AUSTRALIAN PI – KYMRIAH® (TISAGENLECLEUCEL) SUSPENSION

WARNING: CYTOKINE RELEASE SYNDROME

- Cytokine Release Syndrome (CRS), including fatal or life threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life threatening CRS with tocilizumab as per the CRS management algorithm.

1 NAME OF THE MEDICINE

T Cells – Tisagenlecleucel, cryoperserved – T - Kymriah

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each bag of Kymriah contains tisagenlecleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (see Dose and Method of Administration).

1-3 infusion bags containing a total of 1.2 x 10^6 to 6.0 x 10^8 CAR-positive viable T cells in 10 to 50 mL. The quantitative information regarding total cells in the product is presented in the Certificate of Analysis.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Cell suspension.

Appearance: colourless to slightly yellow suspension of cells.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Kymriah is a genetically modified autologous immunocellular therapy indicated for:

- the treatment of paediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse.

- the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Kymriah is not indicated for patients with primary central nervous system lymphoma.

4.2 DOSE AND METHOD OF ADMINISTRATION

For autologous use only.

Pre-treatment conditioning (lymphodepleting chemotherapy)

Lymphodepleting chemotherapy is recommended to be administered before Kymriah infusion unless the white blood cell (WBC) count within one week prior to Kymriah infusion is ≤1,000 cells/microliter. Kymriah cells are recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. The availability of Kymriah must be confirmed prior to starting the lymphodepleting regimen. If there is a more than 4 week delay between completing lymphodepleting chemotherapy and the Kymriah infusion and the WBC count is >1,000 cells/microliter, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving Kymriah.

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

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

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

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

DLBCL: *The recommended lymphodepleting chemotherapy regimen is:*

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

If the patient experienced a previous Grade 4 haemorrhagic 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 IV daily for 2 days).

Dosage

Kymriah is provided as a single, one-time treatment. The amount of tisagenlecleucel provided by the manufacturing facility equates to the dose to be used for each patient, and is within the target dose range indicated below.

Dosage in paediatric and young adult B-cell ALL 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).

Method of administration

For intravenous use only. Do not use a leukocyte depleting filter.

Premedication:

To minimize potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to Kymriah infusion. Corticosteroids should not be used at any time except in the case of a life-threatening emergency (see Special Warnings and Precautions for Use).

Precautions to be taken before administering Kymriah

Kymriah contains genetically-modified human cells. Local biosafety guidelines applicable for handling and disposal of such products should be followed (see Special Precautions for Disposal).

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

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

Preparation for infusion

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

Inspection and thawing of the infusion bag(s): The timing of thaw of Kymriah and infusion should be coordinated. Confirm the infusion time in advance, and adjust the start time for thaw so that Kymriah is available for infusion when the recipient is ready. Once Kymriah has been thawed and is at room temperature, it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

The infusion bag should be placed inside a second, sterile bag in case of a leak and to protect ports from contamination. 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. If more than one infusion bag has been received for the treatment dose, the second bag should not be thawed until after the contents of the first bag have been infused. 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 intravenous infusion should be administered by healthcare providers experienced with immunosuppressed patients and trained for administration of Kymriah and management of patients treated with Kymriah. Tocilizumab and emergency equipment must be available prior to infusion and during the recovery period.

The Kymriah cell product should not be manipulated. For example, Kymriah should **not** be washed (spun down and resuspended in new media) prior to infusion. All contents of the infusion bag(s) should be infused to complete a single dose.

The patient's identity should be matched with the patient identifiers on the infusion bag since Kymriah is for autologous use only. Kymriah should be administered as an IV infusion through latex free IV tubing without a leukocyte depleting filter, approximately at 10 to 20 mL per minute by gravity flow and adjusted as appropriate for smaller children and smaller volumes. Sterile normal saline (NS) 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 normal saline by back priming to assure as many cells as possible are infused into the patient.

Monitoring after infusion

- Following infusion with Kymriah patients should be monitored 2-3 times per week for at least the first week for signs and symptoms of potential cytokine release syndrome, neurological events and other toxicities. Physicians should consider hospitalisation at the first signs/symptoms of cytokine release syndrome and/or neurological events.
- Instruct patients to remain within proximity (ie within 2 hours travel) of the certified healthcare facility for at least 4 weeks following infusion.

Dosage adjustment in:

Renal and hepatic impairment

As a cell based therapy and based on the mechanism of action, renal and hepatic impairment is not expected to impact tisagenlecleucel expansion and cellular kinetics; hence no formal renal and hepatic impairment studies were performed.

