-cells (non-weight based).

Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma:

- 0.6 to 6.0 x 10^8 CAR-positive viable T-cells (non-weight based).

Pediatrics

B-cell ALL: No formal studies have been performed in relapsed or refractory B-cell ALL pediatric patients below 3 years of age.

DLBCL: No formal studies in diffuse large B-cell lymphoma have been performed in pediatric patients younger than 18 years of age.

Geriatrics (≥65 years of age)

B-cell ALL: The safety and efficacy of KYMRIAH in this population has not been established (see **11 ACTION AND CLINICAL PHARMACOLOGY**).

DLBCL: No dose adjustment is required in patients 65 years of age or older (see **11 ACTION AND CLINICAL PHARMACOLOGY**).

4.3 Administration

Preparing the Patient for Kymriah Infusion

Pre-treatment conditioning (Lymphodepleting chemotherapy)

- Confirm availability of KYMRIAH prior to initiating a lymphodepleting regimen

Lymphodepleting chemotherapy is recommended to be administered before KYMRIAH infusion unless the white blood cell (WBC) count within one week prior to infusion is ≤1,000 cells/microliter.

KYMRIAH is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the KYMRIAH infusion and the WBC count is >1,000 cells/microliter, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving KYMRIAH.

Pediatric and Young Adult B-cell ALL:

The recommended lymphodepleting chemotherapy regimen is:

- Fludarabine (30 mg/m^2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenous daily for 2 days starting with the first dose of fludarabine).

If the patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then the following should be used:

- Cytarabine (500 mg/m^2 intravenous daily for 2 days) and etoposide (150 mg/m^2 intravenous daily x 3 days starting with the first dose of cytarabine).

Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma:

The recommended lymphodepleting chemotherapy regimen is:

- Fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine).

If the patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then the following regimen should be used in place of the fludarabine-cyclophosphamide regimen:

- Bendamustine (90 mg/m^2 intravenous daily for 2 days).

Premedication:

To minimize potential acute infusion reactions, it is recommended to premedicate patients with acetaminophen/paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to KYMRIAH infusion. The prophylactic use of systemic corticosteroids should be avoided as it may interfere with the activity of KYMRIAH (see **8 WARNINGS AND PRECAUTIONS**).

Clinical assessment prior to infusion

KYMRIAH treatment should be delayed in certain patients with safety risk factors, including (see also: **8 WARNINGS AND PRECAUTIONS)**:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies.
- Active uncontrolled infection.
- Active chronic Graft Versus Host Disease (GVHD).
- Significant clinical worsening of leukemia burden or rapid progression of lymphoma following lymphodepleting chemotherapy.

Preparing Kymriah for infusion

Patient identity confirmation: Prior to KYMRIAH infusion, the patient's identity must be matched with the patient identifiers on the KYMRIAH infusion bag(s).

Inspection and thawing of the cryobag(s): The timing of thaw of KYMRIAH and infusion should be coordinated. The infusion start time should be confirmed in advance, and adjusted for thaw so that KYMRIAH is available for infusion when the recipient is ready.

The infusion bag should be placed inside a second, bag, to avoid spills in case of a leak and to protect ports from contamination during thawing. The infusion bag(s) should be examined for any breaks or cracks prior to thawing. KYMRIAH should be thawed at 37°C using either water bath or dry thaw method until there is no visible ice in the infusion bag. The infusion bag should be removed immediately from the thawing device and should not be stored at 37°C after thawing is completed.

Inspect the contents of the thawed infusion bag for any visible cell clumps. If visible cell clumps remain, gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing.

Once KYMRIAH has been thawed and is at room temperature (20°C to 25°C), it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

If more than one bag has been received for the treatment dose, the additional bag(s) should not be thawed until after the contents of the first bag have been safely infused.

If the KYMRIAH bag appears to have been damaged or to be leaking or if clumps have not dispersed, it should not be infused, and should be disposed of according to local biosafety procedures. Novartis should then be contacted at 1-833-395-2278.

Administration

KYMRIAH should not be manipulated. For example, KYMRIAH should **not** be washed (spun down and resuspended in new media) prior to infusion. All contents of the infusion bag should be infused.

KYMRIAH should be administered as an intravenous infusion through latex free tubing. Do not use a leukocyte depleting filter. Infuse at approximately 10 to 20 mL per minute by gravity flow. Sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prime the tubing prior to infusion and to rinse it afterwards. When the full volume of KYMRIAH has been infused, the KYMRIAH infusion bag should be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to assure as many cells as possible are infused into the patient.

In clinical trials intravenous push was an alternate method for the administration of low volumes of KYMRIAH. For special precautions for disposal see **12 STORAGE, STABILITY AND DISPOSAL**.

Monitoring after infusion

Following infusion with KYMRIAH patients should be monitored 2 to 3 times for at least the first week for signs and symptoms of cytokine release syndrome, neurological events and other toxicities. Physicians should consider hospitalization at the first signs and symptoms of cytokine release syndrome and/or neurological events.

Patients should be instructed to remain within proximity (2 hours of travel) of a qualified clinical facility for at least 4 weeks following infusion.

4.4 Missed Dose

Not Applicable

5 OVERDOSAGE

Not Applicable

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 6-1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Cell suspension for infusion in one or more bags. 2.0×10^6 to 6.0×10^8 CAR-positive viable T cells, suspended in one or more patient-specific infusion bag(s). The volume in the infusion bag	Dextran, dextrose, dimethylsulfoxide (DMSO), human serum albumin, plasma-Lyte A (multiple electrolytes for injection, Type 1, pH 7.4), and sodium chloride.

	ranges from 10 mL to 50 mL.	

7 DESCRIPTION

KYMRIAH is an immunocellular therapy containing tisagenlecleucel, autologous T cells genetically modified *ex vivo* using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor.

Appearance: colorless to slightly yellow suspension of cells.

8 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

Patients treated with KYMRIAH should not donate blood, organs, tissues, sperms, oocytes or other cells.

Treatment should only be administered in a treatment facility with personnel fully trained and approved for the care of patients receiving KYMRIAH infusion therapy. Fully trained staff will administer the KYMRIAH infusion using precautions for immunosuppressed patients. Emergency equipment must be available prior to infusion and during recovery period. See **4 DOSAGE AND ADMINISTRATION**.

Local guidelines should be followed for the supportive care of immunosuppressed and chemotherapy treated patients including infection management.

Secondary Malignancies

Patients treated with KYMRIAH may develop secondary malignancies or recurrence of their cancer. They should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing (mykymriah.cart@novartis.com or 1-833-395-2278).

Patient information

Prior to infusion, the patient should read the information from 'Patient Medication Information'. In particular, the patient should be carefully educated to inform their doctor immediately if cytokine release syndrome (CRS), neurological symptoms or other toxicities occur after infusion with KYMRIAH, and informed that they should stay within 2 hours distance of where they are given KYMRIAH treatment for at least 4 weeks.

Driving and Operating Machinery

Due to the potential for neurological toxicity, patients receiving KYMRIAH are at risk for altered or decreased consciousness/coordination and/or seizures in the 8 weeks following infusion. Patients are advised to refrain from driving and/or engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery during this period.

Endocrine and Metabolism

Tumor lysis syndrome

Tumor lysis syndrome (TLS), which may be severe, has been observed among patients that received KYMRIAH. To minimize the risk of TLS, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to KYMRIAH infusion. Signs, symptoms, and laboratory abnormalities of TLS including: hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated LDH, should be monitored and managed according to standard guidelines.

Immune

Cytokine release syndrome

Cytokine release syndrome (CRS), including life threatening or fatal events occurred frequently after KYMRIAH infusion. In almost all cases, development of CRS occurred between 1 to 10 days (median onset 3 days, range of 1-22 days) after KYMRIAH infusion in pediatric and young adult B-cell ALL patients and between 1 and 9 days (median onset 3 days, range of 1-51 days) after KYMRIAH infusion in adult DLBCL patients. The median time to resolution of CRS was 8 days (range: 1-36 days) in B-cell ALL and 7 days in DLBCL patients (range: 2-30 days).

Signs and symptoms of CRS may include high fever, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, anorexia, fatigue, headache, hypotension, dyspnea, tachypnea, and hypoxia. Organ dysfunction, including cardiac insufficiency and arrhythmia, renal insufficiency and liver injury with accompanying elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT) or elevated total bilirubin may also be observed. In addition, disseminated intravascular coagulation (DIC) with low fibrinogen levels, capillary leak syndrome (CLS), macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS. Patients should be closely monitored for signs, symptoms, and laboratory abnormalities associated with these events including fever as outlined above. For onset of neurologic events, see **8 WARNINGS AND PRECAUTIONS – Neurologic**, below.

Management of Cytokine Release Syndrome associated with KYMRIAH

CRS should be managed based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 8-1. Anti-interleukin-6 based therapy, such as tocilizumab, has been administered for moderate or severe CRS associated with KYMRIAH. A minimum of two doses of tocilizumab per patient must be available on site prior to KYMRIAH infusion. Treatment centers should ensure that additional doses of tocilizumab can be accessed within 8 hours of the previous dose (see Table

8-1). Corticosteroids may be administered in cases of life-threatening emergencies. Tisagenlecleucel continues to expand and persist following administration of tocilizumab and corticosteroids. Patients with medically significant cardiac dysfunction should be managed by standards of critical care; measures such as echocardiography should be considered. Tumor Necrosis Factor (TNF) antagonists are not recommended for management of KYMRIAH associated CRS.

Risk factors for severe CRS in pediatric and young adult B-cell ALL patients are high tumor burden prior to KYMRIAH infusion, uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infection and early onset of fever or CRS following KYMRIAH infusion. High tumor burden prior to KYMRIAH infusion was identified as a risk factor for developing severe CRS in adult DLBCL patients.

Prior to administration of KYMRIAH in pediatric and young adult B-cell ALL patients, efforts should be made to lower and control the patient's tumor burden.

