KYMRIAH® suspension for intravenous infusion

1 Description

1.1 Active substance and strengths

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

1.2 Excipients

Excipient	Concentration of excipients in stock solution
Plasma-lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1)	31.25% (v/v)
5% Dextrose in 0.45% Sodium Chloride Injection	31.25% (v/v)
25% Human Albumin	20% (v/v)
10% Dextran 40 (LMD) in 5% Dextrose Injection	10% (v/v)
DMSO	7.5% (v/v)

1.3 Dosage forms

Injection. Cell suspension for infusion in one or more bags for intravenous use.

1.4 Appearance

Colorless to slightly yellow suspension of cells.

2 Indication

Kymriah®/™ is a genetically-modified autologous immunocellular therapy indicated for the treatment of:

- pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
- adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
- adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. (This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial.)

3 Dosage and Administration

3.1 Dosage and Administration

Manufacture and release of Kymriah usually takes about 3 to 4 weeks.

Kymriah must be administered in a treatment center that has been qualified by the Marketing Authorization Holder (MAH). Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and

trained for Kymriah administration and management of patients treated with Kymriah. A minimum of two doses of tocilizumab per patient for use in the event of cytokine release syndrome and emergency equipment must be available on site prior to infusion. Treatment center should have timely access to additional doses of tocilizumab (see Table 5-1).

For autologous use only

For intravenous use only. A leukocyte depleting filter should not be used

For single treatment

Dosage regimen

Kymriah is provided as a single, one-time treatment.

Dosage in pediatric and young adult B-cell patients:

- For patients 50 kg and below: 0.2 to 5.0 x 10^6 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).

Dosage in DLBCL and FL patients:

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

Pre-treatment conditioning (Lymphodepleting chemotherapy)

The availability of Kymriah must be confirmed prior to starting the lymphodepleting regimen. For B-cell ALL and DLBCL indications, Kymriah is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. For FL, Kymriah is recommended to be infused 2 to 6 days after completion of the lymphodepleting chemotherapy.

Lymphodepleting chemotherapy may be omitted if a patient is experiencing significant cytopenia, e.g., white blood cell (WBC) count less than 1,000/microliter within one week prior to infusion.

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

B-cell ALL: The recommended lymphodepleting chemotherapy regimen is:

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

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

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

DLBCL and FL: The recommended lymphodepleting chemotherapy regimen is:

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

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

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

3.3 Special Populatoins Dosage and Administration

Renal and hepatic impairment

As a cell based therapy, Kymriah is not expected to undergo renal elimination or hepatic metabolism. No studies have been performed in patients with renal or hepatic impairment.

Pediatric patients

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

DLBCL and FL: The safety and efficacy of Kymriah in pediatric and adoleacnet DLBCL patients below 18 years of age has not been established due to limited evidence.

Geriatric patients (65 years of age or above)

B-cell ALL: The safety and efficacy of Kymriah in this population has not been established.

DLBCL and FL: No dose adjustment is required in patients 65 years of age or above.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)

There is no experience with manufacturing Kymriah for patients with a positive test for HIV or with active HBV or active HCV. Leukapheresis material from these patients will not be accepted for Kymriah manufacturing. Screening for HBV, HCV, and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing.

Active central nervous system (CNS) leukemia or lymphoma

There is limited experience of 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.

Concomitant diseases

Patients with active CNS disorder or inadequate renal, hepatic, pulmonary or cardiac function were excluded from the studies. These patients are likely to be more vulnerable to the consequences of the adverse reactions described after Kymriah infusion and require special attention.

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 section 5 Warnings and precautions).

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies.
- Active uncontrolled infection.

- Active Graft Versus Host Disease (GVHD).
- Significant clinical worsening of leukemia burden or rapid progression of lymphoma following lymphodepleting chemotherapy.

Method of administration

Premedication:

To minimize potential acute infusion reactions, it is recommended to premedicate patients with acetaminophen/paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to Kymriah infusion. The prophylactic use of systemic corticosteroids should be avoided as it may interfere with the activity of Kymriah (see section 5 Warnings and precautions).

Monitoring after infusion

- Following infusion with Kymriah patients should be monitored 2 to 3 times for at least the first week for signs and symptoms of cytokine release syndrome, neurological events and other toxicities. Physicians should consider inpatient observation or hospitalization at the first signs and symptoms of cytokine release syndrome and/or neurological events.
- Patients should be instructed to remain within proximity (2 hours of travel) of a qualified clinical facility for at least 4 weeks following infusion.

Precautions to be taken before handling or administering Kymriah

Kymriah contains genetically-modified human blood cells. Healthcare professionals handling Kymriah should therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases as for any human-derived materials.

Preparation for infusion

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

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

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

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

If more than one infusion bag has been received for the treatment dose, the second bag should not be thawed until after the content of the first bag has been safely 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 and notify Novartis.

Administration

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

Kymriah should be administered as an intravenous infusion through latex free tubing without a leukocyte depleting filter, approximately at 10 to 20 mL per minute by gravity flow. Sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Kymriah has been infused, Kymriah infusion bag should be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to assure as many cells as possible are infused into the patient.

In clinical trials intravenous push was an alternate method for the administration of low volumes of Kymriah. For special precautions for disposal see section 14 Pharmaceutical information.

4 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.

5 Warnings and Precautions

5.1 Warnings / Precautions

Patient information

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

Blood, organ, tissue and cell donation

Patients treated with Kymriah should not donate blood, organs, tissues, sperms, oocytes and other cells.

Cytokine release syndrome

Cytokine release syndrome (CRS), including life threatening or fatal events, occurred frequently after Kymriah infusion. In almost all cases, development of CRS occurred between 1 to 10 days (median onset 3 days) after Kymriah infusion in pediatric and young adult B-cell ALL patients, between 1 and 9 days (median onset 3 days) after Kymriah infusion in adult DLBCL patients and between 1 to 14 days (median onset 4 days) after Kymriah infusion in

adult FL patients. The median time to resolution of CRS was 8 days in B-cell ALL and 7 days in DLBCL patients and 4 days in FL patients.

Signs and symptoms of CRS may include high fever, hypotension, hypoxia, dyspnea, tachypnea, tachycardia, fatigue, headache, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, and, anorexia. Organ dysfunction, including cardiac insufficiency, renal insufficiency and liver injury with accompanying elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT) or elevated total bilirubin may also be observed. In addition, disseminated intravascular coagulation (DIC) with low fibrinogen levels, capillary leak syndrome (CLS), macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) may occcur in the setting of CRS. Patients should be closely monitored for signs or symptoms of these events including fever.

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

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

In all indications, appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any existing infections should be ensured. Infections may also occur during CRS and may increase the risk of a fatal event.