Geriatric patients (65 years of age or older)

DLBCL: No dose adjustment is required in patients over 65 years of age (see Cellular Kinetics; Special Populations).

4.3 CONTRAINDICATIONS

Kymriah is contraindicated in patients with known hypersensitivity to tisagenlecleucel or to any component of the product formulation, (see section 6.1) including dimethyl sulfoxide (DMSO) or dextran 40.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Reasons to delay treatment

Due to the risks associated with Kymriah treatment, infusion should be withheld until resolution of any of the following conditions.

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

Patient information

Prior to infusion, the patient should read the information from 'Patient Education Leaflet". In particular, the patient should be carefully educated to inform their doctor immediately if cytokine release syndrome (CRS) or neurological symptoms occur after infusion with Kymriah, and informed that they should stay within 2 hours distance of where they are given Kymriah treatment for 4 weeks. Ensure that patients understand the risk of manufacturing failure. In case of a manufacturing failure, a second manufacturing of KYMRIAH may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period.

Blood, organ, tissue and cell donation

Patients treated with Kymriah should not donate blood, organs, tissues and cells for transplantation.

Active central nervous system (CNS) leukaemia 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.

Cytokine release syndrome

Cytokine release syndrome (CRS), including fatal or life threatening events, have been frequently observed after Kymriah infusion. In all but 4 cases, development of CRS occurred between 1 to 10 days (median onset 3 days) after Kymriah infusion for paediatric and young adult B-cell ALL patients and between 1 and 9 days (median onset 3 days) after the Kymriah infusion for adult DLBCL patients. The median time to resolution of CRS was 8 days in B-cell ALL and 7 days in DLBCL patients.

Symptoms of CRS may include high fever, rigors, myalgia, arthralgia, nausea, vomiting, diarrhoea, diaphoresis, rash, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnoea, tachypnoea, and hypoxia. Additional organ system adverse events, including transient cardiac insufficiency and arrhythmia, renal insufficiency, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), and elevated bilirubin have been observed. In some cases, disseminated intravascular coagulation (DIC), with low fibrinogen levels, capillary leak syndrome (CLS), and haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS. Patients should be closely monitored for signs or symptoms of these events including fever.

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

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

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

Management of Cytokine Release Syndrome associated with Kymriah

CRS is managed solely based on clinical presentation and according to the CRS management algorithm provided in Table 1**.** Anti-IL-6 based therapies, such as tocilizumab have been administered for moderate or severe CRS associated with Kymriah and a minimum of four doses should be on site and available for administration prior to Kymriah infusion. 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 and measures such as echocardiography should be considered. Tumour Necrosis Factor (TNF) antagonists are not recommended for management of Kymriah associated CRS.

Table 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: - Haemodynamic 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: 12mg/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 events

Neurological events, in particular encephalopathy, confusional state or delirium, occur frequently with Kymriah and can be severe or life threatening. Other manifestations included seizures, aphasia and speech disorder. The majority of neurological events occurred within 8 weeks following Kymriah infusion and were transient. Median time to the first event was 7 days from infusion (range: 2-489) and the median duration was 7 days for patients with r/r ALL. Median time to first event was 6 days from infusion (range: 1-323) and the median duration was 13 days for patients with r/r 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 prior to and during treatment with Kymriah should be employed. Infections are known to complicate the course and management of concurrent CRS.

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

In patients achieving complete remission following Kymriah, resulting low immunoglobulin levels can increase the risk for infections. In patients with low immunoglobulin levels pre-emptive measures

such as immunoglobulin replacement and rapid attention to signs and symptoms of infection should be implemented as per age and standard guidelines.

Prolonged cytopenias

Patients may continue to exhibit cytopenias for several weeks following Kymriah and should be managed per standard guidelines. The majority of patients who had cytopenias at day 28 following Kymriah treatment resolved to Grade 2 or below within three months after treatment. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, 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, the company should be contacted to obtain instructions on patient samples to collect for testing.

Hypogammaglobulinemia

Hypogammaglobulinemia (IgG) and agammaglobulinemia (IgG) can occur in patients with a complete remission after Kymriah infusion. Immunoglobulin levels should be monitored after treatment with Kymriah. 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 viral vaccines during or following Kymriah treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment, and until immune recovery following treatment with Kymriah.

Tumour lysis syndrome

Tumour lysis syndrome (TLS), which may be severe, has been observed. To minimize risk of TLS, patients with elevated uric acid or high tumour 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.

Concomitant disease

Patients with a history of active CNS disorder or inadequate renal, 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 below and require special attention.

Prior bone marrow transplant

It is not recommended that patients receive Kymriah within 4 months of undergoing an allogeneic stem cell transplant (SCT) 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 allogeneic SCT.