In all indications, appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any existing infections should be ensured. Infections may also occur during CRS and may increase the risk of a fatal event. Coagulation parameters should be more frequently monitored in this setting in accordance with local standard of care, including management with cryoprecipitate or fibrinogen concentrate. In addition, clinically significant coagulopathy is often seen with moderate to severe CRS (Grade 3 and 4) and may continue as CRS is beginning to clinically resolve.

Table 8-1 CRS management algorithm

Cytokine release syndrome severity	Management
Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
Cytokine release syndrome requiring mild intervention - one or more of the following: – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
Cytokine release syndrome requiring moderate to aggressive intervention - one or more of the following: – Hemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	• Administer high-dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab. - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour. - Patient weight ≥30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg). Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of cytokine release syndrome. Limit to a maximum total of 4 tocilizumab doses. • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2 mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high-flow oxygen are no longer needed, then taper.

Hypersensitivity Reactions

The medicinal product contains dextran 40 and dimethyl sulfoxide (DMSO). Each of these excipients are known to possibly cause anaphylactic reaction following parenteral administration. All patients should be observed closely during the first minutes of the infusion period.

Infections and febrile neutropenia

Patients with active, uncontrolled infection should not start KYMRIAH treatment until the infection is resolved. Prior to KYMRIAH infusion, infection prophylaxis should follow standard guidelines based on the degree of preceding immunosuppression.

Patients enrolled in tisagenlecleucel studies are known to have a higher risk of infection at enrollment and to have a higher risk of intracurrent illness due to neutropenia, immunosuppression, lymphocyte-depleting chemotherapy, and the B cell aplasia from the direct action of the tisagenlecleucel cells infused. Prolonged neutropenia (laboratory grade 3 or 4 not resolved by Day 28) is a significant contributing factor to the risk of infections post-tisagenlecleucel infusion (see **9 ADVERSE REACTIONS**).

Serious infections, including life threatening or fatal infections, occurred in patients after KYMRIAH infusion. Patients should be monitored for signs and symptoms of infection and treated appropriately. As appropriate, prophylactic antibiotics should be administered and surveillance testing should be employed prior to and during treatment with KYMRIAH. Infections are known to complicate the course and management of concurrent CRS.

Febrile neutropenia was observed in patients after KYMRIAH infusion and may be concurrent with CRS. In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad spectrum antibiotics, fluids and other supportive care, as medically indicated.

In patients achieving complete remission following KYMRIAH, resulting low immunoglobulin levels can increase the risk for infections. In patients with low immunoglobulin levels pre-emptive measures such as immunoglobulin replacement and rapid attention to signs and symptoms of infection should be implemented according to age and standard specific guidelines.

Prolonged cytopenias

Patients may continue to exhibit cytopenias for several weeks following lymphodepleting chemotherapy and KYMRIAH and should be managed per standard guidelines. The majority of patients who had cytopenias at day 28 following KYMRIAH treatment resolved to Grade 2 or below within three months after treatment. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte macrophage colony stimulating factor (GM CSF), have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after KYMRIAH infusion and until CRS has resolved.

The degree and length of cytopenia may be additionally influenced by the history and the intensity of prior chemotherapies and radiation treatments, and prior history of chronic cytopenias and diminished bone marrow reserve.

Hypogammaglobulinemia

Hypogammaglobulinemia and agammaglobulinemia can occur in patients after KYMRIAH infusion. Immunoglobulin levels should be monitored after treatment with KYMRIAH. In patients with low immunoglobulin levels, pre-emptive measures such as infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be taken according to age and standard guidelines.

Live vaccines

The safety of immunization with live vaccines during or following KYMRIAH treatment has not been studied. Vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during KYMRIAH treatment, and until immune recovery following treatment with KYMRIAH.

Prior stem cell transplantation

It is recommended that patients do not undergo allogenic stem cell transplant (SCT) within 4 months prior to receiving KYMRIAH because KYMRIAH may increase the risk of graft versus host disease (GVHD). Leukapheresis for KYMRIAH manufacturing should be performed at least 12 weeks after allogenic SCT.

Viral reactivation

Viral reactivation, e.g. Hepatitis B virus (HBV) reactivation can occur in patients treated with medicinal products directed against B-cells, including Kymriah, and can result in fulminant hepatitis, hepatic failure and death.

Prior treatment with anti-CD19 therapy

There is limited experience with KYMRIAH in patients exposed to prior CD19-directed therapy. KYMRIAH is not recommended if the patient has relapsed with CD19-negative leukemia after prior anti-CD19 therapy.

Interference with serological testing

Due to limited and short spans of identical genetic information between the lentiviral vector used to create KYMRIAH and HIV, some commercial HIV nucleic acid tests (NAT) may give a false positive result (see **10.3 Drug-Laboratory Test Interactions**).

Neurologic

Neurological toxicities, in particular signs and symptoms of encephalopathy, confusional state and/or delirium can occur with KYMRIAH and can be severe or life-threatening. Other manifestations include depressed level of consciousness, seizures, aphasia and speech disorder. The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion and were transient. The median time to onset of neurological events was 7 days in B-cell ALL and 9 days in DLBCL. The median time to resolution was 7 days for B-cell ALL and 13 days for DLBCL.

Neurological events can be concurrent with CRS, following resolution of CRS or in the absence of CRS (see **9 ADVERSE REACTIONS - Neurological/Neurotoxic events**).

Patients should be monitored for neurological events. In case neurological events occur, patients should be diagnostically assessed and managed per local standard of care taking into consideration the underlying pathophysiology.

Sexual Health

Reproduction

Females of reproductive potential should use effective contraception (i.e., methods that result in less than 1% pregnancy rates) after KYMRIAH administration.

Sexually active males who have received KYMRIAH should use a condom during intercourse with a female of reproductive potential or a pregnant woman.

There are insufficient exposure data to provide a recommendation concerning the duration of contraception following treatment with KYMRIAH.

The intention to become pregnant or father a child after KYMRIAH therapy should be discussed with the treating physician. The potential risks to the pregnant woman and/or fetus should be explained.

Fertility

There is no data on the effect of KYMRIAH on male and female fertility. Effects of KYMRIAH on fertility have not been evaluated in animal studies.

Fetal risk

There is a potential for KYMRIAH to cause fetal toxicity. It is not known if KYMRIAH constitutes a risk to a pregnant woman or the fetus, however KYMRIAH cells have the potential to be transferred to the fetus. This may cause fetal toxicity including B-cell lymphocytopenia. Therefore, KYMRIAH is not recommended for women who are pregnant, and pregnancy after KYMRIAH therapy should be discussed with the treating physician. Pregnant women and women of child-bearing potential should be advised of the potential risk to a fetus. See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

8.1 Special Populations

8.1.1 Pregnant Women

KYMRIAH is not recommended for women who are pregnant. There are no available data with KYMRIAH use in pregnant women. No animal studies have been conducted with KYMRIAH to assess whether it can cause fetal harm when administered to a pregnant woman.

It is not known if KYMRIAH has the potential to be transferred to the fetus. Based on its mechanism of action, pregnant women who have received KYMRIAH may develop hypogammaglobulinemia and, if the transduced cells cross the placenta, they may cause fetal toxicity including B-cell lymphocytopenia. Similarly, newborns of mothers treated with KYMRIAH should also be assessed for hypogammaglobulinemia.

Pregnancy testing

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with KYMRIAH.

8.1.2 Breast-feeding

It is unknown whether KYMRIAH cells are transferred into human milk. A risk to the breast-fed infant cannot be excluded. Women who are breast-feeding should be advised of the potential risk to the breast-fed infant.

Following administration of KYMRIAH, breast-feeding should be discussed with the treating physician.

8.1.3 Pediatrics (<18 years of age)

B-cell ALL: No formal studies have been performed in relapsed or refractory B-cell ALL pediatric patients below 3 years of age.

DLBCL: No formal studies in diffuse large B-cell lymphoma have been performed in pediatric patients below 18 years of age.

8.1.4 Geriatrics (≥ 65 years of age)

B-cell ALL: The safety and efficacy of KYMRIAH in this population has not been established (see **11 ACTION AND CLINICAL PHARMACOLOGY**).

DLBCL: No dose adjustment is required in patients 65 years of age or older (see **11 ACTION AND CLINICAL PHARMACOLOGY**).

8.1.5 Renal and hepatic impairment

No studies have been performed in patients with renal or hepatic impairment (see **11 ACTION AND CLINICAL PHARMACOLOGY – Special Population**).

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Safety assessment was based on a total of 194 patients (with pediatric and young adult B-cell ALL and DLBCL) receiving KYMRIAH in two multicenter pivotal clinical studies.

Pediatric and Young Adult relapsed/refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL) (≥3 to 25 years)

The adverse reactions described in this section were characterized in 79 r/r B-cell ALL pediatric and young adult patients infused with KYMRIAH in the multicenter, pivotal clinical study CCTL019B2202 (B2202, ELIANA).

The most common non-hematological adverse reactions (≥40%) within 8 weeks post-infusion were cytokine release syndrome (77%), infections (73%), hypogammaglobulinemia (53%), and pyrexia (42%).

The most common hematological adverse reactions were decreased white blood cells (100%), decreased hemoglobin (100%), decreased neutrophils (100%), decreased lymphocytes (100%) and decreased platelets (97%).

Grade 3 and Grade 4 adverse reactions were reported in 89% of patients.

The most common (>40%) Grade 3 and Grade 4 hematological laboratory abnormalities were decreased white blood cells (97%), decreased lymphocytes (96%), decreased neutrophils (95%), decreased platelets (77%), and decreased hemoglobin (48%).

Grade 3 or 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (82% of patients) compared to after 8 weeks post-infusion (51% of patients).

Six deaths not related to disease progression occurred following KYMRIAH infusion, including 1 death occurred within 30 days of infusion due to cerebral hemorrhage and 5 deaths after 30 days of infusion due to infections (lower respiratory tract bacterial infection and systemic mycosis), encephalitis (unclear etiology), hepatobiliary disease, and death for unknown reason.

