1 TRADENAME

KYMRIAH® cells dispersion for infusion

2 DESCRIPTION AND COMPOSITION

Pharmaceutical form

Cell dispersion for infusion in one to three bags for intravenous use.

Appearance: colorless to slightly yellow suspension of cells.

Active substance

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

Quantitative description of active substance:

1.2 X 10^6 – 6 X 10^8 CAR positive viable T-cells

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)
Cryoserv® (DMSO)	7.5% (v/v)

3 INDICATION

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

- Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (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.

4 DOSAGE REGIMEN 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 6-1).

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 indication, 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).

Special populations

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: There is limited experience with Kymriah in paediatric patients below the age of 3 years. Currently available data in this age group are described in section 12.

DLBCL and FL: No formal studies have been performed in pediatric patients below 18 years of age.

Geriatric patients (65 years of age or above)

B-cell ALL: Limited experience in adult relapsed or refractory B-cell ALL patient population 65 years of age or above is available. 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 (see section 11 Clinical pharmacology).

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 infection. 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 6 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 6 Warnings and precautions).

Clinical assessment prior to infusion

Kymriah treatment should be delayed in certain patients with safety risk factors as detailed in section 6 Warning and precautions.

Monitoring after infusion

- Following infusion with Kymriah, patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurological events and other toxicities.
- Physicians should consider hospitalisation for the first 10 days post-infusion or at the first signs/symptoms of CRS and/or neurological events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- 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 (refer to the Certificate of Conformance for number of bags constituting one dose), the second bag should not be thawed until after the contents of the first bag has been safely infused. Inspect the contents of the thawed infusion bag for any visible cell clumps. If visible cell clumps remain, gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not infuse Kymriah if clumps are not dispersed.

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.

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.

5 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 (see section 6 Warnings and precautions).

6 WARNINGS AND PRECAUTIONS

Patient information

Prior to infusion, the patient should read the information from 'Patient educational leaflet: Important information for the patient, guardians or caregivers'. 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, 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 occur in the setting of CRS. Patients should be closely monitored for signs or symptoms of these events including fever.

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 6-1. Anti-interleukin-6 based therapy such as tocilizumab has been administered for mild or 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 moderate or severe life-threatening emergencies. Tisagenlecleucel continues to expand and persist following administration of tocilizumab and corticosteroids. Patients with medically significant cardiac dysfunction should be managed by standards of critical care; measures such as echocardiography should be considered. Tumor Necrosis Factor (TNF) antagonists are not recommended for management of Kymriah associated CRS.

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

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

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

A detailed treatment algorithm for the management of CRS is presented below in Table 6-1.

Table 6-1 CRS management [a]

CRS severity [b]	**Symptomatic treatment**	**Tocilizumab**	**Corticosteroids**
Grade 1: - Fever [c] ≥ 38°C not attributable to any other cause - No hypoxia - No hypotension	Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms If neutropenic, administer broad spectrum antibiotics and G-CSF. In patients with persistent (> 3 days) or refractory fever, consider managing as per Grade 2 CRS.	Not applicable	Not applicable
Grade 2: - Fever [c] ≥ 38°C not attributable to any other cause Plus - Hypoxia requiring low-flow oxygen supplementation And/or - Hypotension not requiring vasopressors	Continue supportive care as per Grade 1 and include IV fluid bolus and/or supplemental oxygen as needed	Administer tocilizumab 8 mg/kg i.v. over 1 hour (not to exceed 800 mg/dose) Repeat every 8 hours if no improvement in signs and symptoms of CRS, limit to a maximum of three doses in a 24-hour period, with a maximum of four doses total. Manage per Grade 3 if no improvement within 24 hours of starting tocilizumab	If no improvement in hypotension after two fluid boluses and after one to two doses of tocilizumab, may consider dexamethasone 10 mg i.v. (or equivalent) every 12 hours for one to two doses and then reassess.
Grade 3: - Fever [c] ≥ 38°C not attributable to any other cause And/or - Hypoxia requiring high-flow oxygen supplementation Plus - Hypotension requiring a vasopressor with or without vasopressin	Continue as per Grade 2 and include vasopressor as needed. Admit patient to intensive care unit (ICU) Assess cardiac function (echocardiogram) and conduct hemodynamic monitoring.	Tocilizumab as per Grade 2 if maximum dose is not reached within 24-hour period.	Dexamethasone 10 mg i.v. every 6 hours (or equivalent) and rapidly taper once symptoms improve. Manage per Grade 4 if refractory.

CRS severity [b]	Symptomatic treatment	Tocilizumab	Corticosteroids
Grade 4: - Fever [c] ≥ 38°C not attributable to any other cause Plus - Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) And/or - Hypotension: requiring multiple vasopressors (excluding vasopressin)	Continue as per Grade 3 and as necessary, include mechanical ventilation.	Tocilizumab as per Grade 2 if maximum dose is not reached within 24-hour period.	Initiate high-dose methylprednisolone (500 mg i.v. every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg i.v. every 12 hours until improvement to Grade 1). If no improvement, consider methylprednisolone 1000 mg i.v. 2 times a day or alternate therapy[d].

[a]Santomasso et al. 2021.

[b]Monitor complete blood cell count (CBC), comprehensive metabolic panel (CMP), magnesium, phosphorus, c-reactive protein (CRP), lactate dehydrogenase (LDH), uric acid, fibrinogen, prothrombin time (PT)/partial thromboplastin time (PTT), and ferritin. Consider screening for cytomegalovirus infection (CMV) and Epstein-Barr virus (EBV). For patients with fever, assess for infection with blood and urine cultures, and a chest radiograph. If patient is neutropenic, follow institutional neutropenic fever guidelines. For grade 2 or higher, patients should be monitored with continuous cardiac telemetry and pulse oximetry. Perform cardiac monitoring in patients who experience at least grade 2, clinically significant arrhythmia, and additionally as clinically indicated Consider chest or abdominal computed tomography (CT) imaging, brain magnetic resonance imaging (MRI), and/or lumbar puncture.

[c]Fever is not required to grade subsequent CRS severity in patients who receive antipyretics or anticytokine therapy (steroids or tocilizumab). Instead, CRS grading is driven by hypotension and/or hypoxia

[d]Noting limited experience with other agents, alternate options may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, and antithymocyte globulin.

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

Neurological toxicities

Neurological toxicities (also known as immune effector cell-associated neurotoxicity syndrome (ICANS)), 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 occurring 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. To reduce the risk of or manage neurological toxicities (including ICANS) (see above), patients treated with Kymriah may receive supportive treatment based on the most recent American Society of Clinical Oncology (ASCO) guideline, and/or appropriate local institutional / academic guidelines.

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, in some cases with late onset, occurred frequently in patients after Kymriah infusion. Patients should be monitored for signs and symptoms of infection and treated appropriately. As appropriate, prophylactic antibiotics should be administered and surveillance testing should be employed prior to and during treatment with Kymriah. Infections are known to complicate the course and management of concurrent CRS. The possibility of opportunistic infections of the central nervous system should be considered in patients with neurological adverse events and appropriate diagnostic evaluations should be performed.

Febrile neutropenia was observed in patients after Kymriah infusion and may be concurrent with CRS. In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad spectrum antibiotics, fluids and other supportive care, as medically indicated. In patients achieving complete remission following Kymriah, resulting low immunoglobulin levels can increase the risk for infections.

In patients with low immunoglobulin levels pre-emptive measures such as immunoglobulin replacement and rapid attention to signs and symptoms of infection should be implemented according to age and standard specific guidelines.

Prolonged cytopenias

Patients may continue to exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Kymriah and should be managed per standard guidelines. The majority of patients who had cytopenias at day 28 following Kymriah treatment resolved to Grade 2 or below within three months after treatment for 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 or recurrence of their cancer. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19- directed genetically modified autologous T-cell immunotherapies, including Kymriah. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusion, and may include fatal outcomes.

Patients should be monitored life-long for secondary malignancies, including those of T-cell origin. In the event that a secondary malignancy occurs, Novartis should be contacted to obtain

instructions to collect patient samples for testing (patientsafety.sg@novartis.com or +65 6019 6483).

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.

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with Kymriah who have also received prior treatment with other immunosuppressive medications. Cases of fatal outcome have been reported.

Prior treatment with anti CD19 therapy

There is limited experience with Kymriah in patients exposed to prior CD19 directed therapy.

Interference with serological testing

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

Content of dextran 40 and dimethyl sulfoxide (DMSO)

This cell, tissue and gene therapy product (CTGTP) contains 11 mg dextran 40 and 82.5 mg dimethyl sulfoxide (DMSO) per mL. Serious hypersensitivity reactions, including anaphylaxis have been reported (see section 7 Adverse drug reactions). Each of these excipients are known to possibly cause anaphylactic reaction following parenteral administration. All patients should be observed closely during the infusion period.

Content of sodium and potassium

This CTGTP contains 2.43 mg sodium per mL and 0.082 mg potassium per mL.

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 9 Pregnancy, lactation, females and males of reproductive potential).

