PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}KYMRIAH™

Tisagenlecleucel

Cell suspension in infusion bag, 2.0×10^6 to 6.0×10^8 CAR-positive viable T cells, for intravenous use

Novartis Standard

Antineoplastic and immunomodulating agents

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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 3 to 25 years 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.

- the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, 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 **ACTION AND CLINICAL PHARMACOLOGY**).

DLBCL: No dose adjustment is required in patients over 65 years of age (see **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 **DOSAGE FORMS, STRENGHTS, 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

4.1 Dosing Considerations

- **For autologous use only – verify the patient's identity immediately prior to infusion**
- **For intravenous use only. Do not use a leukocyte depleting filter.**
- **For single treatment**
- **Ensure the availability of 4 doses of tocilizumab prior to infusion**

Pre-treatment conditioning (Lymphodepleting chemotherapy)

Lymphodepleting chemotherapy is recommended to be administered before KYMRIAH infusion unless the white blood cell (WBC) count within one week prior to KYMRIAH infusion is ≤1,000 cells/microliter. KYMRIAH cells are recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. If there is a more than 4 week delay 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 (3 to 25 years of age):

The recommended lymphodepleting chemotherapy regimen is:

- Fludarabine (30 mg/m^2 IV daily for 4 days) and cyclophosphamide (500 mg/m^2 IV 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 IV daily for 2 days) and etoposide (150 mg/m^2 IV 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 IV daily for 3 days) and cyclophosphamide (250 mg/m^2 IV 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 IV daily for 2 days).

Safety monitoring prior to infusion

Due to the risks associated with KYMRIAH treatment, infusion should be withheld until resolution of any of the following conditions (see **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 lymphoma following lymphodepleting chemotherapy.
- There is limited experience with the use of KYMRIAH in patients with active CNS leukemia and active CNS lymphoma. Therefore the risk/benefit of KYMRIAH has not been established in these populations.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

KYMRIAH is provided as a single-dose, one-time treatment.

Pediatric and Young Adult B-cell ALL (3 to 25 years of age):

- 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 **ACTION AND CLINICAL PHARMACOLOGY**).

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

4.3 Administration

Precautions to be taken before administering KYMRIAH

KYMRIAH contains genetically-modified human cells. Local biosafety guidelines applicable for handling and disposal of such products should be followed. (See **STORAGE, STABILITY AND DISPOSAL – Special precautions for storage**).

KYMRIAH is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and KYMRIAH may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions when handling leukapheresis material or KYMRIAH to reduce the potential transmission of infectious diseases.

Leukapheresis material from patients with a positive test for human immunodeficiency virus (HIV), hepatitis C (HCV) or active hepatitis B (HBV) will not be accepted for KYMRIAH manufacturing. (see **WARNINGS AND PRECAUTIONS**).

Tocilizumab and emergency equipment must be available prior to infusion and during the recovery period.

Premedication:

To minimize potential acute infusion reactions, it is recommended that patients be pre-medicated with acetaminophen/paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to KYMRIAH infusion. Corticosteroids should not be used at any time except in the case of a life-threatening emergency (see **WARNINGS AND PRECAUTIONS**).

Preparation for infusion

Patient identity confirmation: Prior to KYMRIAH infusion, the patient's identity should 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. Confirm the infusion time in advance, and adjust the start time for thaw so that KYMRIAH is available for infusion when the recipient is ready. Once KYMRIAH has been thawed and is at room temperature, it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

The cryobag should be placed inside a second, sterile bag in case of a leak and to protect ports from contamination. The cryobag(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 bag should be removed immediately from the thawing device and should not be stored at 37°C after thawing is completed and should be kept at room temperature. 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 infused.

If the KYMRIAH bag appears to have been damaged or to be leaking, it should not be infused, and should be disposed of according to local biosafety procedures. Novartis should then be contacted at 1-800-465-2244.

Administration

KYMRIAH intravenous infusion should be administered by healthcare providers experienced with immunosuppressed patients and trained for administration of KYMRIAH and management of patients treated with KYMRIAH.

The KYMRIAH cell product 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 is for autologous use only. The patient's identity should be matched with the patient identifiers on the infusion bag. KYMRIAH should be administered as an IV infusion through latex free IV tubing. Do not use a leukocyte depleting filter. Infuse at approximately 10 to 20 mL per minute by gravity flow, and adjust as appropriate for smaller children and smaller volumes. Sterile normal saline (NS) 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 bag should be rinsed with 10 to 30 mL normal saline by back priming to assure as many cells as possible are infused into the patient.

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 ranges from 10 mL to 50 mL.	Dextran, dextrose, dimethylsulfoxide (DMSO), human serum albumin, plasma-Lyte A (multiple electrolytes for injection, Type 1, pH 7.4), and sodium chloride.

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.

KYMRIAH is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and KYMRIAH may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions when handling leukapheresis material or KYMRIAH to reduce potential for transmission of infectious diseases. (See **WARNINGS AND PRECAUTIONS**).

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 and cells for transplantation.

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 **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.

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) or neurological symptoms occur after infusion with KYMRIAH, and informed that they should stay within 2 hours distance of where they are given KYMRIAH treatment for 3 to 4 weeks.

Driving and Operating Machinery

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving KYMRIAH are at risk for altered or decreased consciousness or coordination in the 8 weeks following infusion. Patients are advised to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery during this initial 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 events, has been observed after KYMRIAH infusion. In almost all the cases, development of CRS occurred between 1 to 10 days (median onset 3 days) after KYMRIAH infusion for pediatric and young adult B-cell ALL patients and between 1 and 9 days (median onset 3 days) after the KYMRIAH infusion for adult DLBCL patients. The median time to resolution of CRS was 8 days in B-cell ALL and 7 days in DLBCL patients. Symptoms of CRS may include high fever, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea, and hypoxia. Additional organ system adverse events, including transient cardiac insufficiency and arrhythmia, renal insufficiency, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), and elevated bilirubin have been observed. In some cases, disseminated intravascular coagulation (DIC), with low fibrinogen levels, capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported 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 **WARNINGS AND PRECAUTIONS – Neurologic**, below.

