NOVARTIS

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:

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 2 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.

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 patients:

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

Pre-treatment conditioning (Lymphodepleting chemotherapy)

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

Kymriah is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. The availability of Kymriah must be confirmed prior to starting the lymphodepleting regimen. 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: 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: No formal studies have been performed in pediatric patients below 3 years of age.

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

Geriatric patients (65 years of age or older)

B-cell ALL: Limited experience in adult relapsed or refractory B-cell ALL patient population 65 years of age or older is available. The safety and efficacy of Kymriah in this population has not been established.

DLBCL: No dose adjustment is required in patients 65 years of age or older (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. 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 content of the first bag have 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.

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 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 and between 1 and 9 days (median onset 3 days) after Kymriah infusion in adult DLBCL patients. The median time to resolution of CRS was 8 days in B-cell ALL and 7 days in DLBCL patients.

Signs and symptoms of CRS may include high fever, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, anorexia, fatigue, headache, hypotension, dyspnea, tachypnea, and hypoxia. Organ dysfunction, including cardiac insufficiency and arrhythmia, renal insufficiency and liver injury with accompanying elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT) or elevated total bilirubin may also be observed. In addition, disseminated intravascular coagulation (DIC) with low fibrinogen levels, capillary leak syndrome (CLS), macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) may occcur 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 moderate or severe CRS associated with Kymriah. A minimum of two doses of tocilizumab per patient must be available on site prior to Kymriah infusion. Treatment center should have timely access to additional doses of tocilizumab. Corticosteroids may be administered in cases of life-threatening emergencies. Tisagenlecleucel continues to expand and persist following administration of tocilizumab and corticosteroids. Patients with medically significant cardiac dysfunction should be managed by standards of critical care; measures such as echocardiography should be considered. Tumor Necrosis Factor (TNF) antagonists are not recommended for management of Kymriah associated CRS.

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.

Table 6-1 CRS management algorithm

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

Neurological toxicities

Neurological toxicities, in particular signs and symptoms of encephalopathy, confusional state and/or delirium can occur with Kymriah and can be severe or life-threatening. Other manifestations include depressed level of consciousness, seizures, decreased 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 was 8 days in B-cell ALL and 6 days in DLBCL. The median time to resolution was 7 days for B-cell ALL and 13 days for DLBCL.

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

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

Infections and febrile neutropenia

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

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

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

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

Prolonged cytopenias

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

Secondary malignancies

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

Hypogammaglobulinemia

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

Live vaccines

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

Tumor lysis syndrome

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

Prior stem cell transplantation

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

Viral reactivation

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

Prior treatment with anti CD19 therapy

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

Interference with serological testing

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

Content of dextran 40 and dimethyl sulfoxide (DMSO)

This medicinal product contains 11 mg dextran 40 and 82.5 mg dimethyl sulfoxide (DMSO) per mL. Each of these excipients are known to possibly cause anaphylactic reaction following parenteral administration. Patients not previously exposed to dextran and DMSO should be observed closely during the first minutes of the infusion period.

Content of sodium and potassium

This medicinal product 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 194 patients (with pediatric and young adult B-cell ALL and DLBCL) receiving Kymriah in two multi-center pivotal clinical studies.

Pediatric and young adult B-cell ALL

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

- The most common non-hematological adverse reactions (≥40%) were cytokine release syndrome (77%), infections (73%), hypogammaglobulinaemia (53%) and pyrexia (42%).
- The most common haematological adverse reactions 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 adverse reactions 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%).
- 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%).

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	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
Coagulopathy	5	6	2	3	0	0	Common
Haemophagocytic lymphohistiocytosis	5	6	2	3	1	1	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							
Arrhythmia	17	22	2	3	1	1	Very common
Cardiac failure	7	9	4	5	2	3	Common
Cardiac arrest	3	4	0	0	3	4	Common

B2202, N=79	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Eye disorders							
Visual impairment	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	14	18	2	3	0	0	Very common
Constipation	14	18	0	0	0	0	Very common
Abdominal distension	3	4	0	0	0	0	Common
Ascites	3	4	0	0	0	0	Common
Stomatitis	3	4	1	1	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	20	25	2	3	0	0	Very common
Fatigue	18	23	0	0	0	0	Very common
Oedema	15	19	1	1	0	0	Very common
Chills	7	9	0	0	0	0	Common
Asthenia	3	4	0	0	0	0	Common
Influenza like illness	2	3	0	0	0	0	Common
Multiple organ dysfunction syndrome	2	3	0	0	2	3	Common
Hepatobiliary disorders							
Hyperbilirubinaemia	5	6	1	1	0	0	Common
Immune system disorders							
Cytokine release syndrome	61	77	17	22	21	27	Very common