Effects on ability to drive and use machines

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

7 ADVERSE DRUG REACTIONS

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 multicenter 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 multicenter, pivotal clinical study CCTL019B2202.

- The most common non-haematological 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

The adverse reactions described in this section were characterized in 97 patients infused with 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 76% 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 (69%) compared to after 8 weeks post-infusion (42%).

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).

Table 7-1 Adverse drug reactions at any time post Kymriah infusion, by primary system organ class, ADR term and maximum CTCAE grade in study B2202 Safety set

B2202, N=79	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Blood and lymphatic system disorders							
Febrile neutropenia	27	34	25	32	2	3	Very common
Anaemia	25	32	9	11	0	0	Very common
Haemorrhage[13]	25	32	6	8	2	3	Very common
Neutropenia	11	14	2	3	7	9	Very common
Thrombocytopenia	9	11	3	4	6	8	Very common
Haemophagocytic lymphohistiocytosis	5	6	2	3	1	1	Common
Coagulopathy	5	6	2	3	0	0	Common
Leukopenia	3	4	1	1	1	1	Common
Lymphopenia	2	3	2	3	0	0	Common
Pancytopenia	2	3	2	3	0	0	Common
Cardiac disorders							
Tachycardia[33]	19	24	2	3	1	1	Very common
Cardiac failure[4]	7	9	4	5	2	3	Common
Cardiac arrest	3	4	0	0	3	4	Common
Eye disorders							
Visual impairment[37]	2	3	0	0	0	0	Common
Gastrointestinal disorders							
Vomiting	25	32	1	1	0	0	Very common
Diarrhoea	23	29	1	1	0	0	Very common
Nausea	21	27	2	3	0	0	Very common
Abdominal pain[1]	14	18	2	3	0	0	Very common
Constipation	14	18	0	0	0	0	Very common
Stomatitis	3	4	1	1	0	0	Common
Abdominal distension	3	4	0	0	0	0	Common
Ascites	3	4	0	0	0	0	Common
Dry mouth	1	1	0	0	0	0	Common
General disorders and administration site conditions							
Pyrexia	33	42	8	10	2	3	Very common
Pain[26]	20	25	2	3	0	0	Very common
Oedema[24]	18	23	6	8	0	0	Very common
Fatigue[10]	18	23	0	0	0	0	Very common
Chills	7	9	0	0	0	0	Common
Asthenia	3	4	0	0	0	0	Common
Multiple organ dysfunction syndrome	2	3	0	0	2	3	Common
Influenza like illness	2	3	0	0	0	0	Common
Hepatobiliary disorders							
Hepatic enzyme increased[15]	24	30	11	14	3	4	Very common
Hyperbilirubinaemia	5	6	1	1	0	0	Common
Immune system disorders							
Cytokine release syndrome	61	77	17	22	21	27	Very common
Hypogammaglobulinaemia[18]	42	53	10	13	0	0	Very common
Infusion related reaction	5	6	1	1	0	0	Common
Graft versus host disease[12]	2	3	2	3	0	0	Common
Infections and infestations							
Infections - pathogen unspecified[20]	45	57	14	18	7	9	Very common
Viral infectious disorders[36]	30	38	15	19	2	3	Very common
Bacterial infectious disorders[3]	23	29	12	15	1	1	Very common
Fungal infectious disorders[11]	12	15	4	5	3	4	Very common
Investigations							
White blood cell decreased*	79	100	5	6	72	91	Very common

B2202, N=79	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Haemoglobin decreased*	79	100	38	48	0	0	Very common
Neutrophil count decreased*	77	98	6	8	69	87	Very common
Lymphocyte count decreased*	77	98	20	25	56	71	Very common
Platelet count decreased*	77	98	13	17	48	61	Very common
Blood bilirubin increased	13	17	9	11	0	0	Very common
International normalised ratio increased	9	11	0	0	0	0	Very common
Blood fibrinogen decreased	7	9	1	1	1	1	Common
Activated partial thromboplastin time prolonged	4	5	1	1	0	0	Common
Prothrombin time prolonged	3	4	0	0	0	0	Common
Fibrin D dimer increased	2	3	1	1	0	0	Common
Weight decreased	2	3	1	1	0	0	Common
Metabolism and nutrition disorders							
Decreased appetite	30	38	11	14	1	1	Very common
Hypokalaemia	20	25	9	11	2	3	Very common
Hypophosphataemia	18	23	8	10	1	1	Very common
Hypocalcaemia	16	20	5	6	0	0	Very common
Hypoalbuminaemia[17]	11	14	1	1	0	0	Very common
Hyperuricaemia	9	11	1	1	0	0	Very common
Hyperglycaemia	8	10	4	5	0	0	Very common
Hyperferritinaemia[16]	8	10	2	3	0	0	Very Common
Hypomagnesaemia	6	8	0	0	0	0	Common
Tumour lysis syndrome	5	6	4	5	1	1	Common
Hyperphosphataemia	5	6	0	0	1	1	Common
Hypercalcaemia	3	4	2	3	0	0	Common
Hyperkalaemia	3	4	1	1	1	1	Common
Hypernatraemia	3	4	1	1	1	1	Common
Hyponatraemia	3	4	0	0	0	0	Common
Hypermagnesaemia	2	3	0	0	0	0	Common
Musculoskeletal and connective tissue disorders							
Musculoskeletal pain[22]	19	24	3	4	0	0	Very common
Arthralgia	11	14	1	1	0	0	Very common
Myalgia	10	13	0	0	0	0	Very common
Nervous system disorders							
Headache[14]	28	35	2	3	0	0	Very common
Encephalopathy[9]	24	30	7	9	0	0	Very common
Tremor[35]	6	8	0	0	0	0	Common
Seizure[30]	5	6	3	4	0	0	Common
Dizziness[7]	4	5	0	0	0	0	Common
Peripheral neuropathy[27]	3	4	0	0	0	0	Common
Speech disorder[32]	2	3	1	1	0	0	Common
Motor dysfunction[21]	1	1	0	0	0	0	Common
Neuralgia[23]	1	1	0	0	0	0	Common
Psychiatric disorders							
Delirium[6]	15	19	3	4	0	0	Very common
Anxiety	13	17	2	3	0	0	Very common
Sleep disorder[31]	9	11	0	0	0	0	Very common
Renal and urinary disorders							
Acute kidney injury[2]	17	22	3	4	8	10	Very common
Respiratory, thoracic and mediastinal disorders							
Cough[5]	21	27	0	0	0	0	Very common
Hypoxia	20	25	10	13	6	8	Very common
Dyspnoea[8]	15	19	3	4	8	10	Very common
Pulmonary oedema[28]	12	15	6	8	1	1	Very common

B2202, N=79	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Nasal congestion	9	11	0	0	0	0	Very common
Pleural effusion	8	10	2	3	1	1	Very common
Tachypnoea	8	10	4	5	0	0	Very common
Oropharyngeal pain[25]	8	10	0	0	0	0	Very common
Acute respiratory distress syndrome	3	4	0	0	3	4	Common
Lung infiltration	1	1	1	1	0	0	Common
Skin and subcutaneous tissue disorders							
Rash[29]	14	18	1	1	0	0	Very common
Pruritus	7	9	0	0	0	0	Common
Erythema	5	6	0	0	0	0	Common
Hyperhidrosis	3	4	0	0	0	0	Common
Night sweats	1	1	0	0	0	0	Common
Vascular disorders							
Hypotension[10]	23	29	8	10	8	10	Very common
Hypertension	15	19	4	5	0	0	Very common
Capillary leak syndrome	2	3	1	1	0	0	Common
Thrombosis[34]	2	3	1	1	0	0	Common
Flushing	1	1	0	0	0	0	Common

[1]Abdominal pain includes PTs of Abdominal pain, Abdominal pain upper

[2]Acute kidney injury includes PTs of Acute kidney injury, Anuria, Azotaemia, Blood creatinine increased, Renal failure, Renal tubular dysfunction, Renal tubular necrosis

[3]Bacterial infectious disorders includes HLGTs of Bacterial infectious disorders

[4]Cardiac failure includes PTs of Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Right ventricular dysfunction

[5]Cough includes PTs of Cough, Productive cough

[6]Delirium includes PTs of Agitation, Delirium, Hallucination, Hallucination, visual, Irritability, Restlessness

[7]Dizziness includes PT of Dizziness

[8]Dyspnoea includes PTs of Acute respiratory failure, Dyspnoea, Respiratory distress, Respiratory failure

[9]Encephalopathy includes PTs of Automatism, Cognitive disorder, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Lethargy, Memory impairment, Mental status changes, Somnolence

[10]Fatigue includes PTs of Fatigue, Malaise

[11]Fungal infectious disorders includes HLGTs of Fungal infectious disorders

[12]Graft versus host disease includes PT of Graft versus host disease

[13]Haemorrhage includes PTs of Anal haemorrhage, Catheter site haemorrhage, Cerebral haemorrhage, Conjunctival haemorrhage, Contusion, Cystitis haemorrhagic, Disseminated intravascular coagulation, Epistaxis, Gastrointestinal haemorrhage, Gingival bleeding, Haemarthrosis, Haematemesis, Haematuria, Haemoptysis, Heavy menstrual bleeding, Melaena, Mouth haemorrhage, Peritoneal haematoma, Petechiae, Pharyngeal haemorrhage, Purpura, Retinal haemorrhage, Vaginal haemorrhage