Management of Cytokine Release Syndrome associated with KYMRIAH

CRS should be managed based on clinical presentation and according to the CRS management algorithm provided in Table 8-1. Anti-IL-6 based therapies, such as tocilizumab have been administered for moderate or severe CRS associated with KYMRIAH and must be on site and available for administration prior to KYMRIAH infusion. Corticosteroids may be administered in cases of life-threatening emergencies. Tumor Necrosis Factor (TNF) antagonists are not recommended for management of KYMRIAH associated CRS.

Table 8-1 CRS management algorithm

Pretreatment	Acetaminophen/paracetamol and diphenhydramine /H1 anti-histamine and prophylaxis for complications of tumor lysis syndrome (TLS) as appropriate
KYMRIAH infusion	
Prodromal syndrome: low grade fever, fatigue, anorexia (hours to days)	
Prodromal	Observation, rule out infection (surveillance cultures), rule out TLS

syndrome management	Antibiotics per local guidelines (febrile neutropenia) Symptomatic support
Symptom progression: High fever, hypoxia, mild hypotension	
1st line management	Oxygen, fluids, vasopressor support, antipyretics Monitor/manage complications of TLS
Further symptom progression (one or more of the following): - Hemodynamic instability despite intravenous fluids and vasopressor support (Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered.) - Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation - Rapid clinical deterioration	
2nd line management	**tocilizumab**: IV infusion - Patient weight <30 kg: 12 mg/kg IV over 1 hour - Patient weight ≥30 kg: 8 mg/kg IV over 1 hour (max dose 800 mg) Hemodynamic and respiratory support
Lack of clinical improvement: If lack of clinical improvement despite prior management, the following management sequence is recommended. At all times, provide hemodynamic and respiratory support, and consider other diagnoses which might cause clinical deterioration (e.g. TLS, sepsis, adrenal insufficiency):	
3rd line management	If no improvement with 1st dose of tocilizumab within 12 to 18 hours, consider corticosteroids: - 2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day Plan rapid taper only after hemodynamic normalization. As steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement If no response to steroids within 24 hours, consider 2nd dose of tocilizumab (dosed as above)
4th line management	If no response to steroids and 2nd dose of tocilizumab within 24 hours or further clinical deterioration, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS.
5th line management	In ongoing CRS despite prior therapy, consider anti-T cell therapies such as cyclophosphamide, anti-thymocyte globulin or alemtuzumab

Risk factors for severe CRS in pediatric and young adult B-cell ALL patients are high pre-infusion tumor burden, uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infection and early onset of fever or CRS following KYMRIAH infusion. Risk factors for developing severe CRS in adult DLBCL patients are not yet known.

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.

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 significant contributing factor to the risk of infections post-tisagenlecleucel infusion (see **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 prior to and during treatment with KYMRIAH should be employed. 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 as per age and standard guidelines.

Prolonged cytopenias

Patients may continue to exhibit cytopenias for several weeks following 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 are not recommended during the first 4 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 (IgG) and agammaglobulinemia (IgG) can occur in patients with a complete remission after KYMRIAH infusion. Immunoglobulin levels should be monitored after treatment with KYMRIAH and managed using infection precautions, antibiotic prophylaxis and immunoglobulin replacement per age and standard guidelines.

Live vaccines

The safety of immunization with live viral vaccines during or following KYMRIAH treatment has

not been studied. Vaccination with live virus 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.

Concomitant immunosuppressive therapy

No pharmacokinetic drug interaction studies have been performed with KYMRIAH. T-cells are known to be susceptible to immune-suppressive agents; however, it is unknown whether KYMRIAH retains the properties of natural T-cells. Immuno-suppressive agents including but not limited to corticosteroids, cytotoxic chemotherapy, immunophilins, mTOR inhibitors, can be lymphotoxic and should be avoided following infusion of KYMRIAH except in the case of life threatening emergencies.

Prior bone marrow transplant

It is not recommended that patients receive KYMRIAH within 6 months of undergoing an allogeneic stem cell transplant (SCT) because of the potential risk of KYMRIAH worsening graft versus host disease (GVHD).

HIV, Hepatitis B, Hepatitis C and viral reactivation

There is no data to support the safe use of KYMRIAH in patients with HIV and hepatitis B and C viral infections.

It is not recommended that patients receive KYMRIAH if they have viral hepatitis as KYMRIAH may increase the risk of viral reactivation.

It is not recommended that HIV patients receive KYMRIAH due to the possible loss of HIV suppression and the theoretical risk of recombination events.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with medicinal products directed against B cells, like KYMRIAH.

There is currently no experience with manufacturing KYMRIAH for patients testing positive for HBV, HCV and HIV.

Screening for HBV, HCV, and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing.

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 leukaemia after prior anti-CD19 therapy.

Interference with serological testing

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 (NAT) may give a false positive result. ELISA or Western Blot tests for the presence of HIV antibodies should be used to provide specificity for HIV infection after administration of KYMRIAH. (see **Drug-Laboratory Test Interactions**).

Neurologic

Neurological toxicities, in particular signs and symptoms of encephalopathy and/or delirium not associated with infection or CRS, can occur with KYMRIAH and can be severe or life-threatening. The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion and were transient. The most common neurological events were encephalopathy, headache, delirium, anxiety, dizziness and tremor. Other observed neurological events included disturbances in consciousness, disorientation, confusion, agitation, seizures, mutism and aphasia. KYMRIAH related CRS can be associated with neurological toxicities. Onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS. (see **ADVERSE REACTIONS, Neurologic events**).