Management of Cytokine Release Syndrome associated with Kymriah

CRS should be managed solely based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 5-1. Anti-interleukin-6 based therapy such as tocilizumab has been administered for moderate or severe CRS associated with Kymriah. A minimum of two doses of tocilizumab per patient must be available on site prior to Kymriah infusion. The treatment center should have timely access to additional doses of tocilizumab. Corticosteroids may be administered in cases of life-threatening emergencies. Tisagenlecleucel continues to expand and persist following administration of tocilizumab and corticosteroids. Patients with medically significant cardiac dysfunction should be managed by standards of critical care; measures such as echocardiography should be considered. Tumor Necrosis Factor (TNF) antagonists are not recommended for management of Kymriah associated CRS.

A detailed treatment algorithm for the management of CRS (Lee et al. 2014) is presented below in Table 5-1.

Table 5-1 CRS management

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
Mild symptoms requiring symptomatic treatment only, e.g.: - low fever	Exclude other causes (e.g. infection) and treat specific symptoms with e.g. antipyretics, anti-	Not applicable	Not applicable

CRS severity	Symptomatic treatment	Tocilizumab	Corticosteroids
- fatigue - anorexia - etc.	emetics, analgesics, etc. If neutropenic, administer antibiotics per local guidelines.		
Symptoms requiring moderate intervention: - high fever - hypoxia - mild hypotension	Antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.	If no improvement after symptomatic treatment administer tocilizumab i.v. over 1 hour: – 8 mg/kg (max. 800 mg) if body weight ≥ 30 kg – 12 mg/kg if body weight <30 kg If no improvement, repeat every 8 hours (max total of 4 doses)*	If no improvement within 12-18 hours of tocilizumab, administer a daily dose of 2 mg/kg i.v. methylprednisolone (or equivalent) until vasopressor and oxygen no longer needed, then taper*.
Symptoms requiring aggressive intervention: - Hypoxia requiring high-flow oxygen supplementation or - Hypotension requiring high-dose or multiple vasopressors	High-flow oxygen Intravenous fluids and high-dose vasopressor Treat other organ toxicities as per local guidelines		
Life-threatening symptoms: - Hemodynamic instability despite i.v. fluids and vasopressors - Worsening respiratory distress - Rapid clinical deterioration	Mechanical ventilation Intravenous fluids and high-dose vasopressor Treat other organ toxicities as per local guidelines		

*If no improvement after tocilizumab and steroids, consider other anti-cytokine and anti-T cell therapies following institutional policy and published guidelines.

Alternative CRS management strategies may be implemented based on appropriate institutional or academic guidelines.

Neurological toxicities

Neurological toxicities, in particular signs and symptoms of encephalopathy, confusional state and/or delirium can occur with Kymriah and can be severe or life-threatening. Other manifestations include depressed level of consciousness, seizures, aphasia and speech disorder. The majority of neurological toxicities occurred within 8 weeks following Kymriah infusion and were transient. The median time to onset of the first neurological events occuring at any time following Kymriah infusion was 8 days in B-cell ALL, 6 days in DLBCL and 9 days for FL. The median time to resolution was 7 days for B-cell ALL, 13 days for DLBCL and 2 days for FL.

Neurological events can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

Patients should be monitored for neurological events. In case of neurological events, patients should be diagnostically worked up and managed depending on the underlying pathophysiology and in accordance with local standard of care.

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.

Serious infections, including life threatening or fatal infections, frequently 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 regular surveillance testing should be employed prior to and during treatment with Kymriah. Infections are known to complicate the course and management of concurrent CRS.

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

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

Prolonged cytopenias

Patients may continue to exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Kymriah and should be managed per standard guidelines. The majority of patients who had cytopenias at day 28 following Kymriah treatment resolved to Grade 2 or below within three months after treatment for pediatric ALL and DLBCL patients, and within 6 months for FL patients. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte macrophage colony stimulating factor (GM CSF), have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after Kymriah infusion and until CRS has resolved.

Secondary malignancies

Patients treated with Kymriah may develop secondary malignancies and, therefore, should be monitored life-long. In the event that a secondary malignancy occurs, Novartis should be contacted to obtain instructions to collect patient samples for testing (add local contact and phone number).

Hypogammaglobulinemia

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

Live vaccines

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

Tumor lysis syndrome

Tumor lysis syndrome (TLS), which may be severe, has occasionally been observed. To minimize risk of TLS, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to Kymriah infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines.

Prior stem cell transplantation

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

Viral reactivation

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

Prior treatment with anti CD19 therapy

There is limited experience with Kymriah in patients exposed to prior CD19 directed therapy. Kymriah is not recommended if the patient has a CD19 negative relapse of leukemia after previous anti-CD19 treatment.

Interference with serological testing

Due to limited and short spans of identical genetic information between the lentiviral vector used to create Kymriah and HIV, some commercial HIV nucleic acid tests (NAT) may give a false positive result.

Content of dextran 40 and dimethyl sulfoxide (DMSO)

This medicinal product contains 11 mg dextran 40 and 82.5 mg dimethyl sulfoxide (DMSO) per mL. Each of these excipients are known to possibly cause anaphylactic reaction following parenteral administration. All patients should be observed closely during the infusion period.

Fetal risk

There is no preclinical or clinical data to assess whether Kymriah constitutes a risk to a pregnant woman or the fetus (see section Use in specific populations).

5.3 Effects on ability to use machines

Due to the potential for neurological toxicities, including alteration of consciousness and seizures, patients receiving Kymriah are at risk for altered or decreased consciousness and 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.

6 Warnings in Special Populations

6.1 Pregnancy

Risk summary

There are no available data with Kymriah use in pregnant women. No animal studies have been conducted with Kymriah to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if Kymriah has the potential to be transferred to the fetus via the placenta and could cause fetal toxicity, including B-cell lymphocytopenia. Kymriah is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Pregnant woman should be advised on the potential risks to the fetus. Pregnancy after Kymriah therapy should be discussed with the treating physician.

Pregnant women who have received Kymriah may have hypogammaglobulinemia. Assessment of immunoglobulin levels is indicated in newborns of mothers treated with Kymriah.

6.2 Lactation

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

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

6.3 Childbearing potential

There is a potential for Kymriah to cause fetal toxicity.

Pregnancy testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with KYMRIAH.

Contraception

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

Sexually active males, who have received Kymriah, should use a condom during intercourse with a female of reproductive potential or a pregnant woman. There are insufficient exposure data to provide a recommendation concerning the duration of contraception following treatment with Kymriah.

Pregnancy or fathering a child after Kymriah therapy should be discussed with the treating physician.

See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

Infertility

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

7 Interactions

No pharmacokinetic/pharmacodynamic drug interaction studies with tisagenlecleucel have been performed.

The co-administration of agents known to inhibit T-cell function has not been formally studied. Administration of tocilizumab and steroids as per the cytokine release syndrome treatment algorithm does not impact the expansion and persistence of CAR-T cells. The co-administration of agents known to stimulate T-cell function has not been investigated and the effects are unknown.

8 Adverse Reactions / Undesirable effects

8.1 Clinically Significant Adverse Reactions

Description of selected adverse drug reactions

Cytokine release syndrome

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

In the ongoing clinical study in DLBCL (N=115), CRS was reported in 57% of patients, (23% with Grade 3 or 4).