Adult r/r Diffuse Large B-cell Lymphoma (DLBCL)

The adverse reactions described in this section were characterized in 115 r/r DLBCL patients, infused with KYMRIAH, in one global multicenter international study, i.e. the ongoing pivotal clinical study CCTL019C2201 (C2201, JULIET).

The most common non-hematological adverse reactions (incidence >25%) were CRS (57%), infections (58%), pyrexia (35%), diarrhea (31%), nausea (29%), hypotension (25%), and fatigue (27%).

The most common hematological adverse reactions were decreased lymphocytes (100%), decreased hemoglobin (99%), decreased white blood cells (99%), decreased neutrophils (97%), and decreased platelets (95%).

Grade 3 and Grade 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and Grade 4 non-hematological adverse reactions were infections (34%) and CRS (23%).

The most common (>25%) Grade 3 and Grade 4 hematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (82%), white blood cell count decreased (78%), hemoglobin decreased (59%), and platelet count decreased (56%).

Grade 3 or 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (82% of patients) compared to after 8 weeks post-infusion (48% of patients).

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse drug reactions from clinical trials (Table 9-1 and Table 9-2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Pediatric and Young Adult r/r B-cell Acute Lymphoblastic Leukemia (ALL) (≥3 to 25 years)

Table 9-1 B-cell ALL: Percentage of patients with adverse drug reactions ≥ 10% in clinical trials[1]

Adverse drug reactions	B2202 (N=79)		
	All grades %	Grade 3 %	Grade 4 %
Blood and lymphatic system disorders			
Febrile neutropenia	34	32	3
Anemia	32	11	0
Hemorrhage [a)]	32	8	3
Neutropenia	14	3	9
Thrombocytopenia	11	4	8
Cardiac disorders			
Arrhythmia [b)]	22	3	1
Gastrointestinal disorders			
Vomiting	32	3	0
Diarrhea	29	1	0
Nausea	27	3	0
Abdominal pain [c)]	18	3	
Constipation	18	0	0
General disorders and administration site conditions			
Pyrexia	42	10	3

Adverse drug reactions	B2202 (N=79)		
	All grades %	Grade 3 %	Grade 4 %
Pain [d)]	25	3	0
Fatigue [e)]	23	0	0
Edema [f)]	19	1	0
Immune system disorders			
Cytokine release syndrome	77	22	27
Hypogammaglobulinemia [g)]	53	13	0
Infections and infestations [h)]			
Infections – pathogen unspecified	57	18	9
Viral infectious disorders	38	19	3
Bacterial infectious disorders	27	15	1
Fungal infectious disorders	15	5	4
Investigations			
International normalized ratio increased	11	0	0
Serum ferritin increased	10	3	0
Metabolism and nutrition disorders			
Decreased appetite	28	14	1
Hypocalcemia	20	6	0
Hypoalbuminemia	14	1	0
Fluid overload	11	5	0
Hyperuricemia	11	1	0

Adverse drug reactions	B2202 (N=79)		
	All grades %	Grade 3 %	Grade 4 %
Hyperglycemia	10	5	0
Musculoskeletal and connective tissue disorders			
Back pain	13	4	0
Myalgia	13	0	0
Arthralgia	10	1	0
Nervous system disorders			
Headache [i)]	35	3	0
Encephalopathy [j)]	30	9	0
Psychiatric disorders			
Delirium [k)]	19	4	0
Anxiety	16	3	0
Sleep disorder [l)]	11	0	0
Renal and urinary disorders			
Acute kidney injury [m)]	22	4	10
Respiratory, thoracic and mediastinal disorders			
Cough [n)]	27	0	0
Hypoxia	25	13	8
Dyspnea [o)]	18	3	10
Pulmonary edema	15	8	1
Nasal congestion	11	0	0

Adverse drug reactions	B2202 (N=79)		
	All grades %	Grade 3 %	Grade 4 %
Oropharyngeal pain	10	0	0
Pleural effusion	10	3	1
Tachypnea	10	5	0
Skin and subcutaneous tissue			
Rash [p)]	18	1	0
Vascular disorders			
Hypotension	29	10	10
Hypertension	19	5	0

[1)]The frequency of ADRs observed is the crude incidence rate

[a)] Hemorrhage includes anal hemorrhage, catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, cystitis hemorrhagic, disseminated intravascular coagulation, epistaxis, gastrointestinal hemorrhage, gingival bleeding, hemarthrosis, hematemesis, hematuria, hemoptysis, melena, menorrhagia, mouth hemorrhage, peritoneal hematoma, petechiae, pharyngeal hemorrhage, purpura, retinal hemorrhage, vaginal hemorrhage

[b)] Arrhythmia includes tachycardia

[c)]Abdominal pain includes abdominal pain and abdominal pain upper

[d)] Fatigue includes fatigue and malaise

[e)] Edema includes face edema, generalised edema, localised edema, and edema peripheral

[f)] Pain includes pain and pain in extremity

[g)]Hypogammaglobulinemia includes blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinemia, immunodeficiency, immunodeficiency common variable and immunoglobulins decreased

[h)] Infections and Infestations presented reflect high-level group terms

[i)] Headache includes headache and migraine

[j)] Encephalopathy includes automatism, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, memory impairment, mental status changes, somnolence

Adverse drug reactions	B2202 (N=79)		
	All grades %	Grade 3 %	Grade 4 %

k) Delirium includes agitation, delirium, hallucination, visual hallucination, irritability, and restlessness

l) Sleep disorder includes insomnia, nightmare, sleep disorder

m)Acute kidney injury includes acute kidney injury, anuria, azotemia, blood creatinine abnormal, blood creatinine increased, renal failure, renal tubular dysfunction and renal tubular necrosis

n) Cough includes cough and productive cough

o) Dyspnea includes dyspnea, respiratory distress, and respiratory failure

p) Rash includes dermatitis, rash, rash maculo-papular, rash papular, and rash pruritic

9.2.1 Less Common Clinical Trial Adverse Reactions (≥1% and <10%)

Selected ADRs which occurred in the pediatric ALL study (B2201) with a frequency of ≥1% and <10% were:

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis, coagulopathy, leukopenia, lymphopenia, pancytopenia

Cardiac disorders: cardiac arrest, cardiac failure [a)]

Eye disorders: Visual impairment

Gastrointestinal disorders: abdominal distension, ascites, stomatitis, dry mouth

General disorders and administration site conditions: chills, asthenia, influenza like illness, multiple organ dysfunction syndrome

Hepatobiliary disorders: hyperbilirubinemia

Immune system disorders: infusion related reaction, graft versus host disease

Investigations: blood fibrinogen decreased, prothrombin time prolonged, activated partial thromboplastin time prolonged, fibrin D dimer increased, weight decreased, blood alkaline phosphatase increased

Metabolism and nutrition disorders: fluid overload, hypomagnesemia, hyperphosphatemia, tumor lysis syndrome, hypercalcemia, hyperkalemia, hypernatremia, hyponatremia, hypermagnesemia

Musculoskeletal and connective tissue disorders: muskuloskeletal pain

Nervous System: tremor, dizziness, seizure [b)], peripheral neuropathy [c)], speech disorder [d)], motor dysfunction [e)], neuralgia

Respiratory, thoracic, and mediastinal disorders: acute respiratory distress syndrome, lung infiltration

Skin and subcutaneous tissue disorders: pruritus, erythema, hyperhydrosis, night sweats

Vascular disorders: capillary leak syndrome, thrombosis, flushing

a) Cardiac failure includes cardiac failure congestive, left ventricular dysfunction, right ventricular dysfunction

b) Seizure includes generalised tonic-clonic seizure

c) Peripheral neuropathy includes hyperaesthesia, hypoesthesia, paresthesia

d) Speech disorder includes aphasia and dysarthria

e) Motor dysfunction includes muscle spasms

Adult r/r Diffuse Large B-cell Lymphoma (DLBCL)

Table 9-2 Adverse Drug Reactions (≥ 10%) reported in the pivotal adult r/r DLBCL study[1]

Adverse drug reactions	C2201, N=115		
	All grades %	Grade 3 %	Grade 4 %
Blood and lymphatic system disorders			
Anemia	48	37	3
Hemorrhage [a)]	22	3	4
Neutropenia	20	6	14
Febrile neutropenia	17	14	3
Thrombocytopenia	13	3	10
Cardiac disorders			
Arrhythmia [b)]	17	5	0
Gastrointestinal disorders			
Diarrhea	31	1	0
Nausea	29	1	0
Constipation	17	1	0

Adverse drug reactions	C2201, N=115		
	All grades %	Grade 3 %	Grade 4 %
Abdominal pain [c)]	10	2	0
General disorders and administration site conditions			
Pyrexia	35	5	0
Fatigue [d)]	27	6	0
Edema [e)]	23	2	0
Pain [f)]	14	3	0
Chills	12	0	0
Immune system disorders			
Cytokine release syndrome	57	15	8
Hypogammaglobulinemia [g)]	17	6	0
Infections and infestations			
Infections - pathogen unspecified	48	20	6
Bacterial infectious disorders	15	8	0
Fungal infectious disorders	11	4	1
Viral infectious disorders	11	2	0
Investigations			
Weight decreased	12	3	0
Metabolism and nutrition disorders			
Hypokalemia	23	9	0
Hypomagnesemia	17	0	0

Adverse drug reactions	C2201, N=115		
	All grades %	Grade 3 %	Grade 4 %
Hypophosphatemia	17	13	0
Decreased appetite	14	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia	10	0	0
Nervous system disorders			
Headache [h)]	21	1	0
Encephalopathy [i)]	16	7	4
Dizziness [j)]	12	2	0
Psychiatric disorders			
Anxiety	10	1	0
Sleep disorder [k)]	10	0	0
Renal and urinary disorders			
Acute kidney injury [l)]	17	3	3
Respiratory, thoracic and mediastinal disorders			
Dyspnea [m)]	21	4	2
Cough [n)]	17	0	0
Skin and subcutaneous tissue disorders			
Rash [o)]	11	0	0
Vascular disorders			
Hypotension [p)]	25	6	3