Patients should be monitored for neurological events during and after resolution of CRS. Supportive care should be given for KYMRIAH associated neurological events and diagnostic work-up should be considered to exclude other causes for these symptoms.

Sexual Health

Reproduction

Sexually active females of reproductive potential should use effective contraception (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 females of reproductive potential or pregnant women.

If either partner has received KYMRIAH, pregnancy should be discussed with the treating physician.

Fertility

There is no data on the effect of KYMRIAH on fertility.

Fetal risk

There is a potential for KYMRIAH to cause fetal toxicity. It is not known if KYMRIAH constitutes a risk to pregnant women or fetuses, 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 reproductive and developmental toxicity 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 with immunoglobulin levels.

Clinical considerations

If a patient intends to become pregnant after receiving KYMRIAH, the potential risks to the patient and to the fetus in light of prior KYMRIAH therapy should be discussed with the treating physician.

Pregnancy testing

Pregnancy status for females of reproductive potential should be verified prior to starting treatment with KYMRIAH.

8.1.2 Breast-feeding

There is no information regarding the excretion of KYMRIAH in human milk, the effect on the breast-fed child or the effects of KYMRIAH on milk production. 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 **ACTION AND CLINICAL PHARMACOLOGY**).

DLBCL: No dose adjustment is required in patients over 65 years of age (see **ACTION and CLINICAL PHARMACOLOGY**).

8.1.5 Renal and hepatic impairment

No studies have been performed in patients with renal or hepatic impairment. (see **ADVERSE REACTIONS - 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.

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 identified in 104 r/r B-cell ALL pediatric and young adult patients in two multi-center studies, i.e. the ongoing pivotal clinical study CCTL019B2202 (B2202, ELIANA) (N=75) and the supportive clinical study CCTL019B2205J (B2205J) (N=29).

The most common non-hematological adverse reactions (≥40%) within 8 weeks post-infusion were cytokine release syndrome (81%), infections (67%), hypogammaglobulinemia (45%), pyrexia (41%) and decreased appetite (40%).

The most common hematological adverse reactions were decreased white blood cells (100%), decreased hemoglobin (100%), decreased neutrophils (98%), decreased lymphocytes decreased (98%) and decreased platelets (95%).

Grade 3 and Grade 4 adverse reactions were reported in 87% of patients.

The most common (>40%) Grade 3 and Grade 4 non-hematological adverse reaction was CRS (44%).

The most common (>40%) Grade 3 and Grade 4 hematological laboratory abnormalities were white blood cells decreased (96%), neutrophils decreased (96%), lymphocytes decreased (93%), platelets decreased (77%), and hemoglobin decreased (50%).

Grade 3 or 4 adverse events were more often observed within the initial 8 weeks post-infusion (83% of patients) compared to after 8 weeks post-infusion (46% of patients).

Seven fatalities not related to disease progression occurred following KYMRIAH infusion, of which 2 deaths occurred within 30 days of infusion. One death was due to embolic stroke related to mucormycosis, 1 death due to cerebral hemorrhage and 3 deaths due to infections (encephalitis, lower respiratory tract bacterial infection and mycosis), 1 due to hepatobiliary disease, and 1 death was due to unknown reason.

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

The adverse reactions described in this section were identified in 106 r/r DLBCL patients, infused with KYMRIAH, in one global multi-center study, i.e. the ongoing pivotal clinical study CCTL019C2201 (C2201, JULIET).

The most common non-hematological adverse reactions (incidence >20%) were CRS (58%), infections–pathogen unspecified (42%), pyrexia (34%), diarrhea (31%), nausea (27%), hypotension (26%), fatigue (26%), edema (23%) and headache (21%).

The most common hematological laboratory abnormalities were lymphocytes decreased (100%), haemoglobin decreased (99%), white blood cells decreased (98%), neutrophils decreased (97%), and platelet decreased (93%).

Grade 3 and Grade 4 adverse reactions were reported in 90% of patients.

The most common Grade 3 and Grade 4 non-hematological adverse reaction was infections (32%) and CRS (23%).

The most common (>40%) Grade 3 and Grade 4 hematological laboratory abnormalities were lymphocytes decreased (94%), neutrophils decreased (81%), white blood cells decreased (77%), hemoglobin decreased (58%), and platelet decreased (54%).

Grade 3 or 4 adverse events were more often observed within the initial 8 weeks post-infusion (86% of patients) compared to after 8 weeks post-infusion (47% 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 + B2205J (N=104)		
	All grades %	Grade 3 %	Grade 4 %
Blood and lymphatic system disorders			
Febrile neutropenia	36	34	2
Cardiac disorders			
Tachycardia [a)]	30	4	1
Gastrointestinal disorders			
Vomiting	36	3	0
Nausea	31	7	0
Diarrhea	28	2	0
Constipation	17	0	0
Abdominal pain [b)]	22	3	0
General disorders and administration site conditions			
Pyrexia	41	10	3

Adverse drug reactions	B2202 + B2205J (N=104)		
	All grades %	Grade 3 %	Grade 4 %
Fatigue [c)]	24	1	0
Edema [d)]	13	0	0
Chills	13	0	0
Pain [e)]	19	3	0
Immune system disorders			
Cytokine release syndrome	81	20	24
Hypogammaglobulinemia [f)]	45	7	0
Infections and infestations[g)]			
Infections – pathogen unspecified	48	13	8
Viral infectious disorders	33	14	1
Bacterial infectious disorder	25	13	1
Fungal infectious disorders	13	4	3
Investigations			
International normalized ratio increased	15	1	0
Metabolism and nutrition disorders			
Decreased appetite	40	19	1
Hypocalcemia	16	6	0
Hypoalbuminemia	13	1	0
Fluid overload	11	5	0
Hyperuricemia	11	1	0
Hyperglycemia	10	6	0
Musculoskeletal and connective tissue disorders			
Back pain	10	3	0
Myalgia	13	0	0
Arthralgia	11	1	0
Nervous system disorders			
Headache [h)]	35	2	0
Encephalopathy [i)]	29	6	1
Psychiatric disorders			
Delirium [j)]	16	3	0
Anxiety	15	3	0
Sleep disorder [k)]	12	0	0
Renal and urinary disorders			