[14]Headache includes PTs of Headache, Migraine

[15]Hepatic enzyme increased includes PTs of Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Transaminases increased

[16]Hyperferritinaemia includes PT of Serum ferritin increased

[17]Hypoalbuminaemia includes PT of Hypoalbuminaemia

[18]Hypogammaglobulinaemia includes PTs of Blood immunoglobulin A decreased, Blood immunoglobulin G decreased, Blood immunoglobulin M decreased, Hypogammaglobulinaemia, Immunodeficiency, Immunodeficiency common variable, Immunoglobulins decreased

[19]Hypotension includes PT of Hypotension

[20]Infections – pathogen unspecified include HLGT of Infections pathogen unspecified

[21]Motor dysfunction includes PT of Muscle spasms

[22]Musculoskeletal pain includes PTs of Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Neck pain, Non-cardiac chest pain

[23]Neuralgia includes PT of Neuralgia

[24]Oedema includes PTs of Face oedema, Fluid overload, Generalised oedema, Localised oedema, Oedema peripheral

[25]Oropharyngeal pain includes PT of Oropharyngeal pain

[26]Pain includes PTs of Pain, Pain in extremity

[27]Peripheral neuropathy includes PTs of Hyperaesthesia, Hypoaesthesia, Paraesthesia

[28]Pulmonary oedema includes PT of Pulmonary oedema

[29]Rash includes PTs of Dermatitis, Rash, Rash maculo-papular, Rash papular, Rash pruritic

[30]Seizure includes PTs of Generalised tonic-clonic seizure, Seizure

[31]Sleep disorder includes PTs of Insomnia, Nightmare, Sleep disorder

[32]Speech disorder includes PTs of Aphasia, Dysarthria

[33]Tachycardia includes PTs of Sinus tachycardia, Tachycardia

[34]Thrombosis includes PT of Thrombosis

[35]Tremor includes PT of Tremor

[36]Viral infectious disorders includes HLGT of Viral infectious disorders

[37]Visual impairment includes PT of Visual impairment

* Frequency is based on laboratory values. Patients are counted only for the worst grade observed post baseline.

Table 7-2 Adverse drug reactions at any time post Kymriah infusion, by primary system organ class, ADR term and maximum CTCAE grade in study C2201 Safety set

C2201, N=115	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Blood and lymphatic system disorders							
Anaemia	55	48	42	37	3	3	Very common
Haemorrhage[13]	25	22	4	4	5	4	Very common
Neutropenia	23	20	7	6	16	14	Very common
Febrile neutropenia	19	17	16	14	3	3	Very common
Thrombocytopenia	15	13	3	3	11	10	Very common
Leukopenia	4	4	2	2	0	0	Common
Pancytopenia	4	4	2	2	1	1	Common
Haemophagocytic lymphohistiocytosis	2	2	0	0	1	1	Common
B-cell aplasia	1	1	1	1	0	0	Uncommon
Lymphopenia	1	1	0	0	0	0	Uncommon
Cardiac disorders							
Tachycardia[33]	16	14	4	4	0	0	Very common
Atrial fibrillation	6	5	2	2	0	0	Common
Cardiac arrest	3	3	0	0	3	3	Common
Cardiac failure[5]	1	1	0	0	1	1	Uncommon
Ventricular extrasystoles	1	1	0	0	0	0	Uncommon
Eye disorders							
Visual impairment[37]	7	6	0	0	0	0	Common
Gastrointestinal disorders							
Diarrhoea	36	31	1	1	0	0	Very common
Nausea	33	29	1	1	0	0	Very common
Constipation	19	17	1	1	0	0	Very common
Abdominal pain[1]	12	10	2	2	0	0	Very common
Vomiting	10	9	1	1	0	0	Common
Stomatitis	7	6	0	0	0	0	Common
Dry mouth	6	5	0	0	0	0	Common
Abdominal distension	4	4	2	2	0	0	Common
Ascites	3	3	0	0	0	0	Common
General disorders and administration site conditions							
Pyrexia	40	35	6	5	0	0	Very common
Fatigue[11]	31	27	7	6	0	0	Very common
Oedema[24]	31	27	3	3	0	0	Very common
Pain[26]	16	14	3	3	0	0	Very common
Chills	14	12	0	0	0	0	Very common
Influenza like illness	10	9	1	1	0	0	Common
Asthenia	8	7	0	0	0	0	Common
Multiple organ dysfunction syndrome	3	3	0	0	3	3	Common
Hepatobiliary disorders							
Hepatic enzyme increased[15]	10	9	1	1	1	1	Common
Hyperbilirubinaemia	3	3	3	3	0	0	Common
Immune system disorders							
Cytokine release syndrome	66	57	17	15	9	8	Very common
Hypogammaglobulinaemia[18]	20	17	7	6	0	0	Very common
Infusion related reaction	3	3	0	0	0	0	Common
Infections and infestations							
Infections - pathogen unspecified[20]	55	48	23	20	7	6	Very common
Bacterial infectious disorders[4]	20	17	9	8	0	0	Very common
Fungal infectious disorders[12]	13	11	5	4	1	1	Very common

C2201, N=115	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Viral infectious disorders[36]	13	11	2	2	0	0	Very common
Investigations							
Lymphocyte count decreased*	115	100	33	29	76	66	Very common
White blood cell decreased*	114	99	40	35	50	44	Very common
Haemoglobin decreased*	114	99	68	59	0	0	Very common
Neutrophil count decreased*	112	97	24	21	70	61	Very common
Platelet count decreased*	109	95	16	14	48	42	Very common
Weight decreased	14	12	4	4	0	0	Very common
Fibrin D dimer increased	5	4	1	1	0	0	Common
Blood fibrinogen decreased	4	4	4	4	0	0	Common
Blood bilirubin increased	3	3	2	2	0	0	Common
Activated partial thromboplastin time prolonged	2	2	2	2	0	0	Common
Metabolism and nutrition disorders							
Hypokalaemia	26	23	10	9	0	0	Very common
Hypophosphataemia	19	17	15	13	0	0	Very common
Hypomagnesaemia	19	17	0	0	0	0	Very common
Decreased appetite	16	14	4	4	0	0	Very common
Hyponatraemia	9	8	4	4	1	1	Common
Hypocalcaemia	6	5	0	0	0	0	Common
Hypercalcaemia	5	4	0	0	1	1	Common
Hypoalbuminaemia[17]	5	4	3	3	0	0	Common
Hyperglycaemia	5	4	2	2	0	0	Common
Hyperferritinaemia[16]	5	4	1	1	0	0	Common
Hyperkalaemia	3	3	0	0	0	0	Common
Hyperuricaemia	2	2	0	0	2	2	Common
Tumour lysis syndrome	2	2	1	1	1	1	Common
Hypermagnesaemia	1	1	1	1	0	0	Uncommon
Hypernatraemia	1	1	0	0	0	0	Uncommon
Hyperphosphataemia	1	1	0	0	0	0	Uncommon
Musculoskeletal and connective tissue disorders							
Arthralgia	16	14	0	0	0	0	Very common
Musculoskeletal pain[22]	15	13	1	1	0	0	Very common
Myalgia	6	5	0	0	0	0	Common
Nervous system disorders							
Headache[14]	24	21	1	1	0	0	Very common
Encephalopathy[10]	18	16	8	7	5	4	Very common
Dizziness[8]	14	12	2	2	0	0	Very common
Peripheral neuropathy[27]	10	9	0	0	0	0	Common
Motor dysfunction[21]	7	6	1	1	0	0	Common
Tremor[35]	7	6	0	0	0	0	Common
Speech disorder[32]	5	4	1	1	0	0	Common
Neuralgia[23]	3	3	1	1	0	0	Common
Seizure[30]	3	3	1	1	0	0	Common
Ataxia[3]	2	2	1	1	0	0	Common
Ischaemic cerebral infarction	1	1	1	1	0	0	Uncommon
Psychiatric disorders							
Anxiety	12	10	1	1	0	0	Very common
Sleep disorder[31]	12	10	0	0	0	0	Very common
Delirium[7]	6	5	3	3	0	0	Common
Renal and urinary disorders							