In the ongoing clinical study in FL (N=97), CRS was reported in 50% of patients. No Grade 3 or 4 events were reported.

Cytokine release syndrome was graded per the Penn criteria in the pediatric and young adult B-cell ALL and DLBCL trials as follows: Grade 1: mild reactions, requiring supportive care; Grade 2: moderate reactions, requiring intravenous therapies; Grade 3: severe reactions, requiring low-dose vasopressors or supplemental oxygen; Grade 4: life-threatening reactions, requiring high-dose vasopressors or intubation; Grade 5: death.

Cytokine release syndrome was graded per the Lee criteria in the FL trial as follows [34]: Grade 1: mild general symptoms requiring symptomatic treatment; Grade 2: symptoms requiring moderate intervention such as low-flow oxygen supplementation or low-dose vasopressor; Grade 3: symptoms requiring aggressive intervention, such as high-flow oxygen supplementation and high-dose vasopressor; Grade 4: life threatening symptoms requiring intubation; Grade 5: death.

For clinical management of CRS, see section 5 Warnings and precautions and Table 6-1.

Infections and febrile neutropenia

In B-cell ALL patients severe infections (greater than Grade 3), which can be life-threatening or fatal, occurred in 48% of patients after Kymriah infusion. The overall incidence (all grades) was 73% (unspecified 57%, viral 38%, bacterial 27%, and fungal 15%) (see section 5 Warnings and precautions). Forty-three % of the patients experienced an infection of any type within 8 weeks after Kymriah infusion.

In DLBCL patients severe infections (greater than Grade 3), which can be life-threatening or fatal, occurred in 34% of patients. The overall incidence (all grades) was 58% (unspecified 48%, bacterial 15%, fungal 11% and viral 11%) (see section 5 Warnings and precautions). 37% of the patients experienced an infection of any type within 8 weeks.

In FL patients severe infections (Grade 3 or 4), occurred in 16% of patients. The overall incidence (all grades) was 50% (unspecified 36%, viral 17%, bacterial 6%, and fungal 2%) (see

section 5 Warnings and precautions). Nineteen % of the patients experienced an infection of any type within 8 weeks.

Severe febrile neutropenia (Grade 3 or 4) was observed in 34% of pediatric and young adult B-cell ALL patients, 17% of DLBCL patients and 12% of FL patients. See section 5 Warnings and precautions for the management of febrile neutropenia before and after Kymriah infusion.

Long term cytopenia

Cytopenias are very common based on prior chemotherapies and Kymriah therapy. All pediatric and young B-cell ALL patients had a Grade 3 or 4 cytopenia at any time post Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 after Kymriah infusion were based on laboratory findings included a decreased count of white blood cells (57%), neutrophils (54%), lymphocytes (44%), thrombocytes (42%), and a decreased hemoglobin (13%).

All adult DLBCL patients experienced Grade 3 and 4 cytopenias at any time post Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 after Kymriah infusion based on laboratory findings included a decreased count of thrombocytes (39%), lymphocytes (29%), neutrophils (25%), white blood cells (21%) and decreased hemoglobin (14%).

In adult patients with FL 99% had Grade 3 and 4 cytopenias at any time post Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 after Kymriah infusion based on laboratory findings included a decreased count of lymphocytes (23%), thrombocytes (17%), neutrophils (16%), white blood cells (13%) and decreased hemoglobin (3%).

Neurotoxic events

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

In pediatric and young adult B-cell ALL patients, manifestations of encephalopathy and/or delirium occurred in 39% of patients (13% Grade 3 or 4) within 8 weeks after Kymriah infusion. In DLBCL patients, these occurred in 20% of patients (11% were Grade 3 or 4) within 8 weeks after Kymriah infusion. In FL patients, these occurred in 9% of patients (1% were Grade 3 or 4) within 8 weeks after Kymriah infusion. Among the neurotoxic events in FL patients, immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 4% of patients (1% Grade 3 or 4), all within 8 weeks of Kymriah infusion.

The other most common neurological event at any time post Kymriah infusion was headache (35% in pediatric and young adult B-cell ALL patients, 21% in DLBCL patients and 26% in FL patients).

Hypogammaglobulinaemia

Hypogammaglobulinaemia was reported in 53% of patients treated with Kymriah for r/r ALL, 17% of patients with r/r DLBCL and 17% of patients with r/r FL.

Pregnant women who have received Kymriah may have hypogammaglobulinaemia. Immunoglobulin levels should be assessed in newborns of mothers treated with Kymriah.

8.2 Clinical Trial Experience

Summary of the safety profile

Safety assessment was based on a total of 291 patients (with pediatric and young adult B-cell ALL, DLBCL and FL) receiving Kymriah in three multi-center pivotal clinical studies.

Pediatric and young adult B-cell ALL

The adverse reactions described in this section were characterized in 79 patients infused with Kymriah in the multi-center, pivotal clinical study CCTL019B2202.

- The most common non-hematological adverse reactions (≥40%) were cytokine release syndrome (77%), infections (73%), hypogammaglobulinaemia (53%) and pyrexia (42%).
- The most common haematological laboratory abnormalities were decreased white blood cells (100%), decreased haemoglobin (100%), decreased neutrophils (100%), decreased lymphocytes (100%) and decreased platelets (97%).
- Grade 3 and Grade 4 adverse reactions were reported in 89% of patients. The most common (>40%) Grade 3 and Grade 4 non-haematological adverse reactions were CRS (48%).
- The most common (>40%) Grade 3 and Grade 4 haematological laboratory abnormalities were decreased white blood cells (97%), decreased lymphocytes (96%), decreased neutrophils (95%), decreased platelets (77%), and decreased haemoglobin (48%).
- Grade 3 or 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (82% of patients) compared to after 8 weeks post-infusion (51% of patients).

DLBCL

The adverse reactions described in this section were characterized in 115 patients infused with Kymriah in one global multicenter international study, i.e. the ongoing pivotal clinical study CCTL019C2201.

- The most common non-haematological adverse reactions were cytokine release syndrome (57%), infections (58%), pyrexia (35%), diarrhoea (31%), nausea (29%), fatigue (27%), and hypotension (25%).
- The most common haematological laboratory abnormalities were decreased lymphocytes (100%), decreased white blood cells (99%), decreased haemoglobin (99%), decreased neutrophils (97%), and decreased platelets (95%).
- Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (34%) and cytokine release syndrome (23%).
- The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (82%), white blood cell count decreased (78%), haemoglobin decreased (59%) and platelet count decreased (56%).

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

FL

Kymriah in one global multicenter international study, i.e. the ongoing pivotal clinical study CCTL019E2202.

- The most common non-haematological adverse reactions (>25%) were cytokine release syndrome (50%), infections (50%), and headache (26%).
- The most common haematological laboratory abnormalities were decreased haemoglobin (94%), decreased lymphocytes (92%), decreased white blood cells (91%), decreased neutrophils (89%), and decreased platelets (89%).
- Grade 3 and 4 adverse reactions were reported in 75% of patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (16%).
- The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (87%), white blood cell count decreased (74%), neutrophil count decreased (71%), platelet count decreased (26%), and haemoglobin decreased (25%).
- Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (70%) compared to after 8 weeks post-infusion (40%).