B2202, N=79	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Hypogammaglobulinaemia	42	53	10	13	0	0	Very common
Infusion related reaction	5	6	1	1	0	0	Common
Graft versus host disease	2	3	2	3	0	0	Common
Infections and infestations							
Infections - pathogen unspecified	45	57	14	18	7	9	Very common
Viral infectious disorders	30	38	15	19	2	3	Very common
Bacterial infectious disorders	21	27	12	15	1	1	Very common
Fungal infectious disorders	12	15	4	5	3	4	Very common
Investigations							
Lymphocyte count decreased*	79	100	20	25	56	71	Very common
Haemoglobin decreased*	79	100	38	48	0	0	Very common
Neutrophil count decreased*	79	100	6	8	69	87	Very common
White blood cell decreased*	79	100	5	6	72	91	Very common
Platelet count decreased*	77	97	13	16	48	61	Very common
Aspartate aminotransferase increased	19	24	8	10	3	4	Very common
Alanine aminotransferase increased	18	23	7	9	0	0	Very common
Blood bilirubin increased	13	16	9	11	0	0	Very common
International normalised ratio increased	9	11	0	0	0	0	Very common
Serum ferritin increased	8	10	2	3	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

B2202, N=79	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Blood alkaline phosphatase increased	1	1	0	0	0	0	Common
Metabolism and nutrition disorders							
Decreased appetite	30	28	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	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
Fluid overload	7	9	5	6	0	0	Common
Hypomagnesaemia	6	8	0	0	0	0	Common
Hyperphosphataemia	5	6	0	0	1	1	Common
Tumour lysis syndrome	5	6	4	5	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							
Back pain	10	13	3	4	0	0	Very common
Myalgia	10	13	0	0	0	0	Very common
Arthralgia	8	10	1	1	0	0	Very common
Musculoskeletal pain	5	6	0	0	0	0	Common
Nervous system disorders							
Headache	28	35	2	3	0	0	Very common

B2202, N=79	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Encephalopathy	24	30	7	9	0	0	Very common
Tremor	6	8	0	0	0	0	Common
Seizure	5	6	3	4	0	0	Common
Dizziness	4	5	0	0	0	0	Common
Peripheral neuropathy	3	4	0	0	0	0	Common
Speech disorder	2	3	1	1	0	0	Common
Motor dysfunction	1	1	0	0	0	0	Common
Neuralgia	1	1	0	0	0	0	Common
Psychiatric disorders							
Delirium	15	19	3	4	0	0	Very common
Anxiety	13	16	2	3	0	0	Very common
Sleep disorder	9	11	0	0	0	0	Very common
Renal and urinary disorders							
Acute kidney injury	17	22	3	4	8	10	Very common
Respiratory, thoracic and mediastinal disorders							
Cough	21	27	0	0	0	0	Very common
Hypoxia	20	25	10	13	6	8	Very common
Dyspnoea	14	18	2	3	8	10	Very common
Pulmonary oedema	12	15	6	8	1	1	Very common
Nasal congestion	9	11	0	0	0	0	Very common
Oropharyngeal pain	8	10	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
Acute respiratory distress syndrome	3	4	0	0	3	4	Common
Lung infiltration	1	1	1	1	0	0	Common

B2202, N=79	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Skin and subcutaneous tissue disorders							
Rash	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	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	2	3	1	1	0	0	Common
Flushing	1	1	0	0	0	0	Common

Abdominal pain includes PTs of Abdominal pain, Abdominal pain upper

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

Arrhythmia includes PTs of Tachycardia

Bacterial infectious disorders includes HLGTs of Bacterial infectious disorders

Cardiac failure includes PTs of Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Right ventricular dysfunction

Cough includes PTs of Cough, Productive cough

Delirium includes PTs of Agitation, Delirium, Hallucination, Hallucination, visual, Irritability, Restlessness