C2201, N=115	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Acute kidney injury[2]	19	17	4	4	3	3	Very common
Respiratory, thoracic and mediastinal disorders							
Dyspnoea[9]	24	21	5	4	2	2	Very common
Cough[6]	20	17	0	0	0	0	Very common
Hypoxia	9	8	3	3	1	1	Common
Oropharyngeal pain[25]	9	8	1	1	0	0	Common
Pleural effusion	6	5	2	2	0	0	Common
Nasal congestion	5	4	0	0	0	0	Common
Pulmonary oedema[28]	3	3	1	1	0	0	Common
Tachypnoea	3	3	0	0	0	0	Common
Skin and subcutaneous tissue disorders							
Rash[29]	13	11	0	0	0	0	Very common
Night sweats	6	5	0	0	0	0	Common
Pruritus	5	4	0	0	0	0	Common
Hyperhidrosis	4	4	0	0	0	0	Common
Erythema	2	2	1	1	0	0	Common
Vascular disorders							
Hypotension[19]	29	25	7	6	3	3	Very common
Thrombosis[34]	7	6	3	3	0	0	Common
Hypertension	5	4	2	2	1	1	Common
Capillary leak syndrome	1	1	0	0	0	0	Uncommon

[1]Abdominal pain includes PTs of Abdominal discomfort, Abdominal pain, Abdominal pain upper

[2]Acute kidney injury includes PTs of Acute kidney injury, Blood creatinine abnormal, Blood creatinine increased

[3]Ataxia includes PTs of Ataxia, Dysmetria

[4]Bacterial infectious disorders includes HLGTs of Bacterial infectious disorders

[5]Cardiac failure includes PT of Cardiac failure congestive

[6]Cough includes PTs of Cough, Productive cough, Upper-airway cough syndrome

[7]Delirium includes PTs of Agitation, Delirium, Irritability

[8]Dizziness includes PTs of Dizziness, Presyncope, Syncope

[9]Dyspnoea includes PTs of Dyspnoea, Dyspnoea exertional, Respiratory distress, Respiratory failure

[10]Encephalopathy includes PTs of Cognitive disorder, Confusional state, Disturbance in attention, Encephalopathy, Lethargy, Memory impairment, Mental status changes, Metabolic encephalopathy, Somnolence, Thinking abnormal

[11]Fatigue includes PTs of Fatigue, Malaise

[12]Fungal infectious disorders includes HLGTs of Fungal infectious disorders

[13]Haemorrhage includes PTs of Anal haemorrhage, Blood urine present, Cerebral haemorrhage, Contusion, Cystitis haemorrhagic, Disseminated intravascular coagulation, Duodenal ulcer haemorrhage, Epistaxis, Eye contusion, Gastrointestinal haemorrhage, Haematemesis, Haematochezia, Haematuria, Large intestinal haemorrhage, Melaena, Mouth haemorrhage, Petechiae, Pharyngeal haemorrhage, Post procedural

haemorrhage, Pulmonary Haemorrhage, Purpura, Retinal haemorrhage, Traumatic haematoma, Tumour haemorrhage, Upper gastrointestinal haemorrhage

[14]Headache includes PTs of Headache, Migraine

[15]Hepatic enzyme increased includes PTs of Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Hepatic enzyme increased, Transaminases increased

[16]Hyperferritinaemia includes PT of Serum ferritin increased

[17]Hypoalbuminaemia includes PT of Hypoalbuminaemia

[18]Hypogammaglobulinaemia includes PTs of Blood immunoglobulin G decreased, Hypogammaglobulinaemia, Immunodeficiency, Immunoglobulins decreased

[19]Hypotension includes PTs of Hypotension, Orthostatic hypotension

[20]Infections - pathogen unspecified includes HLGT of Infections - pathogen unspecified

[21]Motor dysfunction includes PTs of Muscle spasms, Muscle twitching, Myoclonus, Myopathy

[22]Musculoskeletal pain includes PTs of Back pain, Flank pain, Musculoskeletal chest pain, Neck pain, Non-cardiac chest pain

[23]Neuralgia includes PTs of Neuralgia, Sciatica

[24]Oedema includes PTs of Face oedema, Fluid overload, Fluid retention, Generalised oedema, Localised oedema, Oedema peripheral, Peripheral swelling

[25]Oropharyngeal pain includes PTs of Oral pain, Oropharyngeal pain

[26]Pain includes PTs of Pain, Pain in extremity

[27]Peripheral neuropathy includes PTs of Hyperaesthesia, Hypoaesthesia, Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy

[28]Pulmonary oedema includes PTs of Acute pulmonary oedema, Pulmonary oedema

[29]Rash includes PTs of Dermatitis, Dermatitis acneiform, Dermatitis contact, Rash, Rash maculo-papular, Rash papular, Rash pruritic

[30]Seizure includes PTs of Seizure, Status epilepticus

[31]Sleep disorder includes PTs of Insomnia, Sleep disorder

[32]Speech disorder includes PTs of Aphasia, Dysarthria, Speech disorder

[33]Tachycardia includes PTs of Sinus tachycardia, Supraventricular tachycardia, Tachycardia

[34]Thrombosis includes PTs of Deep vein thrombosis, Embolism, Pulmonary embolism, Thrombosis, Vena cava thrombosis, Venous thrombosis

[35]Tremor includes PTs of Dyskinesia, Tremor

[36]Viral infectious disorders includes HLGTs of Viral infectious disorders

[37]Visual impairment includes PTs of Vision blurred, Visual impairment

* Frequency is based on laboratory values. Patients are counted only for the worst grade observed post baseline.

Table 7-3 Adverse drug reactions at any time post Kymriah infusion, by primary system organ class, ADR term and maximum CTCAE grade in study E2202 Safety set

E2202, N=97	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Blood and lymphatic system disorders							
Neutropenia	41	42	21	22	20	21	Very common
Anaemia	25	26	16	17	0	0	Very common
Thrombocytopenia	19	20	4	4	7	7	Very common
Febrile neutropenia	12	12	11	11	1	1	Very common
Leukopenia	8	8	5	5	3	3	Common
Lymphopenia	8	8	5	5	3	3	Common
Haemorraghe[12]	6	6	2	2	0	0	Common
Pancytopenia	3	3	0	0	2	2	Common
Coagulopathy	1	1	1	1	0	0	Common
Haemophagocytic lymphohistiocytosis	1	1	1	1	0	0	Common
Cardiac disorders							
Tachycardia[28]	2	2	0	0	0	0	Common
Atrial fibrillation	1	1	0	0	0	0	Common
Eye disorders							
Visual impairment[32]	2	2	0	0	0	0	Common
Gastrointestinal disorders							
Diarrhoea	21	22	1	1	0	0	Very common
Nausea	15	16	2	2	0	0	Very common
Constipation	14	14	0	0	0	0	Very common
Vomiting	9	9	0	0	0	0	Common
Abdominal pain[1]	8	8	1	1	0	0	Common
Stomatitis	3	3	1	1	0	0	Common
Abdominal distension	2	2	0	0	0	0	Common
Dry mouth	2	2	0	0	0	0	Common
General disorders and administration site conditions							
Pyrexia	19	20	1	1	0	0	Very common
Fatigue[9]	17	18	3	3	0	0	Very common
Oedema[22]	8	8	0	0	0	0	Common
Pain[24]	8	8	0	0	0	0	Common
Chills	7	7	0	0	0	0	Common
Asthenia	6	6	0	0	0	0	Common

E2202, N=97	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Hepatobiliary disorders							
Hepatic enzyme increased[14]	7	7	0	0	1	1	Common
Hyperbilirubinaemia	1	1	1	1	0	0	Common
Immune system disorders							
Cytokine release syndrome	48	50	0	0	0	0	Very common
Hypogammaglobulinaemia[17]	16	17	1	1	0	0	Very common
Infusion related reaction	3	3	2	2	0	0	Common
Graft versus host disease[11]	1	1	1	1	0	0	Common
Infections and infestations							
Infections - pathogen unspecified[19]	35	36	10	10	0	0	Very common
Viral infectious disorders[31]	16	17	3	3	0	0	Very common
Bacterial infectious disorders[3]	6	6	4	4	0	0	Common
Fungal infectious disorders[10]	2	2	0	0	0	0	Common
Investigations							
Haemoglobin decreased*	91	94	24	25	0	0	Very common
Lymphocyte count decreased*	89	92	33	34	51	53	Very common
White blood cell decreased*	88	91	40	41	32	33	Very common
Neutrophil count decreased*	86	89	24	25	45	46	Very common
Platelet count decreased*	86	89	8	8	17	18	Very common
Weight decreased	6	6	0	0	0	0	Common
Blood bilirubin increased	1	1	0	0	0	0	Common
International normalised ratio increased	1	1	0	0	0	0	Common
Metabolism and nutrition disorders							
Hypophosphataemia	9	9	5	5	0	0	Common
Hypokalaemia	9	9	2	2	0	0	Common
Hypomagnesaemia	8	8	0	0	0	0	Common
Decreased appetite	7	7	0	0	0	0	Common
Hyperglycaemia	5	5	1	1	0	0	Common
Hypoalbuminaemia[16]	4	4	1	1	0	0	Common
Hyperkalaemia	4	4	0	0	0	0	Common
Hypercalcaemia	2	2	0	0	1	1	Common
Tumour lysis syndrome	2	2	2	2	0	0	Common
Hyponatraemia	2	2	0	0	0	0	Common
Hypernatraemia	1	1	0	0	1	1	Common
Hyperferritinaemia[15]	1	1	0	0	0	0	Common
Hyperphosphataemia	1	1	0	0	0	0	Common
Musculoskeletal and connective tissue disorders							
Musculoskeletal pain[21]	14	14	1	1	0	0	Very common
Arthralgia	10	10	0	0	0	0	Very common
Myalgia	8	8	0	0	0	0	Common
Nervous system disorders							
Headache[13]	25	26	2	2	0	0	Very common