Table 8-1 Adverse drug reactions observed in clinical studies

Infections and infestations[1)]	
Very common:	Infections - pathogen unspecified, viral infections, bacterial infections
Common:	Fungal infections
Blood and lymphatic system disorders	
Very common:	Anaemia, haemorrhage[2)], febrile neutropenia, neutropenia, thrombocytopenia
Common:	Haemophagocytic lymphohistiocytosis, leukopenia, pancytopenia, coagulopathy, lymphopenia
Uncommon:	B-cell aplasia
Immune system disorders	
Very common:	Cytokine release syndrome, hypogammaglobulinaemia[3)]
Common:	Infusion-related reaction, graft-versus-host disease[4)]
Metabolism and nutrition disorders	
Very common:	Decreased appetite, hypokalaemia, hypophosphataemia, hypomagnesaemia
Common:	Hypoalbuminaemia[5)], hyperglycaemia, hyponatraemia, hyperuricaemia, hypercalcaemia, tumour lysis syndrome, hyperkalaemia, hyperphosphataemia, hypernatraemia, hypermagnesaemia, hyperferritinaemia[6)], hypocalcaemia
Psychiatric disorders	
Common:	Anxiety, delirium[7)], sleep disorder[8)]
Nervous system disorders	
Very common:	Headache[9)], encephalopathy[10)]
Common:	Dizziness[11)], peripheral neuropathy[12)], tremor[13)], motor dysfunction[14)], seizure[15)], speech disorders[16)], neuralgia[17)], immune effector cell-associated neurotoxicity syndrome**
Uncommon:	Ischaemic cerebral infarction, ataxia[18)]
Eye disorders	
Common:	Visual impairment[19)]

Cardiac disorders	
Very common:	Tachycardia[20)]
Common:	Cardiac failure[21)], cardiac arrest, atrial fibrillation
Uncommon:	Ventricular extrasystoles
Vascular disorders	
Very common:	Hypotension[22)]
Common:	Thrombosis[23)], capillary leak syndrome, hypertension
Uncommon:	Flushing
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough[24)], dyspnoea[25)], hypoxia
Common:	Oropharyngeal pain[26)], pulmonary oedema[27)], nasal congestion, pleural effusion, tachypnoea, acute respiratory distress syndrome
Uncommon:	Lung infiltration
Gastrointestinal disorders	
Very common:	Diarrhoea, nausea, vomiting, constipation, abdominal pain[28)]
Common:	Stomatitis, abdominal distension, dry mouth, ascites
Hepatobiliary disorders	
Very common:	Hepatic enzyme increased[29)]
Common:	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Very common:	Rash[30)]
Common:	Pruritus, erythema, hyperhidrosis, night sweats
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, musculoskeletal pain[31)]
Common:	Myalgia
Renal and urinary disorders	
Very common:	Acute kidney injury[32)]
General disorders and administration site conditions	
Very common:	Pyrexia, fatigue[33)], oedema[34)], pain[35)]
Common:	Influenza-like illness, asthenia, multiple organ dysfunction syndrome, chills
Investigations	
Very common:	Lymphocyte count decreased*, white blood cell count decreased*, haemoglobin decreased*, neutrophil count decreased*, platelet count decreased*
Common:	Blood bilirubin increased, weight decreased, blood fibrinogen decreased, international normalised ratio increased, fibrin D dimer increased, activated partial thromboplastin time prolonged, prothrombin time prolonged

1) Infections and infestations presented reflect high-level group terms.
2) Haemorrhage includes anal haemorrhage, blood blister, blood urine present, catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, cystitis haemorrhagic, duodenal ulcer haemorrhage, disseminated intravascular coagulation, epistaxis, eye contusion, gastrointestinal haemorrhage, gingival bleeding, haematochezia, haemarthrosis, haematemesis, haematoma, haematuria, haemoptysis, heavy menstrual bleeding, large intestinal haemorrhage, melaena, mouth haemorrhage, mucosal haemorrhage, oral blood blister, peritoneal haematoma, petechiae, pharyngeal haemorrhage, post-procedural haemorrhage, pulmonary haemorrhage, purpura, retinal haemorrhage, subdural haematoma, traumatic haematoma, tumour haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.
3) Hypogammaglobulinaemia includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, immunodeficiency,

immunodeficiency common variable and hypogammaglobulinaemia.
4) Graft-versus-host Disease (GvHD) includes GvHD, GvHD in gastrointestinal tract, GvHD in skin.
5) Hypoalbuminaemia includes blood albumin decreased, hypoalbuminaemia.
6) Hyperferritinaemia includes hyperferritinaemia, serum ferritin increased.
7) Delirium includes agitation, delirium, hallucination, hallucination visual, irritability and restlessness.
8) Sleep disorder includes sleep disorder, insomnia and nightmare.
9) Headache includes headache and migraine.
10) Encephalopathy includes depressed level of consciousness, mental status changes, automatism, cognitive disorder, confusional state, disturbance in attention, encephalopathy, somnolence, lethargy, memory impairment, metabolic encephalopathy and thinking abnormal.
11) Dizziness includes dizziness, presyncope and syncope.
12) Peripheral neuropathy includes dysaesthesia, paraesthesia, peripheral sensory neuropathy, neuropathy peripheral, hyperaesthesia and hypoaesthesia.
13) Tremor includes dyskinesia and tremor.
14) Motor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy.
15) Seizure includes seizure, generalised tonic-clonic seizures and status epilepticus.
16) Speech disorders includes speech disorders, dysarthria and aphasia.
17) Neuralgia includes neuralgia and sciatica.
18) Ataxia includes ataxia and dysmetria.
19) Visual impairment includes vision blurred and visual impairment.
20) Tachycardia includes sinus tachycardia, supraventricular tachycardia, tachycardia.
21) Cardiac failure includes cardiac failure, left ventricular dysfunction, cardiac failure congestive and right ventricular dysfunction.
22) Hypotension includes hypotension and orthostatic hypotension.
23) Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis.
24) Cough includes cough, productive cough and upper-airway cough syndrome.
25) Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory distress and respiratory failure.
26) Oropharyngeal pain includes oral pain and oropharyngeal pain.
27) Pulmonary oedema includes acute pulmonary oedema and pulmonary oedema.
28) Abdominal pain includes abdominal pain, abdominal pain upper and abdominal discomfort.
29) Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hepatic enzyme increased, transaminases increased.
30) Rash includes dermatitis, dermatitis acneiform, dermatitis contact, rash, rash maculo-papular, rash papular and rash pruritic.
31) Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, neck pain, non-cardiac chest pain.
32) Acute kidney injury includes acute kidney injury, anuria, azotaemia, blood creatinine abnormal, blood creatinine increased, renal failure, renal tubular dysfunction and renal tubular necrosis.
33) Fatigue includes fatigue and malaise.
34) Oedema includes fluid retention, fluid overload, oedema peripheral, generalised oedema, localised oedema, face oedema and peripheral swelling.
35) Pain includes pain and pain in extremity.
* Frequency is based on laboratory values. Patients are counted only for the worst grade observed post baseline.
** Abbreviated as ICANS. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.