Adverse drug reactions	C2201, N=115		
	All grades %	Grade 3 %	Grade 4 %

[1)]The frequency of ADRs observed is the crude incidence rate

[a)] Hemorrhage includes anal hemorrhage, blood urine present, cerebral hemorrhage, contusion, cystitis hemorrhagic, disseminated intravascular coagulation, duodenal ulcer hemorrhage, epistaxis, eye contusion, gastrointestinal hemorrhage, hematemesis, hematochezia, hematuria, large intestinal hemorrhage, melena, mouth hemorrhage, petechie, pharyngeal hemorrhage, post procedural hemorrhage, pulmonary hemorrhage, purpura, retinal hemorrhage, traumatic hematoma, tumor hemorrhage, upper gastrointestinal hemorrhage

[b)] Arrhythmia includes atrial fibrillation, supraventricular tachycardia, tachycardia, ventricular extrasystoles

[c)] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain upper

[d)] Fatigue includes fatigue and malaise

[e)] Edema includes face edema, generalised edema, localized edema, edema peripheral, peripheral swelling

[f)] Pain includes pain and pain in the extremity

[g)] Hypogammaglobulinemia includes blood immunoglobulin G decreased, hypogammaglobulinemia, immunodeficiency, and immunoglobulins decreased

[h)] Headache includes headache and migraine

[i)] Encephalopathy includes cognitive disorder, confusional state, disturbance in attention, encephalopathy, lethargy, memory impairment, mental status changes, metabolic encephalopathy, somnolence, and thinking abnormal

[j)] Dizziness includes dizziness, presyncope, and syncope

[k)] Sleep disorder includes insomnia

[l)] Acute kidney injury includes acute kidney injury, blood creatinine abnormal and blood creatinine increased

[m)] Dyspnea includes dyspnea exertional, respiratory distress, and respiratory failure

[n)] Cough includes cough, productive cough, and upper-airway cough syndrome

[o)] Rash includes dermatitis, dermatitis acneiform, dermatitis contact, rash maculo-papular, rash papular and rash pruritic

[p)] Hypotension includes hypotension and orthostatic hypotension

9.2.2 Less Common Clinical Trial Adverse Reactions (≥1% and <10%)

The ADRs which occurred in the DLBCL study (C2201) with a frequency of ≥1% and <10% were:

Blood and lymphatic system disorders*:* leukopenia, pancytopenia, hemophagocytic lymphohistiocytosis, B-cell aplasia, lymphopenia

Cardiac disorders*:* cardiac arrest, cardiac failure [a)]

Eye disorders: visual impairment [b)]

Gastrointestinal disorders*:* vomiting, stomatitis, dry mouth, abdominal distension, ascites

General disorders and administration site conditions*:* asthenia, influenza-like illness, multiple organ dysfunction syndrome

Heptatobiliary disorders: hyperbilirubinemia

Immune system disorders: infusion related reaction

Investigations: Aspartate aminotransferase increased, blood alkaline phosphatase increased, fibrin d-dimer increased, and serum ferritin increased, blood fibrinogen decreased, blood bilirubin increased, activated partial thromboplastin time prolonged

Metabolism and nutrition disorders*:* hyponatremia, hypocalcemia, hypercalcemia, hyperglycemia, hypoalbuminemia, fluid overload, hyperkalemia, hyperuricemia, tumor lysis syndrome, hypermagnesemia, hypernatremia, hyperphosphatemia

Musculoskeletal and connective tissue disorders: myalgia, back pain, musculoskeletal pain

Nervous System*:* peripheral neuropathy [c)], motor dysfunction [d)], speech disorder [e)], seizure [f)], ischemic cerebral infarction, tremor [g)], ataxia [h)], neuralgia [i)]

Psychiatric disorders: delirium [j)],

Respiratory, thoracic, and mediastinal disorders*:* hypoxia, oropharyngeal pain [k)], pleural effusion, nasal congestion, pulmonary edema [l)], tachypnea

Skin and subcutaneous tissue disorders: night sweats, petechiae, hyperhidrosis, pruritus, erythema

Vascular disorders: thrombosis [m)], hypertension, capillary leak syndrome

[a)] Cardiac failure includes cardiac failure congestive

[b)] Visual impairment includes vision blurred and visual impairment

[c)] Peripheral Neuropathy includes paresthesia, hypoesthesia, hyperaesthesia, peripheral sensory neuropathy, and neuropathy peripheral

[d)] Motor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy

[e)] Speech disorder includes speech disorder, aphasia, and dysarthria

[f)] Seizure includes PTs seizure and status epilepticus

[g)] Tremor includes dyskinesia, and tremor

[h)] Ataxia includes ataxia and dysmetria

[i)] Neuralgia includes neuralgia and sciatica

[j)] Delirium includes delirium, agitation, and irritability

[k)] Oropharyngeal pain includes oral pain and oropharyngeal pain

l) Pulmonary edema includes acute pulmonary edema and pulmonary edema

m) Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis, and venous thrombosis

Description of selected adverse drug reactions

Cytokine release syndrome (CRS)

In the ongoing clinical study in pediatric and young adult B-cell ALL (N=79), serious CRS reactions classified based on the PENN Grading system for CRS (Porter et al 2015) were reported in 77% of patients (48% with Grade 3 or 4) Two deaths occurred within 30 days of KYMRIAH infusion, including one patient, who died from progressive leukemia in the setting of possible CRS and one patient, who experienced fatal intracranial hemorrhage that developed during the course of resolved CRS, abdominal compartment syndrome, coagulopathy and renal failure. Thirty-eight patients were admitted to ICU, 12 patients were intubated, and 8 patients required dialysis during CRS.

In the ongoing clinical study in DLBCL (N=115), CRS was reported in 57% of patients, (22% with Grade 3 or 4), Twenty-seven patients were admitted to ICU, 8 patients were intubated, and 5 patients required dialysis during CRS.

Cytokine release syndrome was graded with the Penn scale as follows: Grade 1: mild reactions, requiring supportive care; Grade 2: moderate reactions, requiring intravenous therapies; Grade 3: severe reactions, requiring low dose vasopressors or supplemental oxygen; Grade 4: life threatening reactions, requiring high dose vasopressors or intubation; Grade 5: death.

For clinical management of CRS, see **WARNINGS AND PRECAUTIONS** and Table 8-1.

Infections and Febrile neutropenia

Infections are common after KYMRIAH infusion and occurred in 34/79 (43%) infused patients with refractory or relapsed ALL. Of these patients, 48% experienced grade 3/4 infection requiring intravenous antibiotics or urgent intervention due to life-threatening consequences in the first 8 weeks following the infusion. The overall incidence was 72% (unspecified 57%, bacterial 27%, viral 38% and fungal 15%) (see **WARNINGS AND PRECAUTIONS**). Forty-three percent of the patients experienced an infection of any type within 8 weeks after KYMRIAH infusion.

In DLBCL patients, severe infections (Grade 3 or 4), which can be life-threatening or fatal, occurred in 34% of patients. The overall incidence (all grades) was 58% (unspecified 48%, bacterial 15%, fungal 11% and viral 11%) (see **WARNINGS AND PRECAUTIONS**). Thirty-four % of the patients experienced an infection of any type within 8 weeks.

Severe febrile neutropenia (Grade 3 or 4) was observed in 34% of pediatric and young adult B-cell ALL patients and in 17% of DLBCL patients. See **WARNINGS AND PRECAUTIONS** for the management of febrile neutropenia before KYMRIAH and after KYMRIAH infusion.

Hematopoietic cytopenias not resolved by day 28

All pediatric and young B-cell ALL patients had a Grade 3 and 4 cytopenia at any time post KYMRIAH infusion. Grade 3 and 4 cytopenias not resolved by day 28 after KYMRIAH infusion were based on laboratory findings included a decreased count of leukocytes (57%), neutrophils (54%), lymphocytes (44%), thrombocytes (42%), and a decreased hemoglobin (13%).

In adult patients with DLBCL 94% had Grade 3 and 4 cytopenias at any time post KYMRIAH infusion. Grade 3 and 4 cytopenias not resolved by 28 days after KYMRIAH infusion based on laboratory findings included a decreased count of thrombocytes (39%), lymphocytes (29%), neutrophils (25%), leukocytes (21%) and decreased hemoglobin (14%).

Neurological/Neurotoxic events

The majority of neurotoxic events occurred within 8 weeks following infusion and were transient.

In pediatric and young adult B-cell ALL patients, manifestations of encephalopathy and/or delirium occurred in 39% of patients (10% Grade 3 or 4) within 8 weeks after KYMRIAH infusion. In DLBCL patients, these occurred in 21% of patients (12% were Grade 3 or 4) within 8 weeks after KYMRIAH infusion.

The other most common neurological event was headache (35% in pediatric and young adult B-cell ALL patients and 21% in DLBCL patients).

9.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hematology laboratory abnormalities are presented in Table 9-3.

Table 9-3 Hematology laboratory abnormalities post-KYMRIAH infusion[1] based on CTCAE

	Ped ALL (N=79)		DLBCL (N=115)	
Laboratory parameter	**All Grades (%)**	**Grades 3 and 4 (%)**	**All Grades (%)**	**Grades 3 and 4 (%)**
Leukocytes decreased	100	97	99	78
Hemoglobin decreased	100	48	99	59
Neutrophil count decreased	100	95	97	82
Lymphocyte count decreased	100	96	100	95
Platelet count decreased	97	77	95	56

[1]Patients are counted only for the worst grade observed post-baseline.

Selected biochemistry laboratory abnormalities worsening from baseline Grades 0-2 to Grades 3-4 are shown in Table 9.4 and Table 9.5.