E2202, N=97	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Dizziness[6]	8	8	1	1	0	0	Common
Motor dysfunction[20]	7	7	0	0	0	0	Common
Peripheral neuropathy[25]	7	7	0	0	0	0	Common
Immune effector cell-associated neurotoxicity syndrome	4	4	0	0	1	1	Common
Encephalopathy[8]	3	3	1	1	0	0	Common
Tremor[30]	3	3	0	0	0	0	Common
Psychiatric disorders							
Sleep disorder[27]	6	6	0	0	0	0	Common
Anxiety	2	2	0	0	0	0	Common
Delirium[5]	1	1	1	1	0	0	Common
Renal and urinary disorders							
Acute kidney injury[2]	4	4	0	0	1	1	Common
Respiratory, thoracic and mediastinal disorders							
Cough[4]	17	18	0	0	0	0	Very common
Dyspnoea[7]	7	7	1	1	0	0	Common
Pleural effusion	6	6	1	1	0	0	Common
Oropharyngeal pain[23]	4	4	0	0	0	0	Common
Nasal congestion	2	2	0	0	0	0	Common
Skin and subcutaneous tissue disorders							
Rash[26]	10	10	0	0	0	0	Very common
Pruritus	9	9	0	0	0	0	Common
Night sweats	3	3	0	0	0	0	Common
Erythema	2	2	0	0	0	0	Common
Hyperhidrosis	1	1	0	0	0	0	Common
Vascular disorders							
Hypotension[18]	9	9	0	0	0	0	Common
Hypertension	5	5	1	1	0	0	Common
Thrombosis[29]	1	1	1	1	0	0	Common

[1]Abdominal pain includes PTs of Abdominal pain, Abdominal pain upper

[2]Acute kidney injury includes PTs of Acute kidney injury, Blood creatinine increased

[3]Bacterial infectious disorders includes HLGT of Bacterial infectious disorders

[4]Cough includes PTs of Cough, Productive cough

[5]Delirium includes PT of Delirium

[6]Dizziness includes PTs of Dizziness, Syncope

[7]Dyspnoea includes PTs of Acute respiratory failure, Dyspnoea

[8]Encephalopathy includes PT of Encephalopathy

[9]Fatigue includes PTs of Fatigue, Malaise

[10]Fungal infectious disorders includes HLGT of Fungal infectious disorders

[11]Graft versus Host Disease (GvHD) includes PTs of GvHD in GI tract, GvHD in skin

[12]Haemorrhage includes PTs of Blood blister, Catheter site haemorrhage, Contusion, Haematochezia, Haematoma, Mucosal haemorrhage, Oral blood blister, Petechiae, Purpura, Subdural haematoma

[13]Headache includes PTs of Headache, Migraine
[14]Hepatic enzyme increased includes PTs of Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Transaminases increased
[15]Hyperferritinaemia includes PT of Hyperferritinaemia
[16]Hypoalbuminaemia includes PTs of Blood albumin decreased, Hypoalbuminaemia
[17]Hypogammaglobulinaemia includes PTs of Blood immunoglobulin G decreased, Hypogammaglobulinaemia
[18]Hypotension includes PTs of Hypotension, Orthostatic hypotension
[19]Infections - pathogen unspecified includes HLGT of Infections - pathogen unspecified
[20]Motor dysfunction includes PTs of Muscle spasms, Myoclonus
[21]Musculoskeletal pain includes PTs of Back pain, Bone pain, Flank pain, Musculoskeletal chest pain, Neck pain, Non-cardiac chest pain
[22]Oedema includes PTs of Fluid retention, Localised oedema, Oedema peripheral, Peripheral swelling
[23]Oropharyngeal pain includes PT of Oropharyngeal pain
[24]Pain includes PTs of Pain, Pain in extremity
[25]Peripheral neuropathy includes PTs of Dysaesthesia, Hypoaesthesia, Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy
[26]Rash includes PTs of Rash, Rash maculo-papular, Rash papular
[27]Sleep disorder includes PT of Insomnia
[28]Tachycardia includes PT of Sinus tachycardia
[29]Thrombosis includes PT of Deep vein thrombosis
[30]Tremor includes PTs of Dyskinesia, Tremor
[31]Viral infectious disorders includes HLGT of Viral infectious disorders
[32]Visual impairment includes PTs of Vision blurred, Visual impairment
*Frequency is based on laboratory values. Patients are counted only for the worst grade observed post baseline.

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, secondary malignancy of T-cell origin.

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; one reported CRS event (grade 5) with onset >1 year after receiving Kymriah had fatal outcome.

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: 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 6 Warnings and precautions and Table 6-1.

Infections and febrile neutropenia

In B-cell ALL patients severe infections (Grade 3 or 4), which can be life-threatening or fatal, occurred in 48% of patients after Kymriah infusion. The overall incidence was 72% (unspecified 57%, bacterial 27%, viral 38%, and fungal 15%) (see section 6 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 (Grade 3 or 4), which can be life-threatening or fatal, occurred in 34% of patients. The overall incidence (all grades) was 58% (unspecified 48%, bacterial 15%, fungal 11% and viral 11%) (see section 6 Warnings and precautions). Thirty-seven % 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 6 Warnings and precautions). Nineteen (19%) 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 6 Warnings and precautions for the management of febrile neutropenia before and after Kymriah infusion.

Hematopoietic cytopenias not resolved by day 28

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 leukocytes (57%), neutrophils (54%), lymphocytes (44%), thrombocytes (42%), and a decreased hemoglobin (13%).

All adult patients with DLBCL 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 thrombocytes (39%), lymphocytes (29%), neutrophils (25%), leukocytes (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), immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 4% of patients (1% Grade 3 or 4) within 8 weeks after 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).

For clinical management of neurological toxicities, see section 6 Warnings and precautions.

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 INTERACTIONS

No pharmacokinetic 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.

9 PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

9.1 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.

9.2 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.

9.3 Females and males of reproductive potential

There is a potential for Kymriah to cause fetal toxicity.

Pregnancy testing

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

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

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.

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.

10 OVERDOSAGE

Not applicable.

11 CLINICAL PHARMACOLOGY

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 variability 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 61.2% 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). These data, signify the potential role of expansion and persistence for eliciting a clinical response. Delayed and lower expansion was observed in non-responding patients (N=12) compared to responding patients (N=105).

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 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], 43	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.

Pharmacotherapeutic group, ATC

ATC code: L01XL04

Mechanism of action (MOA)

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, activation, target cell elimination and persistence of tisagenlecleucel.

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%, 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 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 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 responders. 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 impact of age on cellular kinetics was evaluated across the age range of 22 to 76 years in DLBCL patients (Study C2201). The AUC0-28d 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. These differences are not considered clinically relevant due to high variability associated with the exposure parameters.

FL patients (Study E2202). The AUC0-28d and AUC0-84d in patients ≥65 years of age was observed to be 39.4% and 47.0% lower than patients <65 years, respectively, with comparable ranges of exposures among both age categories. These differences are not considered clinically relevant due to high variability associated with the exposure parameters.

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.

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 76% of Caucasian, 13% of Asian, 1% of Black or African American, and 10% of patients with unknown race.

Body weight

In DLBCL, ALL and FL 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 patients 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 patients 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 patients 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) with a total of 160 patients treated. 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).

Key baseline information for infused patients is presented in Table 12-1. 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.

Table 12-1 B2202: Baseline information in the infused population

Baseline Characteristic	***N=79***
Age (years)	
Mean (standard deviation)	*12 (5.38)*
Median (minimum – maximum)	*11 (3 – 24)*
Age category (years) - n (%)	
<10 years	*32 (40.5)*
≥10 years and <18 years	*33 (41.8)*
≥18 years	*14 (17.7)*
Sex - n (%)	
Male	*45 (57.0)*
Female	*34 (43)*
Disease status (%)	

Primary refractory[1]	*6 (7.6)*
Relapsed disease[2]	*73 (92.4)*
Prior stem-cell transplantation - n (%)	
0	*31 (39.2)*
1	*42 (53.2)*
2	*6 (7.6)*

[1] *Primary refractory: Never had a morphologic complete remission (CR) prior to the study*
[2] *Relapsed disease: Had at least one relapse prior to the study*

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 recovery (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 ORR within 3 months was 82.3% (65/79). The median time from Kymriah infusion to the data cut-off date was 24.2 months (range: 4.5 to 35.1). See Table 12-2 and Figures 12-1 and 12-2 for efficacy results from this study. Fifty-nine of 65 responders achieved CR/CRi by the Day 28 assessment. ORR was consistent across all subgroups. Eight patients who received Kymriah infusion went to transplant while in remission. Kymriah was administered in a qualified Kymriah treatment center in an inpatient and outpatient setting.