Dyspnoea includes PTs of Dyspnoea, Respiratory distress, Respiratory failure

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

Fatigue includes PTs of Fatigue, Malaise

Fungal infectious disorders includes HLGTs of Fungal infectious disorders

Headache includes PTs of Headache, Migraine

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, Melaena, Menorrhagia, Mouth haemorrhage, Peritoneal haematoma, Petechiae, Pharyngeal haemorrhage, Purpura, Retinal haemorrhage, Vaginal haemorrhage

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

Infections – pathogen unspecified include HLGTs of Infections pathogen unspecified

Motor dysfunction includes PTs of Muscle spasms

Oedema includes PTs of Face oedema, Generalised oedema, Localised oedema, Oedema peripheral

Pain includes PTs of Pain, Pain in extremity

Peripheral neuropathy includes PTs of Hyperaesthesia, Hypoaesthesia, Paraesthesia

Rash includes PTs of Dermatitis, Rash, Rash maculo-papular, Rash papular, Rash pruritic

Seizure includes PTs of Generalised tonic-clonic seizure, Seizure

Sleep disorder includes PTs of Insomnia, Nightmare, Sleep disorder

Speech disorder includes PTs of Aphasia, Dysarthria

Viral infectious disorders includes HLGTs of Viral infectious disorders

* 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	25	22	4	3	5	4	Very common
Neutropenia	23	20	7	6	16	14	Very common

C2201, N=115	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Febrile neutropenia	19	17	16	14	3	3	Very common
Thrombocytopenia	15	13	3	3	11	10	Very common
Leukopenia	4	3	2	2	0	0	Common
Pancytopenia	4	3	2	2	1	1	Common
Haemophagocytic lymphohistiocytosis	2	2	0	0	0	0	Common
B-cell aplasia	1	1	1	1	0	0	Uncommon
Lymphopenia	1	1	0	0	0	0	Uncommon
Cardiac disorders							
Arrhythmia	20	17	6	5	0	0	Very common
Cardiac arrest	3	3	0	0	3	3	Common
Cardiac failure	1	1	0	0	1	1	Uncommon
Eye disorders							
Visual impairment	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	12	10	2	2	0	0	Very common
Vomiting	10	9	10	1	0	0	Common
Stomatitis	7	6	0	0	0	0	Common
Dry mouth	6	5	0	0	0	0	Common
Abdominal distension	4	3	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

C2201, N=115	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Fatigue	31	27	7	6	0	0	Very common
Oedema	26	23	2	2	0	0	Very common
Pain	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							
Hyperbilirubinaemia	3	3	3	3	0	0	Common
Immune system disorders							
Cytokine release syndrome	66	57	17	15	9	8	Very common
Hypogammaglobulinaemia	20	17	7	6	0	0	Very common
Infusion related reaction	3	3	0	0	0	0	Common
Infections and infestations							
Infections - pathogen unspecified	55	48	23	20	7	6	Very common
Bacterial infectious disorders	17	15	9	8	0	0	Very common
Fungal infectious disorders	13	11	5	4	1	1	Very common
Viral infectious disorders	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	43	Very common
Haemoglobin decreased*	114	99	68	59	0	0	Very common
Neutrophil count decreased*	112	97	24	21	70	61	Very common

C2201, N=115	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Platelet count decreased*	109	95	16	14	48	42	Very common
Weight decreased	14	12	4	3	0	0	Very common
Aspartate aminotransferase increased	5	4	0	0	0	0	Common
Blood alkaline phosphate increased	5	4	1	1	0	0	Common
Fibrin D dimer increased	5	4	1	1	0	0	Common
Serum ferritin increased	5	4	1	1	0	0	Common
Blood fibrinogen decreased	4	3	4	3	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
Hypomagnesaemia	19	17	0	0	0	0	Very common
Hypophosphataemia	19	17	15	13	0	0	Very common
Decreased appetite	16	14	4	3	0	0	Very common
Hyponatraemia	9	8	4	3	1	1	Common
Hypocalcaemia	6	5	0	0	0	0	Common
Hypercalcaemia	5	4	0	0	1	1	Common
Hyperglycaemia	5	4	2	2	0	0	Common
Hypoalbuminaemia	5	4	3	3	0	0	Common
Fluid overload	3	3	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