Table 9-4 Biochemistry laboratory abnormalities worsening (> 10%) from Baseline Grade 0-2 to Grade 3-4 following treatment with KYMRIAH infusion in Pediatric and Young Adult r/r B-cell ALL based on CTCAE

	Ped ALL (N=79)
Laboratory parameter	**Grades 3 and 4 (%)**
Aspartate Aminotransferase increased	29
Hypokalemia	27
Hypophosphatemia	19
Blood Bilirubin increased	19
Alanine Aminotransferase increased	22
Glucose increased	27

Table 9-5 Biochemistry laboratory abnormalities worsening (> 10%) from Baseline Grade 0-2 to Grade 3-4 following treatment with KYMRIAH infusion in Adult r/r DLBCL Patients based on CTCAE

	DLBCL (N=115)
Laboratory parameter	**Grades 3 and 4 (%)**
Hypophosphatemia	22
Hypokalemia	13
Hypoalbuminemia	10

9.4 Post-Marketing Adverse Reactions

The following adverse drug reactions have been derived from post-marketing experience with KYMRIAH

via spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to tisagenlecleucel exposure.

Frequency not known: anaphylactic reaction/infusion related reaction.

10 DRUG INTERACTIONS

10.1 Overview

The co-administration of agents known to inhibit T-cell function has not been formally studied. T cells are known to be susceptible to immune suppressive agents. The benefit/risk of immuno-suppressive agents including but not limited to corticosteroids, cytotoxic chemotherapy, immunophilins, mTOR inhibitors, should be considered as these agents can be lymphotoxic and may reduce the effectiveness of KYMRIAH. In patients who received tocilizumab and corticosteroids as per the cytokine release syndrome treatment algorithm, tisagenlecleucel transgene levels continued to expand and persist.

The co-administration of agents known to stimulate T cell function has not been investigated and the effects are unknown.

10.2 Drug-Drug Interactions

Pharmacokinetic interactions

No pharmacokinetic drug interaction studies have been performed with KYMRIAH.

The immunization with live vaccines during or following KYMRIAH treatment has not been studied. Vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during KYMRIAH treatment, and until immune recovery following treatment with KYMRIAH.

10.3 Drug-Laboratory Test Interactions

Interference with HIV nucleic acid tests (NAT)

Due to limited short spans of identical genetic information between the lentiviral vector used to create KYMRIAH and HIV, some commercial HIV nucleic acid tests may give a false positive result if the subject has received KYMRIAH

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Tisagenlecleucel is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and

eliminate CD19-expressing malignant and normal cells. The CAR is comprised of a murine single chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T cell activation and antitumor activity while 4-1BB enhances the expansion and persistence of tisagenlecleucel. Upon binding to CD19 expressing cells, the CAR transmits a signal to promote T cell expansion, activation, target cell elimination and persistence of tisagenlecleucel.

11.2 Pharmacodynamics

Among 22 evaluable pediatric and young adult B-cell ALL patients with an ongoing remission at Month 18, 6 (27.3%) and 21 (95.5%) patients reported B cell aplasia (functional marker for CAR T cell persistence: peripheral blood CD19+ B cells <1% among viable WBC or <3% among lymphocyte) at baseline and Month 18, respectively.

In JULIET, most patients had B cell depletion at baseline from previous treatment. Recovery of B cell levels were observed with longer follow-up in some of the responding DLBCL patients after KYMRIAH infusion. Among 26 evaluable DLBCL patients who were responders at Month 18, 25 (96.2%) and 14/23 (60.9%) patients reported B cell aplasia (peripheral blood CD19+ B cell levels < 80 cells/µL) at baseline and Month 18, respectively.

11.3 Pharmacokinetics

Cellular kinetics

Following infusion in pediatric and young adult patients with r/r B cell ALL and in patients with r/r DLBCL, tisagenlecleucel typically exhibited an initial rapid expansion followed by a slower bi-exponential decline. A summary of cellular kinetic parameters estimated from the time course of CAR transgene levels, measured by quantitative polymerase chain reaction (qPCR), following administration of tisagenlecleucel in B-cell ALL and DLBCL patients is provided in Table 11-1 below.

Pediatric and Young Adult Patients with r/r B-cell ALL (≥3 to 25 years)

The maximal expansion (C_{max}) was approximately 61.2% higher in complete response/complete response with incomplete blood count (CR/CRi) patients (n=105) compared with non-responding (NR) patients (n=10) as measured by qPCR. The blood to bone marrow partitioning of tisagenlecleucel in bone marrow was 47.2% of that in peripheral blood at Day 28 while at Months 3 and 6 it distributed at 68.3% and 69%, respectively. CAR transgene was detectable in cerebrospinal fluid in pediatric and young adult B-cell ALL patients. Presence of transgene was detected up to 916 days in peripheral blood in responding patients based on the pooled data from Studies B2202 and B2205J. Delayed and lower expansion was observed in non-responding patients (N=12) compared to responding patients (N=105).

Adult Patients with r/r DLBCL

Tisagenlecleucel underwent significant expansion following infusion.

$AUC_{0\text{-}28d}$ and C_{max} were similar between responder (CR and PR) and non-responder patients (SD, PD, and patients with unknown response status) based on clinical response at month 3. Transgene expression was detected up to 1030 days in responding patients and 685 days in non-responding patients. Transgene persistence results should be interpreted with caution, as they were affected by duration of follow-up.

The blood to bone marrow partitioning in bone marrow was approximately 70% of that present in blood at Day 28 and 50% at Month 3 in responder and non-responder patients. The CNS distribution of tisagenlecleucel in DLBCL patients was not studied.

Table 11-1 Cellular kinetic parameters[#] of tisagenlecleucel in pediatric and young adult patients with r/r B-cell ALL and adult patients with r/r DLBCL patients

Parameter	Summary Statistics	Pediatric ALL Responding Patients N=105	Pediatric ALL Non-Responding Patients N=12	r/r DLBCL Responding Patients (CR and PR) N=43	r/r DLBCL Non-Responding Patients (SD/PD/Unknown) N=72
C_{max} (copies/µg)	Geometric mean (CV%), n	35,300 (154.0), 103	21,900 (80.7), 10	5840 (254.3), 43	5460 (326.8), 65
T_{max} (day)	Median [min;max], n	9.83 [5.70;27.8], 103	20.1 [12.1;62.7], 10	9.00 [5.78;19.8], 43	8.84 [3.04;27.7], 65
AUC_{0-28d} (copies/µg*day)	Geometric mean (CV%), n	309,000 (178.1), 103	232,000 (104.5), 8	61200 (177.7), 40	67000 (275.2), 56
$T_{½}$ (day)[§]	Geometric mean (CV%), n	25.2 (307.8), 71	3.80 (182.4), 4	129 (199.2), 33	14.7 (147.1), 44

N is equal to the total number of patients and n is the number of patients with evaluable PK parameter

[#]parameters estimated from time course of transgene levels (copies of transgene/µg genomic DNA) as measured by qPCR

[§] T½ can be influenced by various factors e.g. patient drop out, early termination, data cut-off date and small patient numbers (in subgroups), and hence should be interpreted with caution.

The cellular kinetic parameter summary for pediatric and young adult ALL patients is based on pooled results from Studies B2202 and B2205J, and summary for adult DLBCL patients is based on Study C2201. See **CLINICAL TRIALS**

Study B2205J was a phase II, single-arm, multicenter trial to determine the efficacy and safety of tisagenlecleucel in pediatric patients with relapsed and refractory B-cell ALL.

Linearity/non-linearity: There is no apparent relationship between dose and AUC_{0-28d} or C_{max}.

Special Populations and Conditions

Age: The impact of age on cellular kinetics was evaluated across the age range of 22 to 76 years in DLBCL patients (Study C2201). The AUC_{0-28d} in patients with ≥65 years of age was observed to be 49.1% and 64.0% lower than patients ≥40 to <65 years and <40 years, respectively. In pediatric and young adult patients with B-cell ALL (Studies B2201 and B2205J), Children < 10 years and between 10-18 years of age had 1.2- to 1.8-fold higher C_{max} and AUC_{0-28d} than young adults (>18 years of age). The clinical implication of these observations is unclear based on the available evidence due to high inter-individual variability associated with the exposure parameters.

Sex: No clinical meaningful difference in tisagenlecleucel cellular kinetics was observed between male and female patients with r/r B-cell ALL or DLBCL.

Body weight: In both B-cell ALL and DLBCL patients, across the weight ranges (14.4 to 137.0 kg, in B-cell ALL patients; and 38.4 to 186.7 kg in DLBCL patients), no clinically meaningful relationship between cellular kinetics and body weight was observed.

Ethnic origin/Race: The impact of ethnicity on cellular kinetics could not be characterized, as the majority of patients treated with KYMRIAH in clinical studies were Caucasian.

Hepatic Insufficiency: No formal hepatic impairment studies were performed.

Renal Insufficiency: No formal renal impairment studies were performed.

Prior stem cell transplantation: In patients with r/r DLBCL, the geometric mean C_{max} in patients who did not receive prior hematopoietic stem cell transplantation (HSCT) therapy (n=43) was approximately 57.8% higher than that in patients who received prior HSCT therapy (n=48). The clinical implication of this observation is unclear based on the available evidence. In pediatric and young adult patients with r/r B-cell ALL, no clinically meaningful difference in cellular kinetics was observed depending on the history of prior HSCT.

Immunogenicity

In clinical studies, humoral immunogenicity of tisagenlecleucel was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients tested positive for pre-dose anti-mCAR19 antibodies in pediatric and young adult B-cell ALL (91.1%) and adult DLBCL (93.9%) patients.

Treatment induced anti-mCAR19 antibodies were detected in 40.5% of pediatric and young adult ALL and 8.7% of adult DLBCL patients.

There was no evidence that the presence of pre-existing and treatment-induced anti-mCAR19 antibodies significantly impacted the cellular kinetics and clinical responses.

Cellular immunogenicity was assessed in B-cell ALL and r/r DLBCL patients by determination of intracellular interferon gamma production in response to mCAR19 peptide stimulation. No apparent relationship was observed between cellular immunogenicity responses and the cellular kinetics and clinical responses.

12 STORAGE, STABILITY AND DISPOSAL

12.1 Incompatibilities

In the absence of compatibility studies, this product must not be mixed with other medicinal products.