Health related quality of life (HRQoL) were evaluated by PedsQL™ and EQ-5D questionnaires completed by patients aged 8 and above. Among patients responding, the mean change from baseline in the PedsQL total score was 13.1 at Month 3 and 15.4 at Month 6 and 25.0 at Month 12, and the mean change from baseline in the EQ VAS score was 16.0 at Month 3 and 15.3 at Month 6 and 21.7 at Month 12, indicating overall clinically meaningful improvement in HRQoL following Kymriah infusion.

Special populations

No differences in efficacy or safety were observed between different age subgroups.

Patients with active CNS leukaemia

There was no patients with active CNS leukemia in study B2202. Of four patients with active CNS leukemia (i.e. CNS-3) included in study B2101J, three experienced cytokine release syndrome (Grade 2-4) and transient neurological abnormalities (Grade 1-3) that resolved within 1 to 3 months of infusion. One patient died due to disease progression and the remaining three patients achieved a CR or CRi and remain alive 1.5 to 2 years after infusion. The risk/benefit of Kymriah has not been established in this population.

Table 12-2 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
[10] OS was defined as time from date of Kymriah infusion to the date of death due to any cause

Figure 12-1 B2202: Duration of remission (DOR)

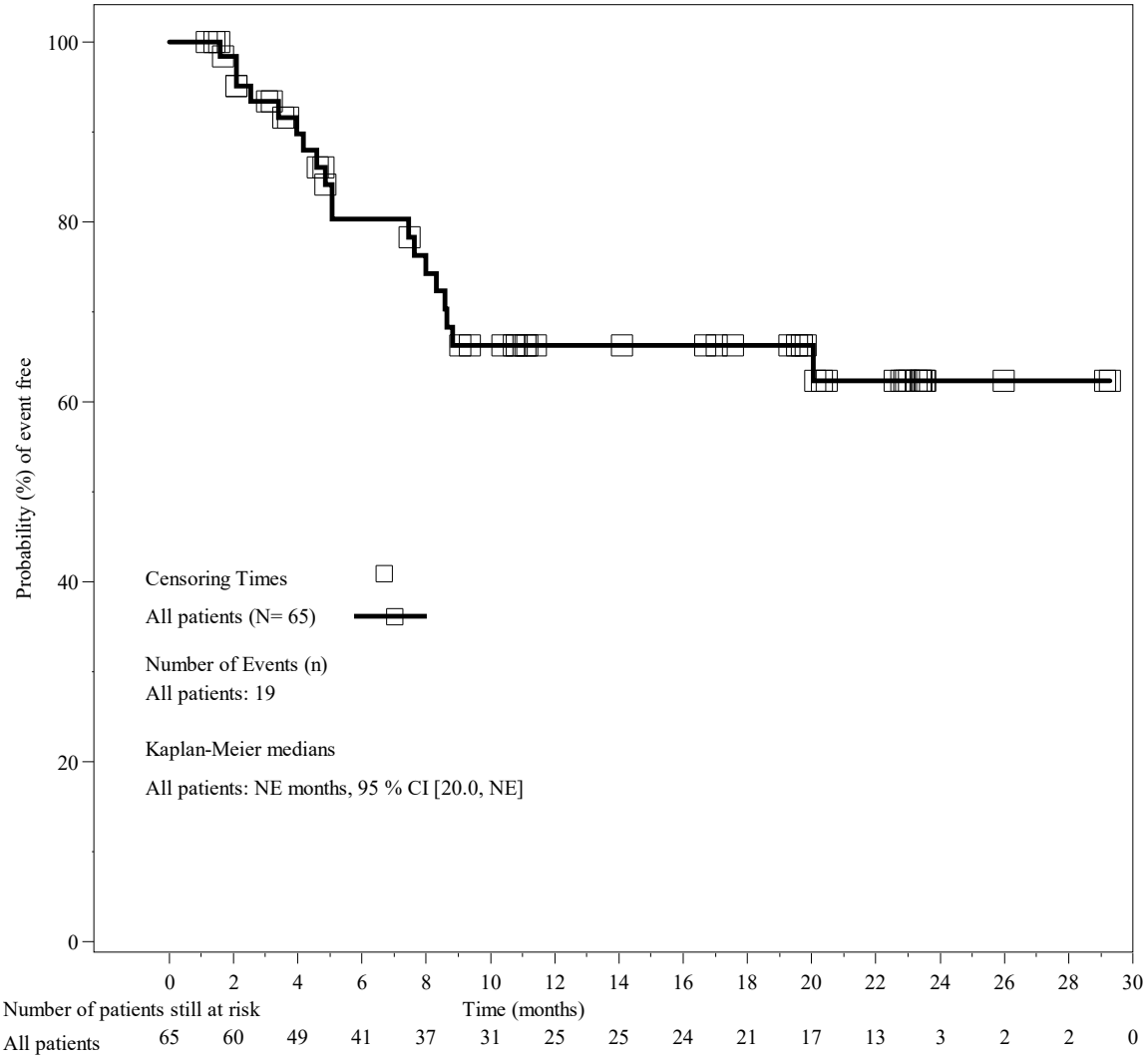
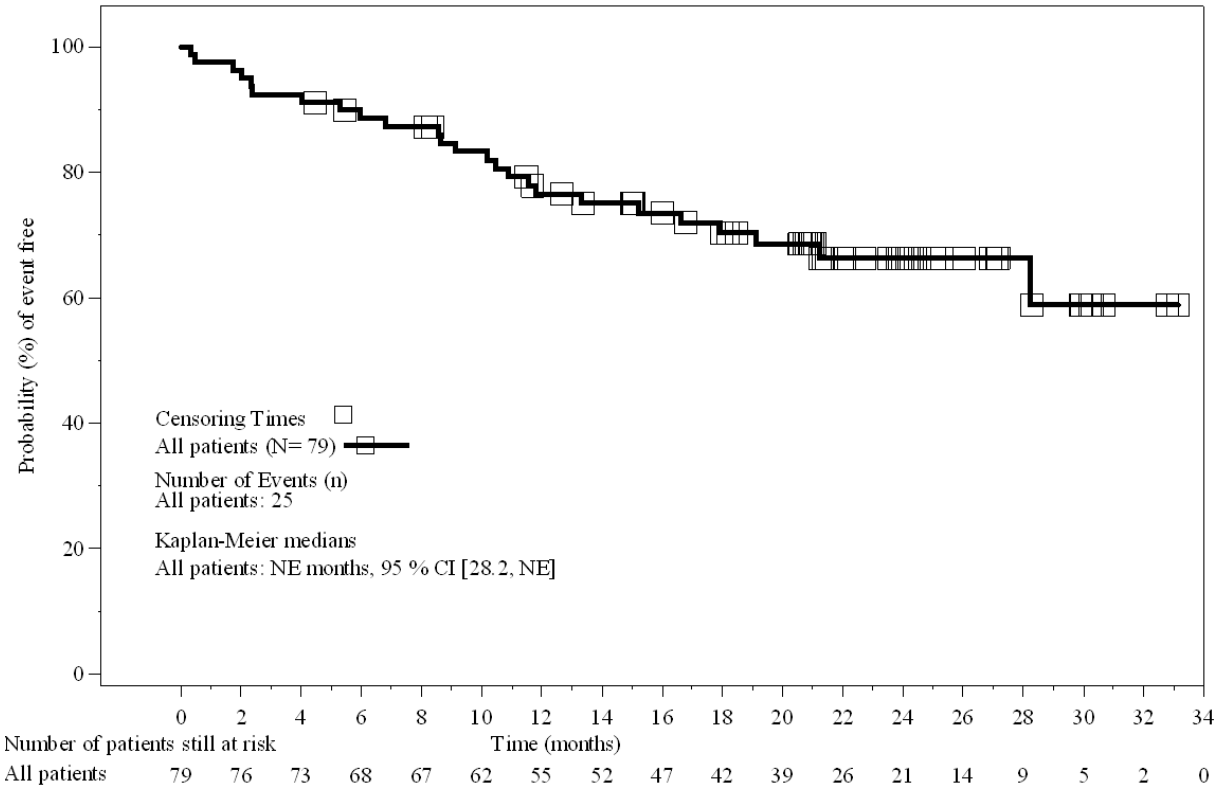


Figure 12-2 B2202: Overall Survival (OS)



CCTL019B2401

An observational study (B2401) was conducted to collect long-term safety and efficacy data in patients infused with tisagenlecleucel from the Center for International Blood and Marrow Transplant Research (CIBMTR) and European Society for Blood and Marrow Transplantation (EBMT) registries. The study included 858 (CIBMTR: 778; EBMT: 80) paediatric and young adult patients with r/r B-cell ALL at time of the data cut-off (04-May-2022). Kymriah manufacture for patients below 3 years of age and with low weight was feasible; 62 patients (CIBMTR: 58, EBMT: 4) were below 3 years of age at time of infusion. The median time from Kymriah infusion to the data cut-off date of the paediatric and young adult patients with r/r B-cell ALL was 28.3 months for CIBMTR and 29.3 months for EBMT.