Adverse drug reactions	B2202 + B2205J (N=104)		
	All grades %	Grade 3 %	Grade 4 %
Acute kidney injury [l)]	19	3	10
Respiratory, thoracic and mediastinal disorders			
Cough [m)]	23	0	0
Hypoxia	24	13	7
Dyspnea [n)]	16	3	11
Pulmonary edema	14	8	2
Epistaxis	13	3	1
Pleural effusion	13	3	1
Tachypnea	10	5	0
Skin and subcutaneous tissue			
Rash [o)]	16	1	0
Vascular disorders			
Hypotension	31	10	13
Hypertension	18	5	0

[1)]The frequency of ADRs observed is the crude incidence rate
[a)] Tachycardia includes sinus tachycardia and tachycardia.
[b)]Abdominal pain includes abdominal pain and abdominal pain upper
[c)] Fatigue includes fatigue and malaise
[d)] Oedema includes face oedema, generalised oedema, localised oedema, and oedema peripheral
[e)] Pain includes pain and pain in extremity
[f)]Hypogammaglobulinemia includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, immunodeficiency, immunodeficiency common variable and hypogammaglobulinaemia
[g)] Infections and infestations are high level group terms.
[h)] Headache includes headache and migraine
[i)] Encephalopathy includes depressed level of consciousness, mental status changes, automatism, cognitive disorder, confusional state, disturbance in attention, encephalopathy, posterior reversible encephalopathy syndrome, somnolence and lethargy
[j)] Delirium includes agitation, delirium, hallucination, visual hallucination, irritability, and restlessness
[k)] Sleep disorder includes insomnia, nightmare, sleep disorder
[l)]Acute kidney injury includes acute kidney injury, anuria, azotaemia, blood creatinine increased, renal failure, renal tubular dysfunction and renal tubular necrosis
[m)] Cough includes cough and productive cough
[n)] Dyspnea includes dyspnea, respiratory distress, and respiratory failure
[o)] Rash includes rash, rash maculo-papular, rash papular, and rash pruritic

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

Selected ADRs which occurred in the pediatric ALL studies (B2201 and B2205J) with a frequency of ≥1% and <10% were:

Blood and lymphatic system disorders: disseminated intravascular coagulation, histiocytosis lymphocytic hemophagocytosis, coagulopathy, Grade 3 and Grade 4 hypofibrinogenemia with Grade 3 and 4 CRS, pancytopenia

Cardiac Disorders: cardiac arrest, cardiac failure

Gastrointestinal disorders: mouth hemorrhage, abdominal distension, ascites, abdominal compartment syndrome

General disorders and administration site conditions: multiple organ dysfunction syndrome

Immune system disorders: graft versus host disease

Investigations: prothrombin time prolonged, activated partial thromboplastin time prolonged

Nervous System: tremor, dizziness, seizure, speech disorder[a], motor dysfunction[b], cerebral hemorrhage

Respiratory, thoracic, and mediastinal disorders: respiratory distress, respiratory failure, acute respiratory distress syndrome, oropharyngeal pain

Skin and subcutaneous tissue disorders: erythema, hyperhydrosis, petechiae

Metabolism and nutrition disorders: hypomagnesemia, tumor lysis syndrome

Vascular disorders: capillary leak syndrome, thrombosis, flushing

Eye disorders: Visual impairment

[a] *Speech disorder includes aphasia and dysarthria.*
[b] *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

Adverse drug reactions	C2201, N=106		
	All grades %	Grade 3 %	Grade 4 %
Blood and lymphatic system disorders			
Febrile neutropenia	17	14	3
Cardiac disorders			
Tachycardia [a)]	13	5	3
Gastrointestinal disorders			
Diarrhea	31	1	0
Nausea	27	1	0
Constipation	16	1	0
General disorders and administration site conditions			
Pyrexia	34	6	0

Adverse drug reactions	C2201, N=106		
	All grades %	Grade 3 %	Grade 4 %
Fatigue [b)]	26	7	0
Edema [c)]	23	2	0
Pain [d)]	15	3	0
Chills	13	0	0
Immune system disorders			
Cytokine release syndrome	58	15	8
Hypogammaglobulinemia [e)]	16	5	0
Infections and infestations			
Infections - pathogen unspecified	42	20	5
Investigations			
Weight decreased	11	3	0
Metabolism and nutrition disorders			
Decreased appetite	12	4	0
Musculoskeletal and connective tissue disorders			
Arthralgia	10	0	0
Nervous system disorders			
Headache [f)]	21	0	0
Encephalopathy [g)]	16	8	4
Dizziness [h)]	11	1	0
Renal and urinary disorders			
Acute kidney injury [i)]	17	3	3
Respiratory, thoracic and mediastinal disorders			
Cough [j)]	19	0	0
Dyspnea [k)]	18	5	1
Vascular disorders			
Hypotension [l)]	26	7	2

[1)] The frequency of ADRs observed is the crude incidence rate
[a)] Tachycardia includes tachycardia and sinus tachycardia.
[b)] Fatigue includes fatigue and malaise.
[c)] Edema includes face edema, generalised edema, localized edema, edema peripheral, peripheral swelling.
[d)] Pain includes pain and pain in the extremity.
[e)] Hypogammaglobulinemia includes blood immunoglobulin G decreased, immunodeficiency, immunodeficiency common variable, immunoglobulins decreased and hypogammaglobulinemia.
[f)] Headache includes headache and migraine.