C2201, N=115	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Hypernatraemia	1	1	0	0	0	0	Uncommon
Hyperphosphataemia	1	1	0	0	0	0	Uncommon
Musculoskeletal and connective tissue disorders							
Arthralgia	11	10	0	0	0	0	Very common
Back pain	6	5	1	1	0	0	Common
Myalgia	6	5	0	0	0	0	Common
Musculoskeletal pain	5	4	0	0	0	0	Common
Nervous system disorders							
Headache	24	21	1	1	0	0	Very common
Encephalopathy	18	16	8	7	5	4	Very common
Dizziness	14	12	2	2	0	0	Very common
Peripheral neuropathy	10	9	0	0	0	0	Common
Motor dysfunction	7	6	1	1	0	0	Common
Tremor	7	6	0	0	0	0	Common
Speech disorder	5	4	1	1	0	0	Common
Neuralgia	3	3	1	1	0	0	Common
Seizure	3	3	1	1	0	0	Common
Ataxia	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	12	10	0	0	0	0	Very common
Delirium	6	5	3	3	0	0	Common
Renal and urinary disorders							
Acute kidney injury	19	17	4	3	3	3	Very common

C2201, N=115	All grades		Grade 3		Grade 4		Frequency category (All grades)
	n	%	n	%	n	%	
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	24	21	5	4	2	2	Very common
Cough	20	17	0	0	0	0	Very common
Hypoxia	9	8	3	3	1	1	Common
Oropharyngeal pain	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	3	3	1	1	0	0	Common
Tachypnoea	3	3	0	0	0	0	Common
Skin and subcutaneous tissue disorders							
Rash	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	3	0	0	0	0	Common
Erythema	2	2	1	1	0	0	Common
Vascular disorders							
Hypotension	29	25	7	6	3	3	Very common
Thrombosis	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

Abdominal pain includes PTs of Abdominal discomfort, Abdominal pain, Abdominal pain upper

Acute kidney injury includes PTs of Acute kidney injury, Blood creatinine abnormal, Blood creatinine increased

Arrhythmia includes PTs of Atrial fibrillation, Supraventricular tachycardia, Tachycardia, Ventricular extrasystoles

Ataxia includes PTs of Ataxia, Dysmetria

Bacterial infectious disorders includes HLGTs of Bacterial infectious disorders
Cardiac failure includes PTs of Cardiac failure congestive
Cough includes PTs of Cough, Productive cough, Upper-airway cough syndrome
Delirium includes PTs of Agitation, Delirium, Irritability
Dizziness includes PTs of Dizziness, Presyncope, Syncope
Dyspnoea includes PTs of Dyspnoea, Dyspnoea exertional, Respiratory distress, Respiratory failure
Encephalopathy includes PTs of Cognitive disorder, Confusional state, Disturbance in attention, Encephalopathy, Lethargy, Memory impairment, Mental status changes, Metabolic encephalopathy, Somnolence, Thinking abnormal
Fatigue includes PTs of Fatigue, Malaise
Fungal infectious disorders includes HLGTs of Fungal infectious disorders
Haemorrhage includes PTs of Anal haemorrhage, Blood urine present, Cerebral haemorrhage, Contusion, Cystitis haemorrhagic, Disseminated intravascular coagulation, Duodenal ulcer haemorraghe, Epistaxis, Eye contusion, Gastrointestinal haemorrhage, Haematemesis, Haematochezia, Haematuria, Large intestinal haemorraghe, Melaena, Mouth haemorrhage, Petechiae, Pharyngeal haemorrhage, Post procedural haemorraghe, Pulmonary Haemorraghe, Purpura, Retinal haemorrhage, Traumatic haematoma, Tumour haemorraghe, Upper gastrointestinal haemorrhage
Headache includes PTs of Headache, Migraine
Hypogammaglobulinaemia includes PTs of Blood immunoglobulin G decreased, Hypogammaglobulinaemia, Immunodeficiency, Immunoglobulins decreased
Hypotension includes PTs of Hypotension, Orthostatic hypotension
Infections - pathogen unspecified includes HLGTs of Infections - pathogen unspecified
Motor dysfunction includes PTs of Muscle spasms, Muscle twitching, Myoclonus, Myopathy
Neuralgia includes PTs of Neuralgia, Sciatica
Oedema includes PTs of Face oedema, Generalised oedema, Localised oedema, Oedema peripheral, Peripheral swelling
Oropharyngeal pain includes PTs of Oral pain, Oropharyngeal pain
Pain includes PTs of Pain, Pain in extremity
Peripheral neuropathy includes PTs of Hyperaesthesia, Hypoaesthesia, Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy
Pulmonary oedema includes PTs of Acute pulmonary oedema, Pulmonary oedema
Rash includes PTs of Dermatitis, Dermatitis acneiform, Dermatitis contact, Rash, Rash maculo-papular, Rash papular, Rash pruritic
Seizure includes PTs of Seizure, Status epilepticus