12.2 Special precautions for storage

KYMRIAH must be stored in a temperature monitored system at ≤ -120°C. The expiry date is indicated on the product label. Do not thaw the product until it is ready to be used.

KYMRIAH must be kept out of the reach and sight of children.

12.3 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Refer to local biosafety guidelines applicable for handling and disposal of products containing genetically-modified organisms.

KYMRIAH products should be transported within the facility in closed, break-proof, leak-proof containers.

Solid and liquid waste: All material having been in contact with KYMRIAH should be handled and disposed of as potentially infectious waste in accordance with local hospital procedures.

13 Special Handling Instructions

KYMRIAH contains genetically-modified blood cells. When handling KYMRIAH, healthcare professionals must take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases as for any human-derived materials. Local biosafety guidelines applicable for handling and disposal of such products should be followed.

PART II: SCIENTIFIC INFORMATION

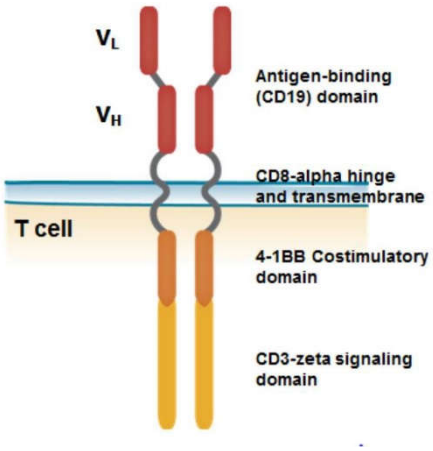
14 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: tisagenlecleucel

Chemical name: Not established

Structure of the chimeric antigen receptor:



Physicochemical properties: Appearance: Colorless to slightly yellow suspension of cells

Product Characteristics

Autologous T-cells genetically modified *ex vivo* using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR).

15 CLINICAL TRIALS

Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

The efficacy of KYMRIAH treatment in pediatric and young adult patients with relapsed or refractory (r/r) B cell ALL was evaluated in one pivotal (B2202) open label, single-arm study of 75 infused patients, who were up to 25 years of age. All patients had leukapheresis products collected and cryopreserved prior to or during study entry.

Trial Design and Study Demographics

Table 15-1 Summary of patient demographics for the pivotal pediatric and young adult r/r B-cell ALL study (B2202)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study B2202 (ELIANA)	Phase II, Multicenter, single-arm, open-label study / Pediatric and young adult patients with relapsed or refractory B-cell ALL	Tisagenlecleucel single infusion For patients ≤50Kg: 0.2 to 5.0x10^6 transduced viable T-cells / kg body weight For patients >50Kg: 0.1 to 2.5x10^8 transduced viable T-cells	N enrolled: 92 N infused: 75	Mean = 12.0 (3-23)	Female: 32 (42.7) Male: 43 (57.3)

The efficacy of KYMRIAH treatment in patients with relapsed and refractory (r/r) pediatric and young adults B-cell ALL, evaluated in Study CCTL019B2202.

Study CCTL019B2202

The pivotal study (B2202) is a multicenter, single-arm, open-label phase II study in pediatric and young adult patients with r/r B-cell acute lymphoblastic leukemia. Ninety-two patients were enrolled, 75 were infused; 17 patients discontinued prior to KYMRIAH infusion (7 patients due to death; 7patients due to KYMRIAH manufacturing related issues; 3 patients due to adverse events). All patients had leukapheresis products collected and cryopreserved prior to or during study entry.

Patients infused were between the age of 3 and 23 years and 8% had primary refractory disease. Sixty-one percent of patients had a prior stem cell transplant. The majority of patients (65/75, 86.7%) received bridging therapy while waiting for KYMRIAH. A total of 72 out of 75 patients who received KYMRIAH infusion also received lymphodepleting chemotherapy after enrollment and prior to the KYMRIAH infusion.

Study Results

Efficacy was established through the primary endpoint of overall remission rate (ORR), which includes best overall response as complete remission (CR) or complete remission with incomplete blood count (CRi) within 3 months post infusion, as determined by Independent Review Committee (IRC) assessment. Secondary endpoints included duration of remission (DOR), and the proportion of patients who achieved CR or CRi with minimal residual disease (MRD) <0.01% by flow cytometry (MRD-negative). The median time from KYMRIAH infusion to the data cut-off date was 13.11 months (range: 2.1 to 23.5). The ORR within 3 months was 81.3% (61/75) (95%CI: 70.7, 89.4). See Table 15-2 for efficacy results from this study. The minimum follow-up time was 1.2+ months and the median duration of response (DOR) was not reached with a 95% confidence interval (CI) of (8.6 months, NE).

Table 15-2 B2202: Efficacy results in pediatric and young adult patients with relapsed/refractory B-cell Acute Lymphoblastic Leukemia (ALL)

	Median time from KYMRIAH infusion to data cut-off **13.1 Months**
Primary Endpoint	**N=75**
Overall Remission Rate (ORR) [1], n (%)	61 (81.3)
95% CI	(70.7, 89.4)
	p<0.0001[2]
CR [3], n (%)	45 (60.0)
CRi [4], n (%)	16 (21.3)
NR[5], n (%)	6 (8.0)
Not evaluable, n (%)	8 (10.7)
Key Secondary Endpoint	**N=75**
CR or CRi with MRD negative bone marrow [6,7], n (%)	61 (81.3)
95% CI	(70.7, 89.4)

	p<0.0001[7]
Duration of remission (DOR)[8]	**N=61**
Duration of response lasting at least 6 months, n (%)[9]	33 (54.1)
Median (months)	Not reached
(95% CI)	(8.6, NE[11])
Range[10]	(1.2+ to 19.3+)
Median Follow-up (95%CI)[12]	10.4 (7.5, 11.1)

[1] Requires remission status to be maintained for at least 28 days without clinical evidence of relapse.

[2] Nominal one-sided exact p-value based on H0: ORR ≤ 20% vs. Ha: ORR >20%.

[3] CR (complete remission) was defined as <5% of blasts in the bone marrow, circulating blasts in blood should be <1%, no evidence of extramedullary disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter) without blood transfusion.

[4] CRi (complete remission with incomplete blood count recovery) was defined as <5% of blasts in the bone marrow, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion.

[5] NR = No Response

[6] MRD (minimal residual disease) negative was defined as MRD by flow cytometry <0.01%.

[7] Nominal one-sided exact p-value based on H0: Rate of MRD negative remission ≤ 15% vs. Ha: > 15%.

[8] DOR was defined as time since onset of CR or CRi to relapse or death due to underlying indication, whichever is earlier (N= 61 for median follow-up of 9.4 months)

[9] Proportion of patients who had duration of response at Month 6 among all the complete responders (CR / CRi) without considering patients might be censored earlier than Month 6.

[10] The Range for median follow-up of 9.4 months includes the 49.2% of patients censored due to ongoing without an event, the 11.5% due to HSCT, the 9.8% of patients censored due to other cancer therapies, and the 1.6% of patients due to other reasons (Note: the 'other' group accounts for the individual that withdrew consent and the individual that was censored due to no more adequate assessments), and the 27.9% of patients had events as disease progression

[11] NE= Not estimable

[12] Kaplan-Meier estimate in months

An updated analysis with longer follow-up was conducted with median time from KYMRIAH infusion to the data cut-off date of 24.2 months (range: 4.5 to 35.1). As of this cutoff, 97 patients were enrolled, 79 were infused; 18 patients discontinued prior to KYMRIAH infusion. Among the 79 infused patients, the ORR by independent review was 82.3% (65/79), the CR rate was 62.0% (49/79) and the CRi rate was 20.3% (16/79). CR or CRi with MRD negative bone marrow was observed among 64 patients (81.0%). The updated median duration of follow-up among responders was 17.5 months (95%CI: 11.1, 20.3) as estimated by the reverse Kaplan-Meier method. The median duration of response was not reached (95%CI: 20.0, not estimable). Among complete responders (CR+CRi) and without accounting for censoring

(N=65), 25 patients *(38.5%)* had a duration of response lasting at least 12 months and 21 patients *(32.3 %)* had a duration of response lasting at least 18 months.

Diffuse Large B-cell Lymphoma (DLBCL)

Trial Design and Study Demographics

Table 15-3 Summary of patient demographics for the pivotal adult r/r DLBCL study (C2201)

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n)**	**Median age (Range)**	**Sex**
Study C2201 (JULIET)	Multicenter, single-arm, phase II, open label study in adult patients with relapsed or refractory DLBCL	Tisagenlecleucel single infusion **Dose Range:** 1.0 x 10^8 to 5 x 10^8 CAR + viable T cells	Enrolled: N= 160	59 (22.0-76.0)	F=59 (36.9%) M= 101 (63.1%)
			Infused: N= 106	57 (22.0-76.0)	F=39 (36.8) M=67 (63.2)
			Evaluable for efficacy: N=68	56 (22.0-74.0)	F=20 (29.4) M=48 (70.6)

The efficacy of KYMRIAH treatment in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL), was evaluated in study CCTL019C2201.

Study CCTL019C2201

The pivotal study (C2201) is a multicenter, single-arm phase II study in adult patients with relapsed or refractory DLBCL. Of 160 patients enrolled, 106 patients received infusion with KYMRIAH including 92 patients who received product manufactured in the U.S., and who were followed for at least 3 months or discontinued earlier. Fifty-four (54) patients did not receive infusion due to the following reasons: KYMRIAH could not be manufactured (n=11); death (n=16), physician decision/primary disease progression (n=16), adverse events (n=3), subject decision (n=2) and protocol deviation (n=1). Among the

92 patients who received infusion with KYMRIAH, 68 patients were evaluable for efficacy. Patients were excluded if they were in complete remission after bridging chemotherapy and before infusion (8 patients) or if they did not have a disease assessment after bridging chemotherapy but before infusion (15 patients), and 1 was excluded because of initial misclassification of a neuroendocrine tumor as DLBCL.