Adverse drug reactions	C2201, N=106		
	All grades %	Grade 3 %	Grade 4 %

g) Encephalopathy includes encephalopathy, cognitive disorder, confusional state, disturbance in attention, lethargy, mental status changes, somnolence, memory impairment, metabolic encephalopathy and thinking abnormal.
h) Dizziness includes dizziness, presyncope, and syncope.
i) Acute kidney injury includes acute kidney injury and blood creatinine increased.
j) Cough includes cough, productive cough, and upper-airway cough syndrome.
k) Dyspnea includes dyspnea, dyspnea exertional, respiratory distress, and respiratory failure.
l) Hypotension includes hypotension and orthostatic hypotension.

9.3 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*:* disseminated intravascular coagulation, pancytopenia, histiocytosis haematophagic,

Cardiac Disorders*:* arrhythmia[a] , cardiac failure

Eye disorders: visual impairment[n]

Gastrointestinal disorders*:* vomiting, abdominal pain[b], anal incontinence

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

Heptatobiliary disorders: hyperbilirubinemia

Infections and infestations*:* fungal infectious disorders, viral infectious disorders, bacterial infectious disorders

Investigations: Aspartate aminotransferase increased, blood alkaline phosphatase increased, fibrin d-dimer increased, and serum ferritin increased

Immune system disorders: immunodeficiency

Metabolism and nutrition disorders*:* fluid overload, hypocalcemia, hyperglycemia, hypoalbuminea, tumor lysis syndrome

Musculoskeletal and connective tissue disorders: myalgia, back pain

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

Psychiatric disorders: anxiety, delirium[g], sleep disorders[h]

Respiratory, thoracic, and mediastinal disorders*:* hypoxia, oropharyngeal pain[i], pleural effusion, pulmonary edema[j]

Skin and subcutaneous tissue disorders: rash[l], dermatitism[m], night sweats, petechiae, hyperhidrosis, pruritus, erythema

Vascular disorders: thrombosis[k], hypertension, capillary leak syndrome

[a] *Arrhythmia includes atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles.*
[b] *Abdominal pain includes abdominal pain and abdominal pain upper.*
[c] *Peripheral Neuropathy includes paraethesia, hypoaesthesia, 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.*
[f] *Seizure includes PTs seizure and status epilepticus.*
[g] *Delirium includes delirium, agitation, and irritability.*
[h] *Sleep disorders includes sleep disorder, insomnia and nightmare.*
[i] *Oropharyngeal pain includes oral pain and oropharyngeal pain.*
[j] *Pulmonary edema includes acute pulmonary edema and pulmonary edema.*
[k] *Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis, and venous thrombosis.*
[l] *Rash includes rash, rash maculo-papular, rash papular and rash pruritic.*
[m] *Dermatitis includes dermatitis, dermatitis acneiform and dermatitis contact.*
[n] *Visual impairment includes vision blurred and visual impairment.*

Description of selected adverse drug reactions

Cytokine release syndrome (CRS)

In the ongoing clinical studies in pediatric and young adult B-cell ALL (N=104), serious CRS reactions classified based on the PENN Grading system for CRS (Porter et al 2015) were reported in 81% of patients (44% with Grade 3 or 4) with a median time to onset of 3 days (range: 1-22) and in only three patients was onset after Day 10. The median CRS duration of 8 days (range 1-36). Forty-seven patients were admitted to ICU, 16 patients were intubated, and 11 patients required dialysis during CRS.

In the ongoing clinical study in DLBCL (N=106), CRS reactions were reported in 58% of patients, (23% with Grade 3 or 4), with a median time to onset of 3 days (range: 1-51) and in only one patients was onset after Day 10. The median duration of 7 days (range 2-30). Twenty-five patients were admitted to ICU, 8 patients were intubated, and 5 patients required dialysis during CRS.

For clinical management of CRS, see **WARNINGS AND PRECAUTIONS** and Table 7-1. Neurological events have occurred in the context of CRS. The timing has been prior to the onset of CRS, during and shortly after the resolution of CRS, and rarely has recurred after apparent resolution of the event.

Febrile neutropenia and infections

Severe febrile neutropenia (Grade 3 or 4) was observed in 36% of pediatric and young adult B-cell ALL patients. See **WARNINGS AND PRECAUTIONS** for the management of febrile neutropenia before KYMRIAH and after KYMRIAH infusion.

Infections are common after KYMRIAH infusion and occurred in 46/104 (44.2%) infused patients with refractory or relapsed ALL. Of these patients, 45.7% 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 67% (bacterial 25%, viral 33%, unspecified 48%, and fungal 13%) (see **WARNINGS AND PRECAUTIONS**). Forty-four percent of the patients experienced an infection of any type by 8 weeks after KYMRIAH infusion.

Severe febrile neutropenia (Grade 3 or 4) was observed 17% of DLBCL patients. See **WARNINGS AND PRECAUTIONS** for the management of febrile neutropenia before KYMRIAH and after KYMRIAH infusion.

In DLBCL patients severe infections (Grade 3 or 4), which can be life-threatening or fatal, occurred in 32% of patients. The overall incidence was 52% (bacterial 9%, viral 9%, unspecified 42%, and fungal 9%) (see **WARNINGS AND PRECAUTIONS**). 34% of the patients experienced an infection of any type within 8 weeks.

Hematopoietic cytopenias not resolved by day 28

In pediatric and young B-cell ALL patients, Grade 3 and 4 cytopenias beyond 28 days were reported based on laboratory findings and included neutropenia (59%), leukopenia (58%), lymphopenia (47%), thrombocytopenia (46%), and anaemia (11%).

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.