Sleep disorder includes PTs of Insomnia, Sleep disorder
Speech disorder includes PTs of Aphasia, Dysarthria, Speech disorder
Thrombosis includes PTs of Deep vein thrombosis, Embolism, Pulmonary embolism, Thrombosis, Vena cava thrombosis, Venous thrombosis
Tremor includes PTs of Dyskinesia, Tremor
Viral infectious disorders includes HLGTs of Viral infectious disorders
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.

Description of selected adverse drug reactions

Cytokine release syndrome

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

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

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

For clinical management of CRS, see 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.

Severe febrile neutropenia (Grade 3 or 4) was observed in 34% of pediatric and young adult B-cell ALL patients and 17% of DLBCL 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%), leukoytes (21%) and decreased hemoglobin (14%).

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 (10% 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.

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

Hypogammaglobulinaemia

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

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 tranferred 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 prescribing information 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 KymriahPregnancy 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 and r/r DLBCL patients, the CAR-T positive cells typically exhibited an initial rapid expansion followed by a slower bi-exponential decline.

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 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

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: not yet available.

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.

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 older)

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.

Gender

Gender is not a significant characteristic influencing tisagenlecleucel expansion in B-cell ALL and DLBCL patients. In Study B2202, there were 43% female and 57% male patients and in Study C2201 there were 38% female and 62% male patients.

Race/ethnicity

There is limited evidence that race/ethnicity impact the expansion of Kymriah in pediatric and young adult ALL and DLBCL. 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.

Body weight

In DLBCL and ALL patients, across the weight ranges ((DLBCL: 38.4 to 186.7 kg; ALL: 14.4 to 137 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 or adult DLBCL 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%) and adult DLBCL (C2201, 93.9%) patients.

Treatment-induced anti-mCAR19 antibodies were found in 40.5% of pediatric and young adult ALL and 8.7% of adult DLBCL 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 and adult r/r DLBCL 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. Ninty-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)