8.3 Post-marketing Experience

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Kymriah via spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to tisagenlecleucel exposure.

Frequency not known: anaphylactic reaction/infusion related reaction, neurotoxicity.

9 Overdose

Not applicable.

10 Clinical Pharmacology

Pharmacotherapeutic group, ATC

ATC code: L01XX71.

10.1 Mechanism of action

Tisagenlecleucel is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. The CAR is comprised of a murine single chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumor activity while 4-1BB enhances the expansion and persistence of tisagenlecleucel. Upon binding to CD19 expressing cells, the CAR transmits a signal to promote T-cell expansion and persistence of tisagenlecleucel.

10.2 Pharmacodynamics

No information avaliable.

10.3 Preclinical safety data

Non-clinical safety assessment of Kymriah addressed the safety concerns of potential uncontrolled cell growth of transduced T-cells *in vitro* and *in vivo* as well as dose-related toxicity, biodistribution and persistence. No such risks were identified based on these studies.

Carcinogenicity and mutagenicity

Genotoxicity assays and carcinogenicity studies in rodents are not appropriate to assess the risk of insertional mutagenesis for genetically-modified cell therapy products. No alternative adequate animal models are available.

In vitro expansion studies with CAR-positive T-cells (Kymriah) from healthy donors and patients (Kymriah) 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, which represents the longest meaningful observation period for immunocompromised mouse models. 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 as no adequate animal model is available.

Juvenile animal studies

Juvenile toxicity studies were not conducted.

11 Pharmacokinetics

Following infusion of Kymriah into pediatric and young adult r/r B-cell ALL, r/r DLBCL and r/r FL patients, the CAR-T positive cells typically exhibited an initial rapid expansion followed by a slower bi-exponential decline. High-interindividual variabilty was associated with the *in vivo* exposure metrics (AUC0-28d and Cmax) across all indications.

Cellular kinetics in pediatric B-cell ALL patients

A summary of cellular kinetic parameters of tisagenlecleucel in pediatric and young adult B-cell ALL patients is provided in Table 11-1 below.

The maximal expansion (Cmax) was approximately 1.6-fold higher in CR/CRi patients (n=103) compared with non-responding (NR) patients (n=10) as measured by qPCR. Transgene persistence has been detected up 916 days in responding patients in pooled studies B2202 and B2205J). Delayed and lower expansion was observed in NR patients compared to CR/CRi patients.

Table 11-1 Cellular kinetic parameters of tisagenlecleucel in pediatric and young adult r/r B-cell ALL (B2202, B2205J)

Parameter	Summary Statistics	Responding Patients (CR/CRi) N=105	Non-Responding Patients (NR) N=12
Cmax (copies/ micrograms)	Geometric mean (CV%), n	35,300 (154.0), 103	21,900 (80.7), 10
Tmax (day)	Median [min;max], n	9.83 [5.70;27.8], 103	20.1 [12.6;62.7], 10

$AUC_{0\text{-}28d}$ (copies/ micrograms*day)	Geometric mean (CV%), n	309,000 (178.1), 103	232,000 (104.5), 8
$T_{½}$ (day)	Geometric mean (CV%), n	25.2 (307.8), 71	3.80 (182.4), 4
T_{last} (day)	Median [min;max], n	166 [20.9; 916], 103	28.8 [26.7; 742], 9

Cellular kinetics in DLBCL patients

A summary of cellular kinetic parameters of tisagenlecleucel in DLBCL patients is provided in Table 11-2 below.

AUC0-28d and Cmax were 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.

Table 11-2 Cellular kinetic parameters of tisagenlecleucel in r/r DLBCL patients

Parameter	Summary Statistics	Responding Patients (CR and PR) N=43	Non-Responding Patients (SD/PD/Unknown) N=72
Cmax (copies/micrograms)	Geometric mean (CV%), n	5840 (254.3), 43	5460 (326.8), 65
Tmax (day)	Median [min;max], n	9.00 [5.78;19.8], 35	8.84 [3.04;27.7],65
AUC0-28d (copies/micrograms*day)	Geometric mean (CV%), n	61200 (177.7), 40	67000 (275.2), 56
T½ (day)	Geometric mean (CV%), n	129 (199.2), 33	14.7 (147.1), 44
Tlast (day)	Median [min;max], n	551 [17.1; 1030], 43	61.4 [19.8; 685], 56

Cellular kinetics in FL patients

A summary of cellular kinetic parameters of tisagenlecleucel in FL patients by BOR is provided in Table 11-3 below.

The geometric mean AUC0-84d in responders (CR and PR) was similar to that in non-responders (SD and PD) based on clinical BOR. However, the geometric mean AUC0-28d value of responders was 186% higher compared to non-responders, while the geometric mean Cmax value was 109% higher in responders compared to non-responders. However, considering the high inter-individual variability, small number of non-responders, overlapping expansion ranges observed between responders and non-responders, the exposure differences should be interpreted with caution.

Table 11-3 Cellular kinetic parameters of tisagenlecleucel in r/r FL patients

Parameter	Summary Statistics	Responding Patients (CR and PR) N=81	Non-Responding Patients (SD/PD) N=12

Cmax (copies/micrograms)	Geometric mean (CV%), n	6280 (331), 67	3000 (1190), 8
Tmax (day)	Median [min;max], n	9.92 [2.62, 28.0], 67	13.0 [7.73,16.0], 8
AUC0-28d (copies/micrograms*day)	Geometric mean (CV%), n	57500 (261), 66	20100 (18100), 7
T½ (day)	Geometric mean (CV%), n	43.8 (287), 43	24.4 (180), 6
Tlast (day)	Median [min;max], n	191 [19.9, 558], 73	107 [18.7, 366], 10

Concomitant therapy with tocilizumab and corticosteroids

In patients treated with tocilizumab or low dose steroids for the management of CRS, tisagenlecleucel transgene continues to expand and persist following administration of tocilizumab and low dose steroids.

Cellular kinetics

Distribution

In pediatric and young adult B-cell ALL patients, tisagenlecleucel has been shown to be present in the blood as well as bone marrow beyond 2 years. The blood to bone marrow partitioning of Kymriah in bone marrow was 47.2% of that present in blood at Day 28 while at Months 3 and 6 it distributes at 68.3% and 69% (Study B2202 and B2205J), respectively. Tisagenlecleucel also traffics and persists in cerebrospinal fluid in pediatric and young adult B-cell ALL patients (Study B2101J) for up to 1 year.