HIV, Hepatitis B, Hepatitis C and viral reactivation

There is no data to support the safe use of Kymriah in patients with HIV and hepatitis B and C viral infections. It is not recommended that patients receive Kymriah if they have viral hepatitis because of the potential risk of viral reactivation. It is not recommended that patients receive Kymriah if they have HIV because of the possible effect on loss of HIV viral suppression and the theoretical risk of recombination events.

Viral Reactivation

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

Hepatitis cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive, and also in patients who are HBsAg negative but hepatitis B core antibody (anti-HBc) positive. HBV reactivation has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Perform screening for HBV, HCV, and HIV in accordance with institutional procedures before collection of cells for manufacturing.

Prior treatment with an anti-CD19 therapy

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

Use in the elderly

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

DLBCL: The safety and efficacy of KYMRIAH have been established in geriatric patients (See Clinical Trials). No dose adjustment is required in patients over 65 years of age (see Cellular Kinetics; Special Populations).

Paediatric use

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

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

Effects on laboratory tests

Due to limited short spans of identical genetic information between the lentiviral vector used to create Kymriah and HIV, some commercial HIV nucleic acid tests (NAT) may give a false positive result post-treatment with Kymriah. ELISA or Western Blot tests for the presence of HIV antibodies should be used to provide specificity for HIV infection after administration of Kymriah.

Content of dextran 40 and dimethyl sulfoxide (DMSO)

This medicinal product contains 10 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No cellular kinetic or biodynamic drug interaction studies with tisagenlecleucel have been performed.

The co-administration of agents known to inhibit T-cell function and stimulate T-cell function have not been formally studied.

The potential for biodynamic drug interactions exists for drugs administered as part of conditioning regimens such as rituximab with Kymriah. Rituximab and Kymriah can cause B cell aplasia. B-cell levels are measured over time in all patients as a mechanism to evaluate the potential for biodynamic interactions.

Live vaccines

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

Concomitant therapy with tocilizumab and corticosteroids

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy – Pregnancy Category C

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. 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.

If a patient intends to become pregnant after receiving Kymriah, the patient should be apprised of the potential risks to the fetus.

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

Use in lactation

There are no data regarding the presence of Kymriah in human milk, the effect on the breast-fed child or the effects of Kymriah on milk production. A risk to the newborn/infant cannot be excluded. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Kymriah and any potential adverse effects from Kymriah on the breast-fed infant or from the underlying maternal condition.

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

Females and males of reproductive potential

There is a potential for Kymriah to cause fetal toxicity.

Pregnancy testing

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

Contraception

Sexually active females of reproductive potential should use highly effective contraception (methods that result in less than 1% pregnancy rates) after Kymriah administration.

Sexually active males who have received Kymriah should use a condom during intercourse with females of reproductive potential or pregnant women.

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

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pediatric and young adult B-cell ALL

The adverse reactions described in this section were identified in 104 patients in two multi-center studies, i.e. the ongoing pivotal clinical study CCTL019B2202 (N=75) and the supportive clinical study CCTL019B2205J (N=29).

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

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

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

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

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

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

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

Tabulated summary of adverse drug reactions from clinical trials

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

Table 2 B-cell ALL: Percentage of patients with adverse drug reactions in clinical trials[1]

Adverse drug reactions	B2202 + B2205J, N=104			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Infections and infestations[a)]				
Infections - pathogen unspecified	48	13	8	Very common
Viral infectious disorders	33	14	1	Very common
Bacterial infectious disorders	25	13	1	Very common
Fungal infectious disorders	13	4	3	Very common
Blood and lymphatic system disorders				
Febrile neutropenia	36	34	2	Very common
Disseminated intravascular coagulation	6	2	-	Common
Coagulopathy	6	2	-	Common
Histiocytosis haematophagic	5	2	1	Common
Pancytopenia	3	2	1	Common
Immune system disorders				
Cytokine release syndrome	81	20	24	Very common
Hypogammaglobulinaemia[b)]	45	7	-	Very common
Graft versus host disease	1	1	-	Common
Metabolism and nutrition disorders				
Decreased appetite	40	19	1	Very common
Hypokalaemia	30	12	3	Very common
Hypophosphataemia	21	11	1	Very common
Hypocalcaemia	16	6	-	Very common
Hypoalbuminaemia	13	1	-	Very common
Fluid overload	11	5	-	Very common
Hyperglycaemia	10	6	-	Very common
Hyperphosphataemia	11	-	1	Very common
Hyperuricaemia	11	1	-	Very common
Hypomagnesaemia	6	-	-	Common
Tumor lysis syndrome	4	3	1	Common
Psychiatric disorders				
Delirium[c)]	16	3	-	Very common
Anxiety	15	3	-	Very common
Nervous system disorders				
Headache[d)]	35	2	-	Very common
Encephalopathy[e)]	29	6	1	Very common
Dizziness	8	-	-	Common
Tremor	6	-	-	Common
Seizure[f)]	5	2	-	Common