The median age of the 68 patients included in the efficacy analysis was 56 years (range 22 to 74 years), 81% of patients had Stage III-IV disease, 53% received 3 or more prior lines of treatment for DLBCL. Forty-four percent of patients had received prior stem cell transplant. Fifty-six percent of patients were refractory to the last line of treatment. All patients had leukapheresis starting material collected and cryopreserved prior to or during study entry. The majority of patients (60/68) received bridging therapy while waiting for KYMRIAH and 90% received lymphodepleting chemotherapy. KYMRIAH was given as a single dose intravenous infusion. 78% had primary DLBCL not otherwise specified (NOS) and 22% had DLBCL following transformation from follicular lymphoma, of whom 17% were identified as high grade lymphoma; 15% had either double or triple hits in MYC/BCL2/BCL6 genes, 57% had Germinal center B-cell (GCB) type cell of origin and 40% had non-GCB type.

Patients with T-cell rich/histiocyte-rich large B-cell lymphoma (THRBCL), primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), EBV-positive DLBCL of the elderly, prior allogeneic HSCT, ECOG performance ≥2, auto-immune disease, ongoing infections such as HIV, HBV, HCV, active CNS disease or other ongoing neurological disease (e.g., Guillain-Barré) were not enrolled in the study.

The efficacy of KYMRIAH was evaluated through the primary endpoint of best overall response rate (ORR), which includes complete response (CR) and partial response (PR) as determined by an independent review committee (IRC) assessment based on the Lugano Classification (Cheson et al 2014). Secondary endpoints included duration of response (DOR).

Among the 68 patients (Table 15-4) included in the primary analysis, the best ORR was 50.0% (34/68) with a 95% confidence interval (CI) of (37.6%, 62.4%). Twenty-two patients (32.4%) achieved CR and 12 (17.6%) achieved PR. The median duration of response (DOR) was not reached (95% CI: 5.1, NE). Response durations were longer in patients who achieved CR (median not reached, 95% CI: 10.0, NE), as compared to patients with a best response of PR (median DOR 3.4 months). No patient who received KYMRIAH infusion went to transplant while in response. See Table 15-4 for efficacy results of this study.

Study Results

Table 15-4 Efficacy results in adult patients with r/r DLBCL (C2201)

	Median time from KYMRIAH infusion to data cut-off **9.4 Months**
Primary Endpoint	**N=68**
Overall Response Rate (ORR) (CR+PR), n (%)	34 (50%)
(95% CI) [d]	(37.6, 62.4)

Complete Response (CR), n (%)	22 (32%)
(95% CI) [d]	(21.5, 44.8)
Partial Response (PR), n (%)	12 (18%)
(95% CI) [d]	(9.5, 28.8)
Duration of response (DOR)	N=34
Overall DOR for responders (months)	
Median (months) (95% CI) [a,b,d]	Not reached (5.1, NE)
Range [c]	(0.03+ to 11.3+)
Median Follow-up (95%CI) [b,d]	9.4 (7.9, 10.8)
Duration of response lasting at least 9 months, n (%)[e]	11 (32.4)
DOR if BOR is CR	N = 22
Median (months) (95% CI) [a,b,d]	NE (10.0, NE)
Range [c]	(1.5+ to 11.3+)
DOR if BOR is PR	N=12
Median (months) (95% CI) [a,b,d]	3.4 (1.0, NE)
Range [c]	(0.03+ to 11.3+)

CR, Complete Response; DOR, Duration of Response: NE, not estimable, PR, partial response

[a] Among all responders. DOR measured from date of first objective response to date of progression or death from relapse.

[b] Kaplan-Meier estimate in months

[c] A + sign indicates a censored value (follow-up of 9.5 months). 55.9% of patients censored due to ongoing without an event, 8.8% of patients censored due to new cancer therapy, other than HSCT, 2.9% of patients censored due to death due to reason other than DLBCL, and the 35.5% had disease progression or death due to DLBCL.

[d] The 95% CIs were exact Clopper-Pearson Cis

[e] Proportion of patients who had duration of response at Month 9 among all the complete responders (CR / CRi) without considering patients might be censored earlier than Month 9.

An updated analysis with longer follow-up was conducted with median time from KYMRIAH infusion to the data cut-off date of 22.7 months (range: 20.8-23.1). As of this cut-off, 167 patients were enrolled, 115 were infused and 52 patients discontinued prior to KYMRIAH infusion. Among the 115 patients who received infusion with KYMRIAH, 75 patients were evaluable for efficacy. Among the 75 evaluable patients, the ORR by independent review was 53.3% (40/75), the CR rate was 38.7% (29/75) and the PR rate was 14.7% (11/75). The median duration of response was not reached (95%CI: 5.8, not estimable). Among these 29 patients, 13 patients initially had an overall disease response of PR which improved to CR over time; in most of these cases (11/13) PR to CR conversion occurred within 6 months post-tisagenlecleucel infusion. The updated median duration of follow-up among responders was 22.7 months (95%CI: 20.8, 23.1) as estimated by the reverse Kaplan-Meier method. The median durations of response

among patients who achieved either CR or PR were 20.8 months (95%CI: 18.7, not estimable) and 1.6 months (95%CI: 0.8, 3.4), respectively. Among all the 40 responders (CR+PR), and without accounting for censoring, 19 patients (47.5%) had a duration of response lasting at least 12 months and 17 patients (42.5%) had a duration of response lasting at least 18 months.

16 NON-CLINICAL TOXICOLOGY

In vitro and in vivo non-clinical studies assessed KYMRIAH's biodistribution, persistence, and potential for uncontrolled cellular proliferation. KYMRIAH was predominantly detected in the spleen, lung, kidney, and bone marrow and persisted for up to 217 days post-injection in xenograft mouse models of leukemia. Neither the *in vitro* nor the *in vivo* studies suggested that KYMRIAH was associated with uncontrolled cellular proliferation.

Safety pharmacology and repeated dose toxicity

Safety pharmacology studies were not conducted.

No repeated dose toxicity studies were conducted.

Carcinogenicity and mutagenicity

Genotoxicity assays and carcinogenicity studies in rodent models were not performed for KYMRIAH.

In vitro expansion studies with CAR-positive T-cells (tisagenlecleucel) from healthy donors and patients showed no evidence for transformation and/or immortalization of T-cells. *In vivo* studies in immunocompromised mice did not show signs of abnormal cell growth or signs of clonal cell expansion for up to 7 months after receiving KYMRIAH. A genomic insertion site analysis of the lentiviral vector was performed on KYMRIAH products from 14 individual donors (12 patients and 2 healthy volunteers). There was no evidence for preferential integration near genes of concern or preferential outgrowth of cells harboring integration sites of concern.

Reproductive toxicity

No non-clinical reproductive safety studies were conducted.

Juvenile animal studies

Juvenile toxicity studies were not conducted.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrKYMRIAH®
[Kim-RAH-ya]

(Tisagenlecleucel)

Read this carefully before you start taking KYMRIAH®. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about KYMRIAH.

Serious Warnings and Precautions

The following serious side effects have been seen in people taking KYMRIAH:

- High fever and chills which may be symptoms of a serious condition called Cytokine Release Syndrome (CRS). Other symptoms of CRS are difficulty breathing, nausea, vomiting, diarrhea, muscle pain, joint pain, low blood pressure, or dizziness/light-headedness.
- Neurological problems like altered or decreased consciousness, delirium, confusion, agitation, seizures, difficulty speaking and understanding speech, loss of balance

KYMRIAH should only be administered by an experienced healthcare professional at specialized treatment centres.

What KYMRIAH is

KYMRIAH is made from some of your own normal white blood cells called T-cells. T-cells are important for your immune system (the body's defences) to work properly. KYMRIAH comes in infusion bags.

What is KYMRIAH used for?

KYMRIAH is used to treat:

- B-cell acute lymphoblastic leukemia (B-cell ALL) - a form of cancer composed of some types of white blood cells that have become malignant. It can be used in children and young adults up to and including 25 years of age.
- Diffuse large B-cell lymphoma (DLBCL) - a form of cancer composed of some types of white blood cells that have become malignant, mostly in the lymph nodes. KYMRIAH can be used in adults (18 years of

age or older) for whom DLBCL has returned after other treatments or when other treatments did not work.

How does KYMRIAH work?

The normal T-cells are taken from your blood and a new gene is put into the T-cells so that they can target the cancer cells more effectively. When KYMRIAH is infused into your blood, the modified T-cells find and kill the cancer cells.

If you have any questions about how KYMRIAH works or why this medicine has been prescribed for you, ask your doctor.

What are the ingredients in KYMRIAH?

Medicinal ingredients: tisagenlecleucel

Non-medicinal ingredients: Dextran, dextrose, dimethylsulfoxide (DMSO), human serum albumin, plasma-Lyte A (multiple electrolytes for injection, Type 1, pH 7.4), and sodium chloride.

KYMRIAH comes in the following dosage forms:

KYMRIAH is provided as a cell suspension in one or more infusion bags. KYMRIAH is administered as an intravenous infusion for one time only.

What KYMRIAH looks like:

KYMRIAH is supplied as an infusion bag containing a cloudy to clear, colorless to slightly yellow suspension of cells (tisagenlecleucel).

Do not use KYMRIAH:

If you are allergic (hypersensitive) to tisagenlecleucel or any of the other ingredients of KYMRIAH.

If you think you may be allergic, ask your doctor for advice.

To help avoid side effects and ensure proper use, talk to your healthcare professional before receiving KYMRIAH. Talk about any health conditions or problems you may have, including:

- If you have had a stem cell transplantation in the last 4 months. Your doctor will check if you have signs or symptoms of graft versus host disease (GvHD). This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhea and bloody stools.
- If you have any lung or heart or blood pressure problems.
- If you notice the symptoms of your lymphoma or leukemia are getting worse. If you have leukemia

this might include fever, feeling weak, bleeding gums, bruising. If you have lymphoma, this might included unexplained fever, feeling weak, night sweats, sudden weight loss.