In DLBCL adult patients (Study C2201), Kymriah has been detected for up to 3 years in peripheral blood and up to Month 9 in bone marrow for complete responder patients. The blood to bone marrow partitioning in bone marrow was nearly 70% of that present in blood at Day 28 and 50% at Month 3 in responder and non-responder patients.

In adult FL patients (Study E2202), Kymriah has been detected for up to 18 months in peripheral blood and up to Month 3 in bone marrow for complete responder patients. The blood to bone marrow partitioning in bone marrow was 54% at Month 3 in responder and non-responder patients.

Metabolism

Not applicable, Kymriah is an immunocellular therapy.

Elimination

The elimination profile of Kymriah includes a decline in peripheral blood in a bi-exponential manner and bone marrow.

Linearity/non-linearity

There is no apparent relationship between dose and AUC0-28d or Cmax.

Special populations

Geriatric population (65 years of age or above)

The scatter plot of kinetic parameters (AUC0-28d and Cmax) relative to age (DLBCL patients 22 to 76 years, FL patients 29 to 73 years) showed that there was no significant relationship between cell kinetic parameters and age. **Gender**

Gender is not a significant characteristic influencing tisagenlecleucel expansion in B-cell ALL, DLBCL patients and FL patients. In Study B2202, there were 43% female and 57% male patients and in Study C2201 there were 38% female and 62% male patients. In Study E2202, there were 34% female and 66% male patients. Further, in Study E2202, the geometric means of the exposure parameters (Cmax and AUC0-28d) were shown to be 111% and 106% higher, respectively, in female patients compared to male patients. Although the interpretation of expansion in relation to gender is difficult due to overlapping ranges and high inter-subject variability.

Race/ethnicity

There is limited evidence that race/ethnicity impact the expansion of Kymriah in pediatric and young adult ALL, DLBCL and FL. In Study B2202 there were 73.4% of Caucasian, 12.7% of Asian and 13.9% of other ethnic patients.

In Study C2201, there were 85% of Caucasian, 9% of Asian, 4% of Black or African American patients, and three patients (3%) with unknown race.

In Study E2202, there were 75% of Caucasian, 13% of Asian, 1% of Black or African American, and 10% of patients with unknown race.

Body weight

In DLBCL, FL and ALL patients, across the weight ranges ((DLBCL: 38.4 to 186.7 kg; ALL: 14.4 to 137 kg ; FL: 44.3 to 127.7 kg), the scatter plots of qPCR cellular kinetic parameters versus weight revealed no apparent relationship between cellular kinetic parameters with weight.

Renal and hepatic impairment

Kymriah was not studied in patients with hepatic and renal impairment.

Prior stem cell transplantation

Prior stem cell transplantation did not impact the expansion/persistence of tisagenlecleucel in pediatric and young adult B-cell ALL patients, adult DLBCL or adult FL patients.

Immunogenicity

In clinical studies, humoral immunogenicity of tisagenlecleucel was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients tested positive for pre-dose anti-mCAR19 antibodies in pediatric and young adult ALL (B2202, 91.1%), adult DLBCL (C2201, 93.9%) and adult FL (E2202; 66.0%) patients.

Treatment-induced anti-mCAR19 antibodies were found in 40.5% of pediatric and young adult ALL, 8.7% of adult DLBCL and 28.7% of adult FL patients. Pre-existing and treatment-induced antibodies were not associated with an impact on clinical response nor did they have an impact on the expansion and persistence of tisagenlecleucel. There is no evidence that the presence of pre-existing and treatment-induced anti-mCAR19 antibodies impacts the safety or effectiveness of Kymriah.

T-cell immunogenicity responses were not observed in pediatric and young adult B-cell ALL, adult r/r DLBCL and adult FL patients.

12 Clinical Studies

Acute Lymphoblastic Leukemia (ALL)

The safety and efficacy of Kymriah treatment in patients with relapsed and refractory (r/r) pediatric and young adults B-cell ALL, were evaluated in one pivotal study (B2202) and two supportive studies (B2205J and B2101J). All patients had leukapheresis products collected and cryopreserved prior to or during study entry.

CCTL019B2202 (Study 1)

The pivotal study (B2202) is a multicenter, single-arm, open-label phase II study in pediatric and young adult patients with r/r B-cell acute lymphoblastic leukemia. Ninety-seven patients were enrolled, 79 were infused; 18 patients discontinued prior to Kymriah infusion (7 patients due to death; 8 patients due to Kymriah manufacturing related issues; 3 patients due to adverse events).

Patients infused were between the age of 3 and 24 years and 8% had primary refractory disease. Sixty-one percent of patients had a prior stem cell transplant. The majority of patients (69/79, 87%) received bridging therapy while waiting for Kymriah. A total of 76 out of 79 patients who received Kymriah infusion also received lymphodepleting chemotherapy after enrollment and prior to the Kymriah infusion.

Efficacy was established through the primary endpoint of overall remission rate (ORR), which includes best overall response as complete remission (CR) or complete remission with incomplete blood count (CRi) within 3 months post infusion, as determined by Independent Review Committee (IRC) assessment, as well as secondary endpoints including duration of remission (DOR), and the proportion of patients who achieved CR or CRi with minimal residual disease (MRD) <0.01% by flow cytometry (MRD-negative). The median time from Kymriah infusion to the data cut-off date was 24.2 months (range: 4.5 to 35.1). The ORR within 3 months was 82.3% (65/79). See Table 12-1 for efficacy results from this study. ORR was consistent across all subgroups. Eight patients who received Kymriah infusion and achieved CR or CRi went to transplant while in remission Kymriah was administered in a qualified Kymriah treatment center in an inpatient and outpatient setting.

Table 12-1 B2202: Efficacy results in pediatric and young adult patients with relapsed/refractory B-cell Acute Lymphoblastic Leukemia (ALL)

Primary Endpoint	N=79

Overall Remission Rate (ORR) [1,2], n (%)	65 (82.3)
95% CI	(72.1, 90.0)
	p<0.0001
CR [3], n (%)	49 (62.0)
CRi [4], n (%)	16 (20.3)
NR[5], n (%)	7 (8.9)
Not evaluable, n (%)	7 (8.9)
Key Secondary Endpoint	**N=79**
CR or CRi with MRD negative bone marrow [6,7], n (%)	64 (81.0)
95% CI	(70.6, 89.0)
	p<0.0001
Duration of remission (DOR)[8]	**N=65**
% event free probability at 12 months	66.3
% event free probability at 18 months	66.3
Median (months) (95% CI)	Not reached (20.0, NE[9])
Other Secondary Endpoint	**N=79**
Overall survival (OS)	
% survival probability at 12 months	76.4
% survival probability at 24 months	66.3
Median (months) (95% CI)	Not reached (28.2, NE[9])

[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, circulating blasts in blood should be <1%, 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=65)
[9] NE= Not estimable

Diffuse large B-cell lymphoma (DLBCL)

The safety and efficacy of Kymriah treatment in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) who received ≥2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous haematopoietic stem cell transplantation (HSCT), was evaluated in an open-label, pivotal, single-arm study. 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, Richter's transformation, and Burkitt lymphoma were not enrolled in study C2201.