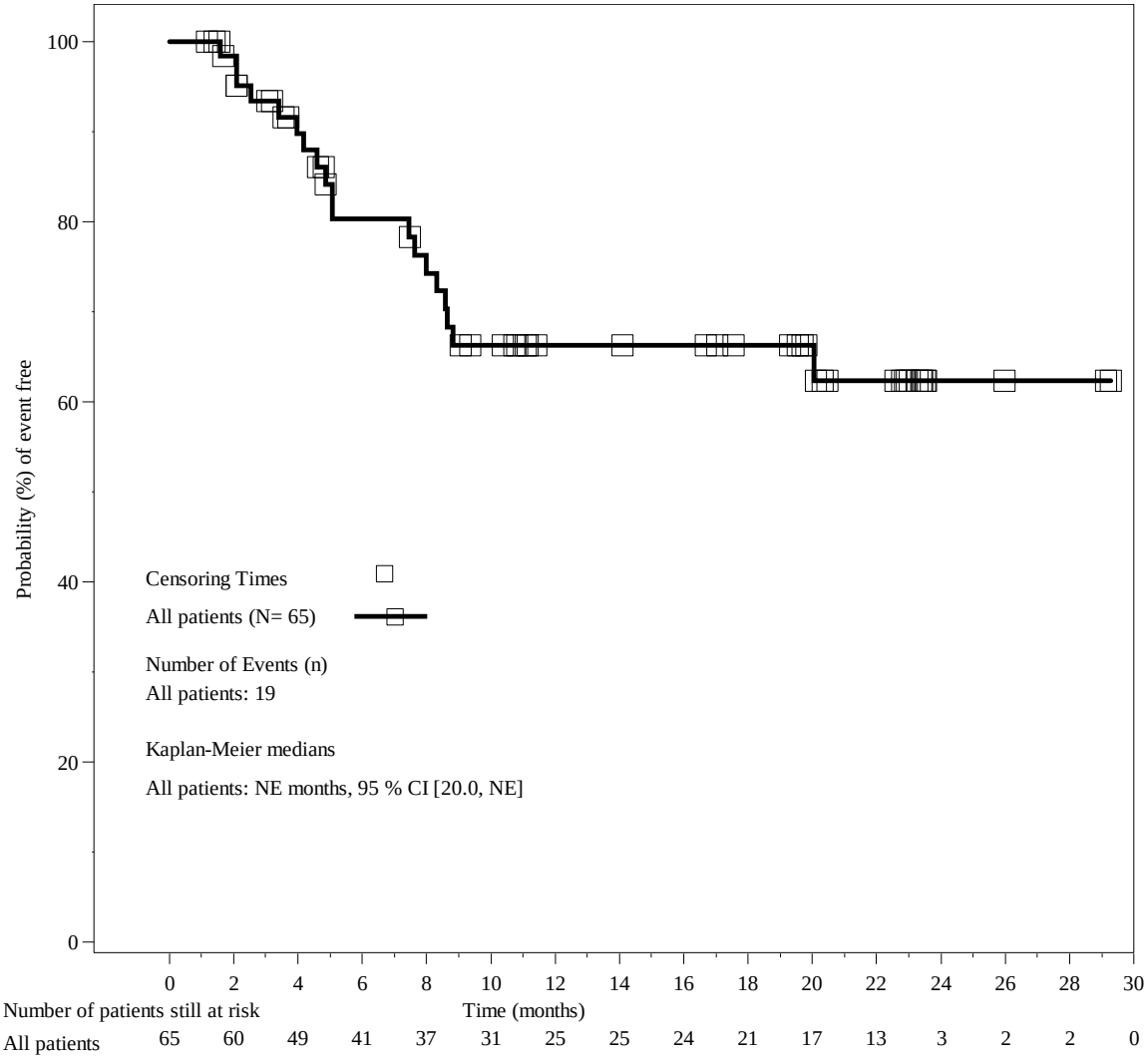
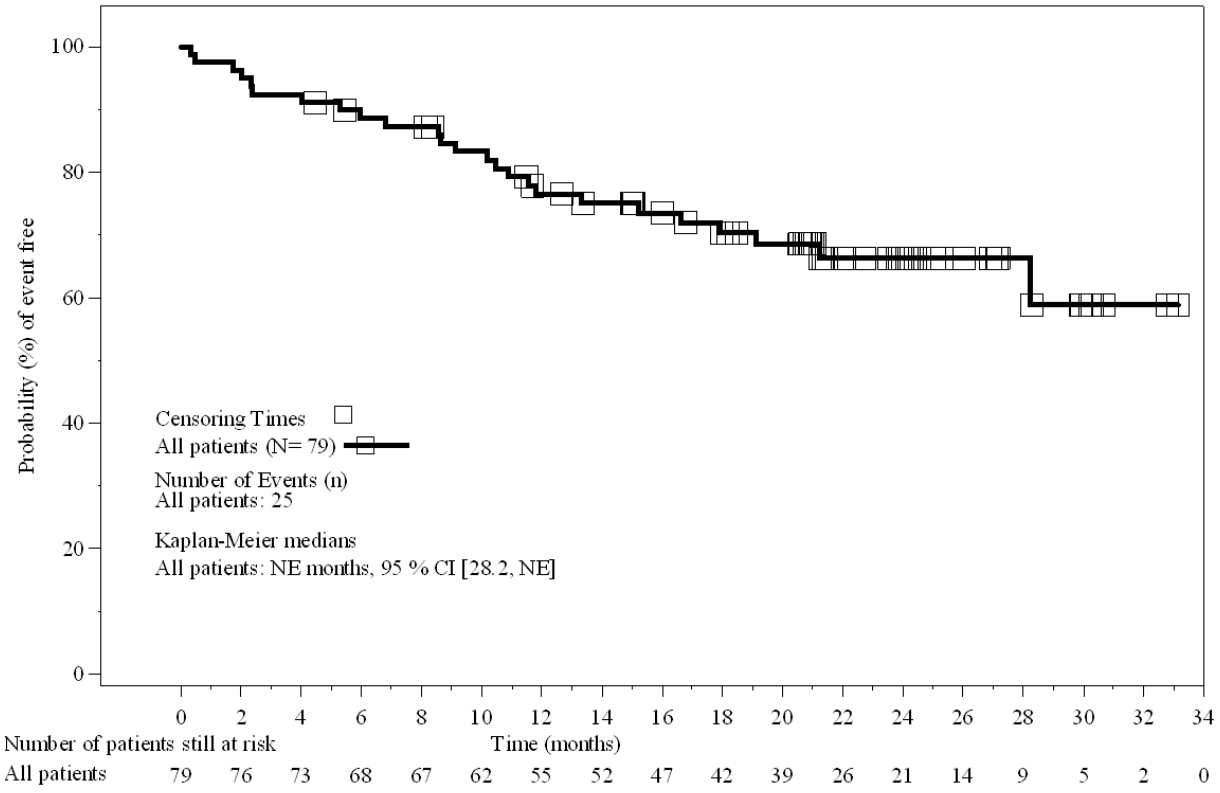