In adult patients with DLBCL Grade 3 and 4 cytopenias beyond 28 days were reported based on laboratory findings and included thrombocytopenia (40%), lymphopenia (25%), neutropenia (25%), leukopenia (20%) and anemia (14%).

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.

Neurological events

The majority of neurological 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 38% of patients (11% 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).

In DLBCL patients, neurological events of any grade occurred among 24.5% of patients anytime post-infusion. Manifestations of encephalopathy and/or delirium occurred in 21% of patients (11% were Grade 3 or 4) within 8 weeks after KYMRIAH infusion. The other most common neurological event was headache (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=104)		DLBCL (N=106)	
Laboratory parameter	**All Grades (%)**	**Grades 3 and 4 (%)**	**All Grades (%)**	**Grades 3 and 4 (%)**
White Blood Cells	100	96	98	77

decreased				
Hemoglobin decreased	100	50	99	58
Platelets decreased	95	77	93	54
Neutrophils decreased	98	96	97	81
Lymphocytes decreased	98	93	100	94

[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=104)
Laboratory parameter	**Grades 3 and 4 (%)**
Increased Aspartate Aminotransferase	29
Hypokalemia	27
Hypophosphatemia	16
Increased Bilirubin	18
Increased Alanine Aminotransferase	20

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=106)
Laboratory parameter	**Grades 3 and 4 (%)**
Hypophosphatemia	21
Hypokalemia	12

9.4 Post-Marketing Adverse Reactions

Currently there are no post-marketing adverse reactions data available

10 DRUG INTERACTIONS

10.1 Overview

No drug interaction studies with tisagenlecleucel have been performed.

10.2 Drug-Drug Interactions

Pharmacokinetic interactions

No pharmacokinetic drug interaction studies have been performed with KYMRIAH.

T-cells are known to be susceptible to immune-suppressive agents; however, it is unknown whether KYMRIAH retains the properties of natural T-cells. Immuno-suppressive agents including but not limited to corticosteroids, cytotoxic chemotherapy, immunophilins, mTOR inhibitors, can be lymphotoxic and should be avoided following infusion of KYMRIAH except in the case of life threatening emergencies.

The immunization with live viral vaccines during or following KYMRIAH treatment has not been studied. Vaccination with live virus 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.

Pharmacodynamic interactions

The potential for pharmacodynamic drug interactions exists for drugs administered as part of conditioning regimens such as rituximab, with KYMRIAH. Rituximab and KYMRIAH can cause B cell aplasia.

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 NAT may give a false positive result. Enzyme-linked immunosorbent assay (ELISA) or Western Blot tests for the presence of HIV antibodies should be used to provide specificity for the detection of HIV infection after administration of KYMRIAH.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

KYMRIAH 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 KYMRIAH. Upon binding to CD19 expressing cells, the CAR transmits a signal to promote T cell expansion, activation, target cell elimination and persistence of KYMRIAH.

11.2 Pharmacodynamics

Cardiac electrophysiology

KYMRIAH is a cell product and is not expected to prolong the QT interval; hence no formal QT study was conducted.

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 2-fold higher in complete response/complete response with incomplete blood count (CR/CRi) patients (n=79) 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 617 days in peripheral blood in responding patients based on the pooled data from Studies B2202 and B2205J.

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 524 days in responding patients and 374 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=80	Pediatric ALL Non-Responding Patients N=11	r/r DLBCL Responding Patients (CR and PR) N=35	r/r DLBCL Non-Responding Patients (SD/PD/Unknown) N=57
C_{max} (copies/µg)	Geometric mean (CV%), n	32,700 (163.4), 79	19,500 (123.7), 10	6,210 (226.1), 35	5,360 (388.8), 52
T_{max} (day)[‡]	Median [min;max], n	9.83 [0.0111;27.8],	20.0 [0.0278;62.7],	9.83 [5.78;16.8], 35	8.88 [3.04;27.7], 52

		79	10		
$AUC_{0\text{-}28d}$ (copies/µg*day)	Geometric mean (CV%), n	300,000 (193.4), 78	210,000 (111.7), 8	64,300 (156.1) 33	69,600 (273.9), 41
$AUC_{0\text{-}84d}$ (copies/µg*day)	Geometric mean (CV%), n	463000 (228.9), 66	652000 (131.0), 3	100,000 (144.9), 33	128,000 (172.5), 20
$T_{½}$ (day)[§]	Geometric mean (CV%), n	21.7 (196.8), 65	2.70 (154.4), 3	81.6 (165.2), 25	15.4 (156.0), 34

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

[‡]A total of 5 pediatric and young adult ALL patients had an early T_{max} (< 0.03 days), the next lowest T_{max} occurs at 5.7 days. Early T_{max} may not be representative of the true maximal expansion, rather the amount of transgene present in the catheter from which sample was collected.

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

[§] T1/2 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-ALL.

Concomitant therapy with tocilizumab and corticosteroids: In patients treated with tocilizumab or corticosteroids for the management of CRS, tisagenlecleucel transgene continue to expand and persist following administration of tocilizumab and corticosteroids.

Linearity/non-linearity: Dose and cellular kinetic parameters are independent, thus there is no apparent relationship with $AUC_{0\text{-}28d}$ and C_{max} with dose.

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 $AUC_{0\text{-}28d}$ 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 $AUC_{0\text{-}28d}$ 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 parameters and small sample size.

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.

In Studies B2202 and B2205J there were 79.8% of Caucasian, 7.7% of Asian and 12.5% of other ethnic patients. In Study C2201, there were 91% of Caucasian, 4% of Asian, 4% of Black or African American patients, and one patient (1%) with unknown race.

Hepatic Insufficiency: No formal hepatic impairment studies were performed.

Renal Insufficiency: No formal renal impairment studies were performed.