CCTL019C2201

The pivotal study (C2201) is a multicenter, single-arm phase II study in adult patients with relapsed or refractory DLBCL. Of 167 patients enrolled, 115 patients received infusion with Kymriah. For 13 patients Kymriah could not be manufactured. Reasons for discontinuation prior to Kymriah infusion included death (n=16), physician decision/ primary disease progression (n=16), adverse event (n=4), subject decision (n=2) and protocol deviation (n=1).

Median age of infused patients was 56 years (range 22 to 76 years), 76.5% of patients had Stage III-IV disease, 51% had received 3 or more prior lines of treatment for DLBCL. Forty-nine percent of patients had received prior stem cell transplant. Fifty-five percent of patients were refractory to last line of treatment. All patients had leukapheresis starting material collected and cryopreserved prior to or during study entry. The majority of patients (103/115, 90%) received bridging therapy while waiting for Kymriah and 107/115 patients (93%) received lymphodepleting chemotherapy. Kymriah was given as a single dose intravenous infusion in a qualified Kymriah treatment center in an inpatient and outpatient setting.

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 IRC assessment based on the Lugano Classification (Cheson et al 2014) as well as secondary endpoints including duration of response (DOR). The primary endpoint was assessed in 99 patients who received Kymriah manufactured at the Novartis U.S. facility and who have been followed for at least 3 months or discontinued earlier after Kymriah administration.

Among the 99 patients (Table 12-2) included in the primary analysis, the best ORR was 53.5% (53/99) with a 95% confidence interval (CI) of (43.2%, 63.6%). Forty patients (40.4%) achieved CR and 13 (13.1%) achieved PR. Among these 40 patients, 15 patients initially had an overall disease response of PR which improved to CR over time; most patients (13/15) achieved PR to CR conversion within 6 months post-tisagenlecleucel infusion. No patient who received Kymriah infusion went to transplant after achieving CR or PR.

Subgroup analyses demonstrated a homogeneous and consistent treatment effect across major demographic and prognostic subgroups.

Table 12-2 C2201: Efficacy results in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant

Primary Endpoint (patients included in the primary analysis)	**N=99**
Overall Response Rate (ORR) (CR+PR) [1,2], n (%) 95% CI	53 (53.5) (43.2, 63.6) p<0.0001
CR, n (%)	40 (40.4)
PR, n (%)	13 (13.1)
Duration of response (DOR)[3]	N=53
Median (months) (95% CI) % relapse free probability at 12 months % relapse free probability at 18 months	Not reached (10.0, NE[5]) 63.2% 63.2%

Other Secondary Endpoints (all patients)	N=115
Overall survival (OS)[4]	
Median (months) (95% CI)	10.3 (6.6, 21.1)
% survival probability at 12 months	47.9%
% survival probability at 24 months	39.1%

[1] ORR was calculated based on the first 99 patients who received Kymriah manufactured at the Novartis U.S. facility and have completed at least 3 months follow up, or discontinued earlier

[2] The p-value is displayed as a descriptive statistic only, with no inferential interpretation (since the null hypothesis of ORR <20% was already rejected with p<0.0001 at a previous interim analysis).

[3] DOR was defined as time from achievement of CR or PR, whichever occurs first, to relapse or death due to DLBCL (N=53)

[4] OS was defined as time from date of Kymriah infusion to the date of death due to any cause (N=115)

[5] Not estimable

Follicular lymphoma (FL)

The safety and efficacy of Kymriah treatment in adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) were evaluated in a Phase II, single arm, multicenter open label study.

CCTL019E2202

The pivotal study E2202 (ELARA trial) is a multicenter, single-arm open label Phase II study in adult patients with r/r FL. The study included patients who were refractory to or relapsed within 6 months after completion of a second or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent), relapsed during or within 6 months after completion of anti-CD20 antibody maintenance therapy following at least two lines of therapy, or relapsed after autologous hematopoietic stem cell transplant (HSCT). The study excluded patients with active or serious infections, transformed lymphoma or other aggressive lymphomas, prior allogeneic HSCT, or disease with active CNS involvement.

Of 98 patients who enrolled and underwent leukapheresis, 97 patients received infusion with Kymriah. One patient achieved a complete response prior to infusion which was attributed to their prior line of therapy and was subsequently discontinued from the study due to physician decision prior to infusion. Of the 97 patients infused with Kymriah, 94 patients had measurable disease at baseline per Independent Review Committee (IRC) and were included in the efficacy analysis (Efficacy Analysis Set [EAS]). Kymriah was delivered for all enrolled patients.

Among the 94 patients in the efficacy population, important clinical characteristics include: median age was 57 years (range 29 to 73 years), 86% of patients had Stage III-IV disease at study entry, 61% had high FLIPI score, 65% had bulky disease at baseline, 79% were refractory to last line of treatment, 69% were double refractory, 37% received prior autologous stem cell transplant, and 65% had progression of disease within 24 months (POD24) of initiating their first anti-CD20 combination therapy. The median number of prior therapies was 4 (range: 2 to 13), with 26% having 2 prior lines, 20% having 3 prior lines, and 54% having ≥4 prior lines; 20% had received a PI3K inhibitor. Forty-four patients (47%) received bridging therapy between leukapheresis and administration of Kymriah and all patients received lymphodepleting chemotherapy. For all infused patients, Kymriah was administered as a single dose intravenous infusion in an inpatient or outpatient (18%) setting.

Efficacy was evaluated through the primary endpoint of complete response rate (CRR) determined by an IRC based on Lugano classification (Cheson et al 2014) as well as secondary endpoints of overall response rate (ORR), duration of response (DOR) and progression-free survival (PFS) per IRC, and overall survival (OS). The first disease assessment was scheduled to be performed at Month 3 post-infusion.

Among the 94 patients with measurable disease prior to infusion included in the efficacy analysis, with a median follow-up duration of 17 months, CR was observed in 65 patients (69%, 95% CI: 58.8, 78.3); 16 (17%) achieved PR. The ORR per IRC assessment was 86% (81 patients) (95% CI: 77.5, 92.4). All responders achieved their response (CR or PR) at the first performed post-infusion disease assessment. Of the 65 patients who achieved a CR, 15 patients initially had a PR. The majority of the patients converted to CR within 6 months post-infusion. No patient who received Kymriah infusion went to transplant while in response (CR or PR).