Among the patients below 3 years of age included in the efficacy set (n=53), CR (including CRi) as BOR was reported for 41 patients (77.4%) (95% CI: 63.8, 87.7) and all 20 patients in CR (including CRi) and with reported MRD data were MRD-negative during follow-up. The estimated DOR rate at month 12 (censoring for SCT) was 73.8% (95% CI: 49.5, 87.6).

The overall safety experience in patients below 3 years of age with r/r B-cell ALL was generally consistent with the known safety profile of tisagenlecleucel.

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), were evaluated in an open-label, pivotal, single-arm, study (115 DLBCL patients in total).

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. Approximately 31% of patients discontinued the study prior to Kymriah infusion. 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), patient decision (n=2) and protocol deviation (n=1) or adverse events (n=4) while awaiting Kymriah manufacturing in the clinical study.

Key baseline information for infused patients is presented in Table 12-3. The majority of patients (103/115, 86%) 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.

Table 12-3 C2201: Baseline information in the infused population

Baseline Characteristic	***N=115***
Age (years)	
Mean (standard deviation)	*54 (13.1)*
Median (minimum – maximum)	*56 (22 - 76)*
Age category (years) - n (%)	
<65 years	*89 (77.4)*
≥65 years	*26 (22.6)*
Sex - n (%)	
Male	*71 (61.7)*
Female	*44 (38.3)*
Prior haematopoietic stem cell transplant (SCT) - n (%)	
No	*59 (51.3)*
Yes	*56 (48.7)*
Number of prior lines of antineoplastic therapy – n (%)	
1	*5 (4.3)*
2	*51 (44.3)*
3	*36 (31.3)*
≥4	*23 (20.0)*
Disease status (%)	

Refractory to last line of therapy	*63 (54.8)*
Relapse to last line of therapy	*52 (45.2)*

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) (Table 12-4). 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 12-4) 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 regardless of prior lines of therapy (ORR 51.9% and 55.3% in patients with ≤2 lines of therapies and >2 lines of therapies, respectively), prior SCT (ORR of 49.1% and 59.1% in patients without or with previous SCT, respectively), relapsed or refractory disease (ORR 64.6% and 43.1 %, respectively) or biological factors such as cell of origin (ORR 55.6% in non-GCB and 49.0% in GCB subtype) and double-hit/triple hit lymphoma with Bcl-2 and c-myc expression (ORR of 41.2% in patients with double-hit/triple hit lymphoma).

Table 12-4 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	**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	N=115
Overall survival (OS)[4] Median (months) (95% CI) % survival probability at 12 months % survival probability at 24 months	 10.3 (6.6, 21.1) 47.9% 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

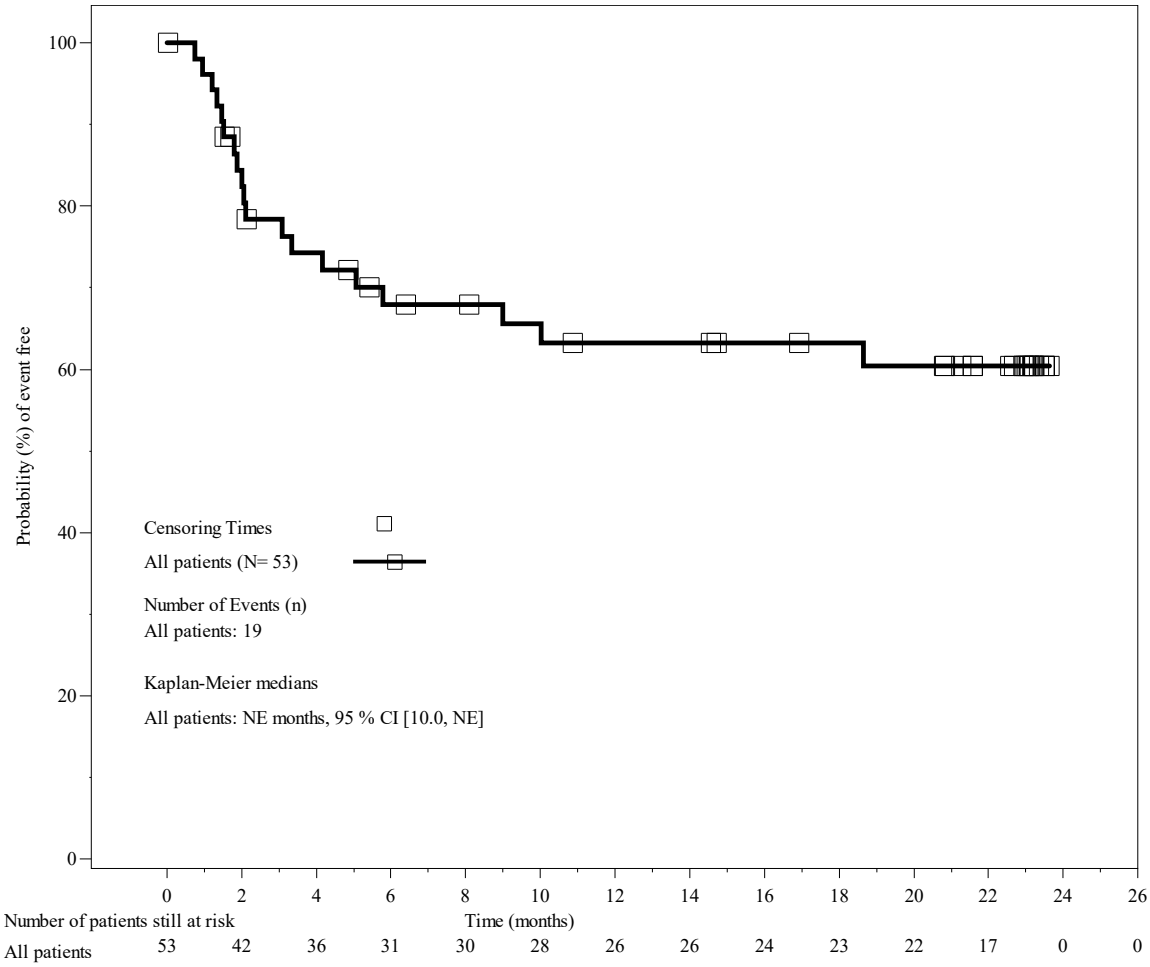
[2] The p-value is displayed as a descriptive statistic only, with no inferential interpretation (since the null hypothesis of ORR <20% was already rejected with p<0.0001 at a previous interim analysis).