Prior 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 patients with r/r B-cell ALL, no clinically meaningful difference in cellular kinetics was observed depending on the history of prior HSCT.

Immunogenicity

Humoral immunogenicity of tisagenlecleucel was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. In pediatric and young adult B-cell ALL, the majority of patients (84.6%) tested positive for pre-dose anti-mCAR19. Treatment induced anti-mCAR19 antibodies were detected in 34.6 % of patients.

In DLBCL patients, pre-existing and treatment-induced anti-mCAR19 was detected in 91.4 and 5% of patients, respectively. 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 mCAR19 peptide stimulation. The cellular immunogenicity responses did not correlate with *in vivo* expansion and persistence of tisagenlecleucel and Month 3 response.

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

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

The cryobag should be placed inside a second, sterile bag in case of a leak and to protect ports from contamination. The cryobag(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 bag should be removed immediately from the thawing device and should not be stored at 37°C after thawing is completed and should be kept at room temperature. If more than one bag has been received for the treatment dose, the second bag should not be thawed until after the contents of the first bag have been infused.

If the KYMRIAH bag appears to have been damaged or to be leaking, it should not be infused, and should be disposed of according to local biosafety procedures.

KYMRIAH is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and KYMRIAH may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions when handling leukapheresis material or KYMRIAH to reduce the potential transmission of infectious diseases when handling the product.

PART II: SCIENTIFIC INFORMATION

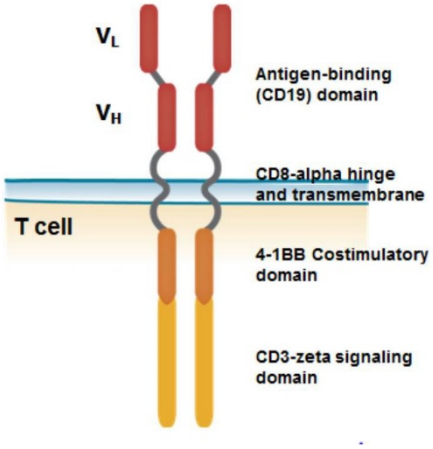
14 PHARMACEUTICAL INFORMATION

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.

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 patients r/r B-cell ALL study

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 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; 7 patients 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. 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 was the sum of proportion of patients who achieved complete remission (CR) or complete remission with incomplete blood count recovery (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 complete

remission (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 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)

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**
Probability at 6 months	79.5
Median[9] (months)	Not reached
(95% CI)	(8.6, NE[9,10])
Range	(1.2+, 19.3+)

[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] Norminal 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)
[9] The Range 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 % of events
[10] NE= Not estimable

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

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 (5 infusions were pending at the time of analysis), 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: manufacturing failure (n=11); death (n=16), physician decision (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. 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. 44% had undergone prior autologous HSCT.

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-Barre) 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 14-4 for efficacy results of this study.

Study Results

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

Primary Endpoint	**N=68**
Overall Response Rate (ORR) (CR+PR), n (%) (95% CI) [d]	34 (50%) (37.6, 62.4)
Complete Response (CR), n (%) (95% CI) [d]	22 (32%) (21.5, 44.8)
Partial Response (PR), n (%) (95% CI) [d]	12 (18%) (9.5, 28.8)
Duration of response (DOR)	N=34
Overall DOR for responders (months) Median (months) (95% CI) [a,b,d] Range [c] Median Follow-up (95%CI) [b,d] Probability at 9 months	 Not reached (5.1, NE[5]) (0.03+, 11.3+) 9.4 (7.9, 10.8) 64.2
DOR if BOR is CR	N = 22

Median (months) (95% CI) [a,b,d] Range [c]	NE (10.0, NE) (1.5+-11.3+)
DOR if BOR is PR	N=12
Median (months) (95% CI) [a,b,d] Range [c]	3.4 (1.0, NE) (0.03+-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. 55.9 % of patients censored due to ongoing without an event, 8.8% of patients censored due to new cancer therapy, other than HSCT, and the 35.3 % had disease progression or death due to DLBCL.

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

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™
(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:

- These cells are called 'T-cells'
- They are important for your immune system and for fighting your cancer.
- It comes in infusion bags.

What is KYMRIAH used for?

KYMRIAH is used to treat:

- B-cell Acute lymphoblastic leukaemia (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 from 3 to 25 years of age with this cancer.
- 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 are genetically modified so that they can find and kill the cancer cells more effectively. When you have an infusion of KYMRIAH into your blood, the modified T-cells will stick to the cancer cells and cause them to die.

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 6 months.
- If you have any lung or heart or blood pressure problems.
- If you have a sign or symptom of a serious graft versus host disease (GVHD), i.e. when transplanted cells attack your body, such rashes, nausea, vomiting, diarrhea, including bloody stools.
- If you notice the symptoms of your leukemia worsening, such as fever, weakness, bleeding at the gums, bruising.
- If you notice the symptoms of your lymphoma worsening, such as unexplained fever, weakness, night sweats, sudden weight loss.
- If you have any infections. Your infection will be treated before KYMRIAH infusion.
- If you have ever had viral hepatitis B or C or HIV.
- If you have recently been vaccinated.
- If you are pregnant, think you may be pregnant, or plan to become pregnant (see section Pregnancy and breast-feeding).

Other warnings you should know about:
Tell your doctor immediately if you get any of these symptoms after administration of KYMRIAH:
- If you experience feeling warm, fever, chills or shivering. These can be symptoms of an infection.
- If you develop frequent infections with sore throat or mouth ulcers, these may be symptoms of a low level of white blood cells (neutropenia with high fever).
- High fever and chills may also 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. When occurring, these symptoms are almost always noticed within the first 9 or 10 days after infusion and last for about 7 or 8 days.
- If you experience neurological problems like altered or decreased consciousness,

delirium, confusion, agitation, seizure, difficulty speaking and understanding, and loss of balance. When occurring, these symptoms usually begin in the first 8 weeks after the infusion, but some of these symptoms can occur weeks or months later as well.