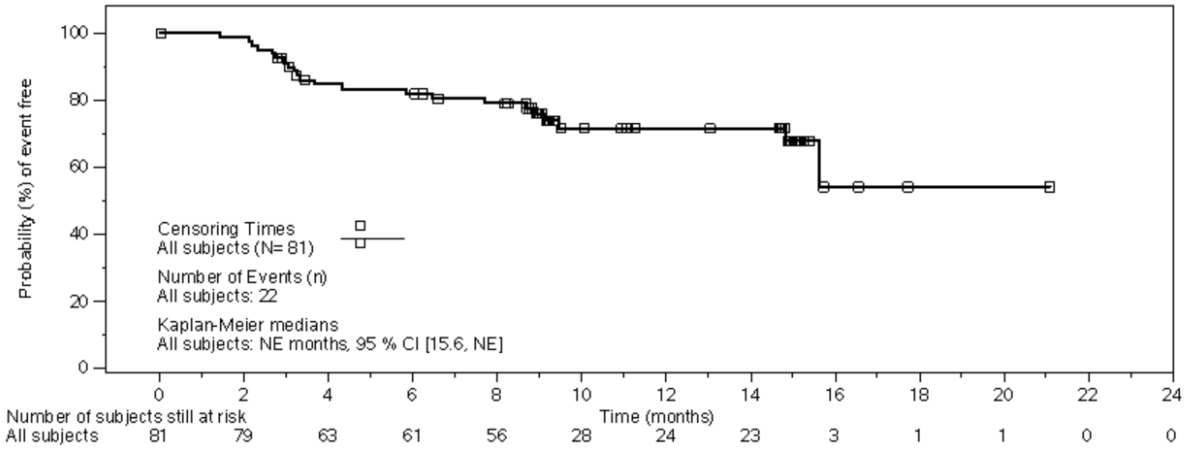
The probability for a patient to remain in response (DOR) ≥9 months was 76% (95% CI: 64.6, 84.2), while the probability for a patient who achieved a CR to remain in response ≥9 months was 87% (95% CI: 74.7, 93.1). The probability of remaining progression-free (PFS) at month 12 was 67% (95% CI: 56.0, 75.8), while the probability of survival (OS) at month 12 was 95% (95% CI: 88.0, 98.2).

Subgroup analyses demonstrated a homogeneous and consistent CRR across all subgroups, including the following high-risk prognostic subgroups: high FLIPI score (CRR of 63%), prior HSCT (CRR of 66%), POD24 (CRR of 59%), and double refractoriness (CRR of 66%).

Table 12-3 Study E2202: Efficacy results in adult patients with r/r FL

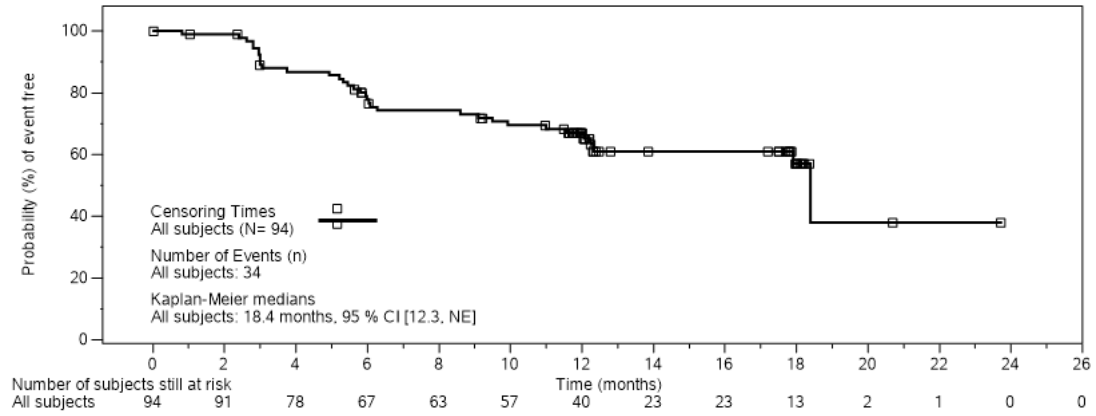
	Efficacy population N=94
Complete response rate (CRR), n (%)	65 (69.1)
95% CI	(58.8, 78.3)
Overall response rate (ORR), n (%)	81 (86.2)
95% CI	(77.5, 92.4)
Duration of response (DOR), months	
Median (95% CI)	Not reached (15.6, NE*)
% relapse free probability at 9 months, (95% CI)	76.0 (64.6, 84.2)
DOR in patients achieving BOR of CR, months	
Median (95% CI)	Not reached (15.6, NE)
% relapse free probability at 9 months, (95% CI)	86.5 (74.7, 93.1)
Progression-free survival (PFS), months	
Median (95% CI)	18.4 (12.3; NE)
PFS at month 12, % (95% CI)	67.0 (56.0, 75.8)
Overall survival (OS), months	
Median (95% CI)	Not reached
OS at month 12, % (95% CI)	95.3 (88.0, 98.2)
**NE: Not estimable*	

Figure 12-2 Kaplan-Meier plot of duration of response (DOR, CR+PR) by IRC assessment (Efficacy Analysis Set [EAS])



- Time is relative to onset of response, 1 month=30.4375 days.

Figure 12-3 Kaplan-Meier plot of progession-free survival (PFS) by IRC assessment (EAS



- Time is relative to tisagenlecleucel infusion, 1 month=30.4375 days.

Descriptive indirect comparison

Two pre-specified analyses using non-interventional studies (a retrospective chart review and electronic health records) were conducted to provide context for interpreting the E2202 results. These analyses evaluated the effect of prescribing tisagenlecleucel vs standard of care therapies in patients who were enrolled in the E2202 study. Balance in key prognostic factors between the E2202 study and two external cohorts was achieved using propensity score methodology and weighting patients in external cohorts by their odds to be in the E2202 study based on their baseline characteristics.

Table 12-4 Indirect comparison of efficacy results in external control patients with r/r FL versus Study E2202

	Chart review N=143*	Electronic Health records N=98**
Difference in CR[1], 95% CI	31.8 (18.1, 45.3)	51.4 (21.2, 68.8)
Difference in ORR[1], 95% CI	22.0 (9.4, 34.5)	27.4 (-3.0, 65.0)
OS HR[2], 95% CI	0.20 (0.02, 0.38)	0.41 (0.11, 1.47)
Time to new therapy or death HR[2], 95% CI	0.31 (0.14, 0.49)	0.34 (0.15, 0.78)
PFS HR[2] considering new anti-cancer therapy as event, 95% CI	0.60 (0.34, 0.86)	0.45 (0.27, 0.83)

** Sample size after weighting (i.e., sum of weights) was 99.*

*** Sample size after weighting (i.e., sum of weights) was 88. CR and ORR are based on N=72 patients for whom the response assessment was available.*

[1] Difference in % from values obtained for Study E2202 population and the medical records review populations.

[2] Hazard ratio calculated by Cox proportional hazard model for indirect comparison between the Study E2202 population and the medical records review populations.

13 How Supplied / Storage and Handling

13.1 How Supplied

EVA Infusion Bag.

13.2 Shelf Life

The expiry date is indicated on the product label.

13.3 Storage Condition

Kymriah must be stored in a temperature monitored system at ≤-120°C. Do not thaw the product until it is ready to be used.

13.4 Special precautions for storage

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

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.

14 Patient Counseling Information

Please see ‘Patient leaflet: Information for the patient or carer’.

15 References

TWI-240223

CTL019 CDS v. 2.2 (12-Aug-2021) and EMA SmPC May 2022