[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)*

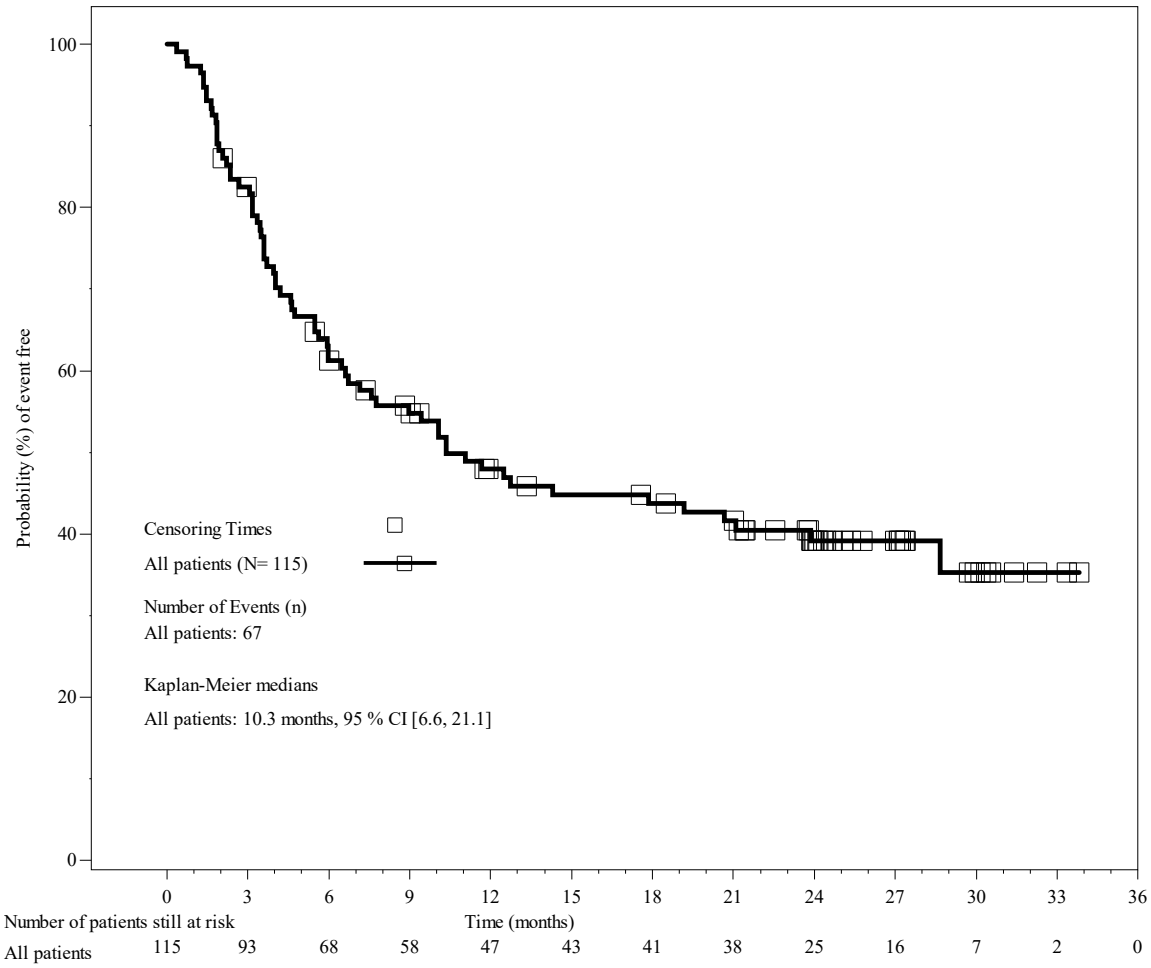
[5] *Not estimable*

Figure 12-3 Kaplan-Meier plot of duration of response (DOR) by IRC assessment for responders in main cohort (Efficacy Analysis Set)



- Only patients who achieved CR or PR were included.
- Time was relative to onset of response, 1 month=30.4375 days.

Figure 12-4 Kaplan-Meier plot of overall survival (OS) (Full analysis set)



Follicular lymphoma

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. The baseline information in all infused population(N=97) is provided in Table 12-5 below.

Table 12-5 Study E2202: Baseline information in the infused population

	Infused patients N=97 n (%)
Age (years)	
Mean (standard deviation)	56.5 (10.39)
Median (minimum – maximum)	57.0 (29-73)
Age category (years) – n (%)	
<65 years	73 (75.3)
≥65 years	24 (24.7)
Sex – n (%)	
Male	64 (66.0)
Female	33 (34.0)
Stage III/IV disease at study entry – n (%)	83 (85.6)
High FLIPI score[1] – n (%)	58 (59.8)
Bulky disease at baseline[2] – n (%)	62 (63.9)
Number of prior lines of antineoplastic therapy – n (%)	
2	24 (24.7)
3	21 (21.6)
4	25 (25.8)
≥5	27 (27.8)
Median (minimum – maximum)	4.0 (2.0 - 13.0)
Disease status – n (%)	
Refractory to last line of therapy	76 (78.4)
Relapse to last line of therapy	17 (17.5)
Double refractory[3] – n (%)	66 (68.0)
Progression of disease within 24 months (POD24)[4] – n (%)	61 (62.9)
Prior haematopoietic stem cell transplant (HSCT) – n (%)	35 (36.1)
Prior PI3K inhibitor – n (%)	20 (20.6)

1 FLIPI includes 5 labelled prognostic factors; FLIPI = sum (where prognostic factor = 'Yes'); Low: 0-1 criteria met; intermediate: 2 criteria met; high: 3 or more met.
2 Bulky disease defined per IRC as imaging showing any nodal or extra nodal tumour mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm.
3 Double refractory is defined as patients who failed to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen
4 POD24: subjects with primary refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb containing treatment.

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).

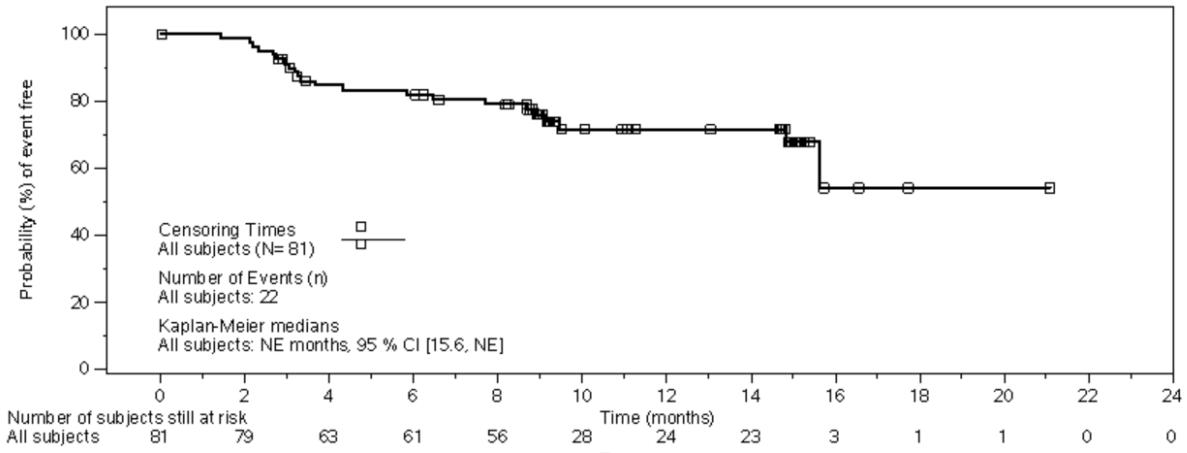
The probability for a patient to remain in response (DOR) ≥9 months was 76% (95% CI: 64.6, 84.2), while the probability for a patient who achieved a CR to remain in response ≥9 months was 87% (95% CI: 74.7, 93.1). The probability of remaining progression-free (PFS) at month 12 was 67% (95% CI: 56.0, 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 12-6 Study E2202: Efficacy results in adult patients with r/r FL

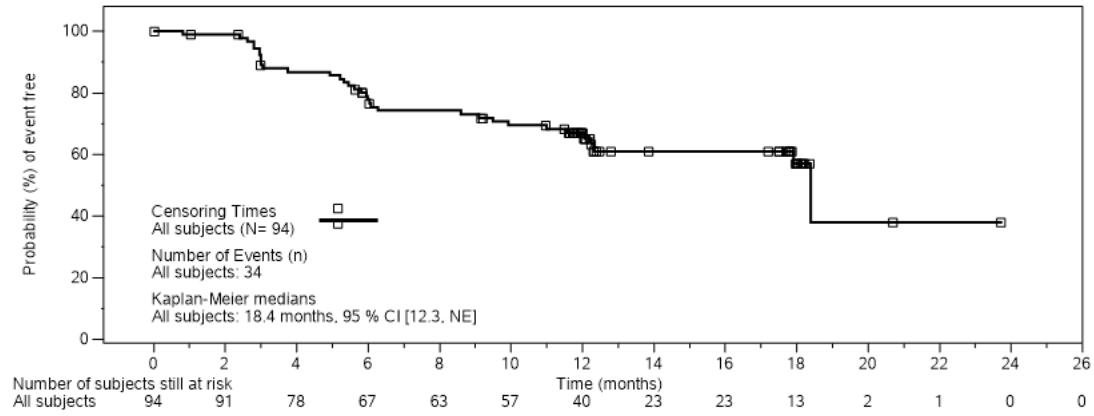
	Efficacy population N=94
Complete response rate (CRR), n (%) **95% CI**	65 (69.1) (58.8, 78.3)
Overall response rate (ORR), n (%) **95% CI**	81 (86.2) (77.5, 92.4)
Duration of response (DOR), months	
Median (95% CI)	Not reached (15.6, NE*)
% relapse free probability at 9 months, (95% CI)	76.0 (64.6, 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 12-5 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 12-6 Kaplan-Meier plot of progression-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 12-7 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 NON-CLINICAL 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.

In the absence of validated non-clinical *in vivo* models, cytokine release syndrome (CRS) or tumor lysis syndrome (TLS) could not be assessed in animal studies.

Safety pharmacology and repeated dose toxicity

Safety pharmacology studies were not conducted due to the limited tissue distribution of the target (i.e. CD19 is exclusively expressed on B-cells in blood and lymphatic tissues) and because the pharmacological principle, (i.e. target specific T-cell mediated cytotoxicity) does not warrant such safety studies.

No repeated dose toxicity studies were conducted.

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.

14 PHARMACEUTICAL INFORMATION

Incompatibilities

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

Special precautions for storage.

Kymriah must be stored and transport in a temperature monitored system at ≤-120°C, e.g. in a container for cryogenic storage (Dewar) in the vapour phase of liquid nitrogen. 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

Shelf Life and in-use stability information

9 months

The product should be administered immediately after thawing. After thawing, the product should be kept at room temperature (20°C-25°C) and infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

Instructions for use and handling

See section 4 Dosage regimen and administration.

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.

Manufacturer

See folding box

Presentation

Kymriah is a cell dispersion for infusion. It is supplied as one to three infusion bag(s) containing a cloudy to clear, colourless to slightly yellow dispersion of cells. Each CS50 (50ml) or RD50 (50ml) bag contains 10 to 30ml of dispersion and each CS250 (250ml) or RD250 (250ml) bag contains 30 to 50ml of dispersion.

Not all presentation may be available locally.

Novartis Pharma AG, Basel, Switzerland.