- If you have had hepatitis B (HPV), hepatitis C (HBC) or human immunodificiency virus (HIV) infection.
- If you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.
- If you are pregnant, think you may be pregnant, or plan to become pregnant (see section Pregnancy and breast-feeding and Contraception for women and men).
- If you have an infection. The infection will be treated before the KYMRIAH infusion.

Monitoring before and after your treatment with KYMRIAH

Before receiving KYMRIAH

Before you are given KYMRIAH infusion, your doctor will:

- Check your lung, heart and blood pressure functions.
- Check to see if you are pregnant.
- Look for any signs of infection. Any active infection will be treated before administration of KYMRIAH.
- Check if your lymphoma or leukemia is getting worse.
- Check for signs of a medical complication called “graft versus host disease (GvHD)” that may occur usually after a prior transplant.
- Check your blood for uric acid and how many cancer cells there are in the blood. This will show if you are likely to have ‘tumor lysis syndrome (TLS)’ - if needed, you will be given medicines to help reduce the chance of this.
- Check if you have any antibodies to hepatitis B or C or HIV in the blood.

After receiving KYMRIAH

- Your doctor will regularly monitor your blood counts after you receive KYMRIAH as you may experience a reduction in the number of blood cells and blood components such as decreases in different types of normal white blood cells and/or a reduction on your normal antibodies that help fight infection.
- Your doctor will regularly check for signs of cytokine release syndrome or neurological problems
- Some types of HIV testing may be affected – ask your doctor about this.
- Do not donate blood, organs, tissues, sperms, oocytes and other cells.
- You should be monitored life-long to check if your lymphoma or leukemia returns or a new cancer occurs. In the event that a new cancer occurs, your doctor or you should contact Novartis (mykymriah.cart@novartis.com or 1-833-395-2278).
- You should be monitored for neurological events.

- You should be monitored for signs and symptoms of infection.
- You should be monitored for signs and symptoms of TLS.

Children

KYMRIAH has not been studied in children and adolescents below 18 years of age with diffuse large B-cell lymphoma and should not be administered in this age group for diffuse large B-cell lymphoma.

Older people (above 65 years of age)

Patients aged 65 years or older with diffuse large B-cell lymphoma can be administered KYMRIAH in the same way as younger adults.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with KYMRIAH:

- 'Live' vaccines – in particular, do not receive 'live' vaccines:

  - In the 6 weeks before being given a short course of chemotherapy ("lymphodepleting" chemotherapy) to prepare your body for the KYMRIAH cells

  - During KYMRIAH treatment

  - After treatment while the immune system is recovering.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor for advice before taking KYMRIAH. This is because the effects of KYMRIAH in pregnant or breast feeding women are not known, and it may harm your unborn baby or your newborn/infant.

Your doctor will check with you if you are pregnant.

If you become pregnant or think you may be pregnant after treatment with KYMRIAH, talk to your doctor immediately.

Your doctor will discuss with you the potential risk(s) of receiving KYMRIAH during pregnancy or breast-feeding.

Contraception for women and men

Women of child-bearing potential should use effective birth control after being given Kymriah. Ask your doctor about options of effective birth control.

Sexually active males receiving KYMRIAH should use a condom for intercourse.

Discuss pregnancy or fathering a child with your doctor if you have received KYMRIAH.

Driving and using machines

Do not drive, use machines, or take part in activities that need you to be alert. KYMRIAH can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks following infusion.

How you will receive KYMRIAH:

KYMRIAH will always be given to you by a qualified health care professional in a qualified treatment center.

KYMRIAH contains human blood cells. Your doctor handling KYMRIAH will therefore take appropriate precautions (wearing gloves and glasses for example) to avoid potential transmission of infectious diseases.

Collection of blood to manufacture KYMRIAH

KYMRIAH is made from your own white blood cells.

- Your doctor will take some of your blood using a tube placed in your vein - this is called 'leukapheresis'. This can take 3 to 6 hours and may need to be repeated.
- Your blood cells are frozen and sent away to manufacture KYMRIAH. It takes about 3 to 4 weeks to make KYMRIAH, but the time may vary.
- While awaiting KYMRIAH manufacture, the underlying disease may worsen and progress and your healthcare provider may give you therapy to stabilize your cancer. This may induce side effects which can be severe or life-threatening. The treating physician will inform you about potential side effects of this therapy.
- In addition, before you get KYMRIAH, your healthcare provider may give you chemotherapy for a few days to prepare your body.
- KYMRIAH is a treatment that is manufactured specifically for you. There are situations where KYMRIAH cannot be successfully manufactured and be given to you. In some cases, a second manufacturing of KYMRIAH may be attempted.

Medicines given before KYMRIAH administration

During the 30 to 60 minutes before being given KYMRIAH you may receive other medicines to help to reduce infusion reactions and/or fever. These may include acetaminophen and an H1 antihistamine such as diphenhydramine.

How you are given KYMRIAH

- Your doctor will check that the individual patient identifiers on the KYMRIAH infusion bag match up to you.
- Your doctor will give KYMRIAH by infusion, which means it will be given as a drip through a tube in your vein. This usually takes less than 1 hour.

KYMRIAH is a one-time treatment.

After you are given KYMRIAH

Plan to stay within proximity (2 hours' travel) from the hospital where you were treated for at least 4 weeks after you have been given Kymriah. Your doctor will recommend that you return to the hospital 2 to 3 times a week for at least the first week and will consider whether you need to stay at the hospital as an in-patient after infusion. This is so your doctor can check if your treatment is working and help you if you have any side effects.

What are possible side effects from using KYMRIAH?

Listed below are the most common (but not all) possible side effects you may feel when taking KYMRIAH. If you experience any side effects, including those not listed here, contact your healthcare professional.

Very common:

- Abdominal pain, constipation, weight loss
- Muscle weakness, muscle spasms
- Excessive emotional distress (anxiety)
- Sleep disturbances
- Muscle cramps
- Symptoms of high blood sugar like thirst, low urine output, dark urine, dry flushed skin, irritability
- Swelling of the arms or legs

Common:

- Swelling of the belly
- Changes or loss of vision
- Sore throat, stuffy nose, flu-like symptoms
- Bloating, mouth sores, dry mouth

- Skin reactions such as rash, hot flushes, night sweats, itching (pruritus), skin reddening (erythema), excessive sweating (hyperhidrosis)

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
VERY COMMON		
Fever, chills, shivering, nausea, vomiting, tiredness, dizziness, pain where the infusion needle is inserted, blisters, itching, and/or shortness of breath or wheezing during or shortly after infusion (possible infusion reaction)		**√**
Feeling warm, fever, chills or shivering, coughing (possible symptoms of an infection)		**√**
Bleeding or bruising more easily (possible symptoms of low levels of cells in the blood known as platelets)		**√**
Frequent infections, weakness, fatigue, fever, chills and/or shivering, sore throat, mouth ulcers , rash, swelling, yellow or pale skin, yellow eyes, uncontrolled internal or external bleeding, blood in the urine, breathlessness, abnormal body movement, irritability (possible symptoms of blood disorders)		**√**
Extreme tiredness, weakness and shortness of breath (may be symptoms of a lack of red blood cells)		**√**
High fever, chills, muscle pain, joint pain, nausea, vomiting, diarrhea, excessive sweating, rash, loss of appetite, fatigue, headache, dizziness/light‑headedness, shortness of breath, heavy breathing, rapid breathing, blue discoloration of lips or extremities (possible symptoms of CRS)		**√**
Side effects affecting the respiratory organs, like, coughing, rapid breathing, painful breathing, shortness of breath or labored breathing, breathlessness (possible symptom of pulmonary edema, a build-up of fluid in the alveoli (air spaces)		**√**

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
in the lungs, which keeps oxygen from getting into the blood)		
Personality changes, headache, confusion, paralysis of part or all of the body, stiff neck, abnormal speech and eye movement (possible symptoms of encephalopathy or metabolic encephalopathy)		√
Dizziness, light-headedness (possible symptoms of hypotension)		√
Viral or bacterial or fungal infections		√
Swollen ankles (possible symptoms of low levels of albumin in the blood)		√
State of severe confusion (delirium)		√
Blue discoloration of lips or extremities (hypoxia)		√
Severely decreased urine output (possible symptoms of acute kidney injury)		√
COMMON		
Tiredness, confusion, muscle twitching, convulsions (possible symptoms of low level of sodium in blood)		√
Side effects affecting the nervous system, including involuntary shaking of the body (tremor), tingling or numbness (paresthesia), impaired memory or thinking (cognitive disorders), sensation of numbness or tingling in finger and toes (peripheral neuropathy), uncontrollable movements or actions of the body including tremors, jerks, twitches, spasms, contractions, or gait problems (motor dysfunction, ataxia), difficulty in speaking or understanding speech (speech disorders)		√
Fever, malaise, yellow color of your skin and eyes (possible symptoms of hemophagocytic lymphohistiocytosis)		√
Producing less urine than normal and/or muscle spasms (possible symptoms of tumor lysis syndrome)		√

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Weakness or paralysis of limbs or face, difficulty speaking (possible symptoms of a stroke)		√
Convulsions, fits (seizures)		√
Severe nerve pain (neuralgia)		√
Fast and/or irregular heartbeat, breathlessness, difficulty breathing when lying down, swelling of the feet or legs, stopped heartbeat (possible symptoms of heart failure, worsening of heart failure or cardiac arrest)		√
Swelling and edema (possible symptoms of capillary leak syndrome in context of CRS)		√
High fever, chills, difficulty to breath, yellow skin and eyes, bloody stools, severely decreased urine output (possible symptoms of multiple organ dysfunction syndrome)		√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Reporting Suspected Side Effects

For the general public: Should you experience a side effect following immunization, please report it to your doctor, nurse, or pharmacist.

Should you require information related to the management of the side effect, please contact your healthcare provider. The Public Health Agency of Canada, Health Canada and Novartis Pharmaceuticals Canada Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

If you want more information about KYMRIAH:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website http://hc-sc.gc.ca/index-eng.php; the manufacturer's website http://www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by:

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Last Revised:

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