Figure 12-2 B2202: Overall Survival (OS)



Diffuse large B-cell lymphoma (DLBCL)

The safety and efficacy of Kymriah treatment in adults 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 %, repectively) 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

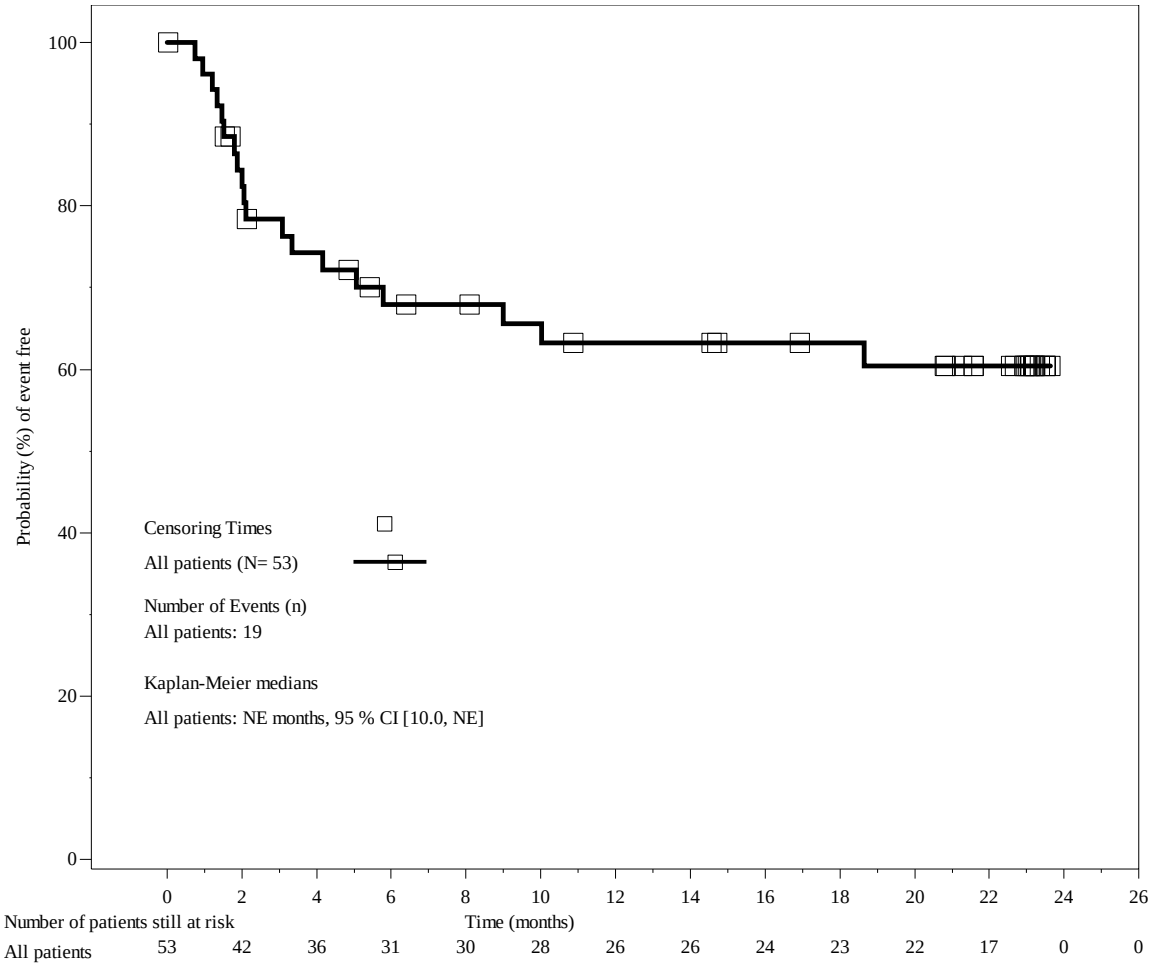
[2] The p-value is displayed as a descriptive statistic only, with no inferential interpretation (since the null hypothesis of ORR <20% was already rejected with p<0.0001 at a previous interim analysis).