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 cancer is getting worse.
- Check for signs of a medical complication called "Graft versus Host Disease" that may occur usually after a prior transplant.
- Check your blood for something called uric acid and how many cancer cells there are in the blood. This will show if you are likely to have 'tumor lysis syndrome' - 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 and cells for transplants.

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 this medicine.

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

Women of child-bearing potential and male patients
The effects of KYMRIAH in pregnant women are not known, but it may harm your unborn baby.

Pregnancy status should be verified before starting treatment. KYMRIAH should only be used if the result is negative. Women who could become pregnant should use effective birth control after being given KYMRIAH. Ask your doctor about options of effective birth control.

If you become pregnant or think you are pregnant after treatment with KYMRIAH, tell your doctor right away.

Sexually active males treated with KYMRIAH should use a condom for intercourse.

Driving and using machines
Do not drive, use heavy machines, or engage in hazardous activities for 8 weeks following the KYMRIAH infusion. KYMRIAH can cause neurological problems such as altered or decreased consciousness, confusion and seizures.

How you will receive KYMRIAH:
Your doctor or a physician will always give KYMRIAH to you.

Giving blood to make 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.
- Before you are given KYMRIAH, your doctor may give you chemotherapy for a few days to prepare your body and possibly to control your cancer.

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

- Prior to KYMRIAH infusion, your doctor will check that your identity is matching with the patient identifiers on the KYMRIAH infusion bag.
- Your doctor will give KYMRIAH through a tube in your vein. This usually takes less than 1 hour.
- Plan to stay within 2 hours distance of where you were given your treatment for at least 3 to 4 weeks after you have been given KYMRIAH. Your doctor will check to see if your treatment is working and help you with any side effects.

KYMRIAH is given to you only once.

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 not listed here, contact your healthcare professional

Very common:
- Loss of appetite, Weight loss
- Fast heart beat (tachychardia)
- Headache
- Dizziness
- Cough
- Shortness of breath, labored breathing, breathlessness, rapid breathing
- Abdominal pain, Constipation, Diarrhea
- Nausea, Vomiting
- Fever
- Tiredness (fatigue)
- Chills
- Altered state of consciousness
- Nose bleeding
- Reduced level of calcium in the blood, sometimes leading to cramps
- Thirst, low urine output, dark urine, dry flushed skin, irritability (possible symptoms of high level of sugar in blood)
- Headache, dizziness (possible symptoms of hypertension)
- Excessive emotional distress (anxiety)
- Pain in muscles, bones or joints (musculoskeletal pain, myalgia, arthralgia), Pain in extremity, Back pain

Common:
- Yellow skin and eyes (possible symptoms of high level of bilirubin in the blood)
- Decreased immunoglobulins in your blood that will lead to frequent and persistent infections
- Involuntary shaking of the body (tremor)
- Difficulty in speaking or understanding speech (dysphasia)
- Tingling or numbness (paresthesia)
- Bloating (abdominal distension)
- Dry mouth
- Mouth sores (stomatitis)
- Weakness (asthenia)
- Itching (pruritus)
- Skin reddening (erythema)
- Excessive sweating (hyperhidrosis)
- Red or purple, flat, pinhead spots under the skin (petechiae)
- Night sweats

- Tiredness, chills, sore throat, joint or muscles aching (possible symptoms of influenza-like illness)
- Hot flushes
- Blood in urine (haematuria)
- Difficulty and pain when passing urine (dysuria)

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
VERY COMMON		
Feeling warm, fever, chills or shivering (possible symptoms of an unspecified pathogen)		√
Spontaneous bleeding or bruising (Low levels of blood platelets)		√
Frequent infections, weakness, fever, chills, sore throat or mouth ulcers due to infections (possible symptoms of low level of white blood cells or febrile neutropenia)		√
Weakness, spontaneous bleeding or bruising and frequent infections, fever, chills, and sore throat (possible symptoms of low level of red blood cells)		√
High fever, chills, difficulty breathing, nausea, vomiting, diarrhea, muscle pain, joint pain, low blood pressure, or dizziness/light-headedness. (possible symptom of CRS)		√
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)		√
Muscle weakness, muscle spasms, abnormal heart rhythm (possible symptoms of low levels of potassium in the blood)		√
Dizziness, light headedness (possible symptom of hypotension)		√
Swelling of limbs (edema peripheral)		√
COMMON		
Viral or bacterial or fungal infections		√
Blood clotting, internal and external bleeding (possible symptom of disseminated intravascular coagulation)		√
Swollen ankles (possible symptom of low levels of albumin in the blood)		√
Tiredness, confusion, muscle twitching, convulsions (possible symptom of low level of sodium in blood)		√
A syndrome of pathologic immune activation		√

characterized by clinical signs and symptoms of extreme inflammation (histiocytosis hematophagic)		
Producing less urine than normal and/or muscle spasms, possible symptom of an increase in potassium, phosphate and uric acid in the blood that can cause kidney problems (possible symptom of tumor lysis syndrome)		√
State of severe confusion (delirium)		√
Weakness of paralysis of limbs or face, difficulty speaking (possible symptom of ischemic cerebral infraction)		√
Convulsions, fits (Seizures)		√
Severe nerve pain (neuralgia)		√
Irregular heart beat (possible symptom of atrial fibrillation)		√
Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (possible symptom of heart failure)		√
Blue discoloration of lips or extremities (hypoxia)		√
Swelling and edema (possible symptom of capillary leak syndrome in context of CRS)		√
Severely decrease urine output (possible symptom of acute kidney injury)		√
High fever, chills, difficulty to breath, yellow skin and eyes, bloody stools, severely decreased urine output (possible symptom 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 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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