[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)

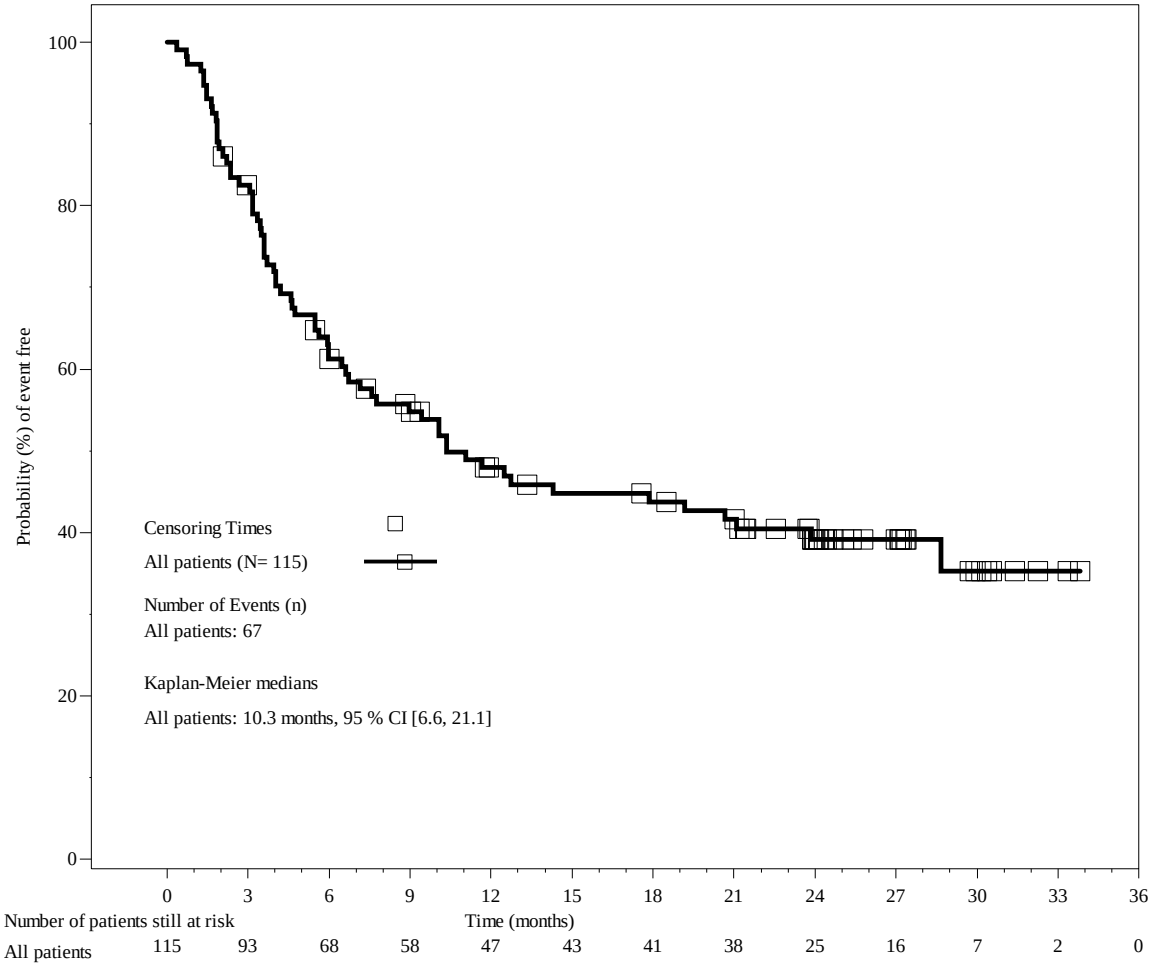
[5] Not estimable

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)



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

1) Novartis Pharmaceuticals Corporation, 220 East Hanover Avenue Morris Plains, NJ 07950, USA
2) Cell Therapies Pty Ltd, 305 Grattan Street Melbourne, VIC 3000, Australia

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) bag contains 10 to 30ml of dispersion and each CS250 (250ml) bag contains 30 to 70ml of dispersion.

Not all presentation may be available locally.

Novartis Pharma AG, Basel, Switzerland.