Adverse drug reactions	B2202 + B2205J, N=104			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Cerebral haemorrhage	2	-	2	Common
Dysphasia[g)]	2	1	-	Common
Cardiac disorders				
Tachycardia[h)]	30	4	1	Very common
Cardiac failure[i)]	7	6	1	Common
Cardiac arrest	3	-	3	Common
Vascular disorders				
Hypotension	31	10	13	Very common
Hypertension	18	5	-	Very common
Capillary leak syndrome	3	1	1	Common
Flushing	3	-	-	Common
Respiratory, thoracic and mediastinal disorders				
Hypoxia	24	13	7	Very common
Cough	23	-	-	Very common
Pulmonary oedema	14	8	2	Very common
Epistaxis	13	3	1	Very common
Pleural effusion	13	3	1	Very common
Tachypnoea	10	5	-	Very common
Interstitial lung disease	1	-	1	Common
Gastrointestinal disorders				
Vomiting	36	3	-	Very common
Nausea	31	7	-	Very common
Diarrhoea	28	2	-	Very common
Abdominal pain[j)]	22	3	-	Very common
Constipation	17	-	-	Very common
Mouth haemorrhage	5	3	-	Common
Abdominal distension	4	-	-	Common
Ascites	3	-	-	Common
Abdominal compartment syndrome	1	-	1	Common
Hepatobiliary disorders				
Hyperbilirubinaemia	7	3	-	Common
Skin and subcutaneous tissue disorders				
Rash	10	-	-	Very common
Pruritus	8	-	-	Common
Erythema	7	-	-	Common
Hyperhydrosis	7	-	-	Common
Petechiae	6	1	-	Common
Rash maculo-papular	4	2	-	Common

Adverse drug reactions	B2202 + B2205J, N=104			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Rash papular	4	-	-	Common
Musculoskeletal and connective tissue disorders				
Pain in extremity	16	1	-	Very common
Myalgia	13	-	-	Very common
Arthralgia	11	1	-	Very common
Back pain	10	3	-	Very common
Musculoskeletal pain	7	-	-	Common
Renal and urinary disorders				
Acute kidney injury[k)]	19	3	10	Very common
Haematuria	7	3	1	Common
Dysuria	4	-	-	Common
General disorders and administration site conditions				
Pyrexia	41	10	3	Very common
Fatigue	24	1	-	Very common
Chills	13	-	-	Very common
Face oedema	9	2	-	Common
Oedema peripheral	8	2	-	Common
Generalized oedema	6	-	-	Common
Multiple organ dysfunction syndrome	3	1	2	Common
Investigations				
Aspartate aminotransferase increased	30	11	7	Very common
Alanine aminotransferase increased	28	13	-	Very common
Blood bilirubin increased	15	9	-	Very common
International normalised ratio increased	15	1	-	Very common
Blood creatinine increased	13	4	1	Very common
Prothrombin time prolonged	9	1	-	Common
Blood fibrinogen decreased	9	2	2	Common
Activated partial thromboplastin time prolonged	7	1	-	Common

[1)]The frequency of ADRs observed is the crude incidence rate
[a)]Infections and infestations are high level group terms.
[b)]Hypogammaglobulinemia includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased and hypogammaglobulinaemia
[c)] Delirium includes agitation, delirium, hallucination, visual hallucination, irritability, and restlessness
[d)] Headache includes headache and migraine
[e)] Encephalopathy includes depressed level of consciousness, mental status changes, automatism, cognitive disorder, confusional state, disturbance in attention, encephalopathy, posterior reversible encephalopathy syndrome, myoclonus, somnolence and lethargy
[f)]Seizure includes generalized tonic-clonic seizure, and seizure.
[g)]Dysphagia includes dysphagia, dysarthria, speech disorder, and aphasia
[h)] Tachycardia includes sinus tachycardia and tachycardia.
[i)] Cardiac failure includes cardiac failure, left ventricular dysfunction, cardiac failure congestive and right ventricular dysfunction
[j)]Abdominal pain includes abdominal pain, abdominal pain lower and abdominal pain upper
[k)]Acute kidney injury includes acute kidney injury, anuria, azotaemia, renal failure, renal tubular dysfunction and renal tubular necrosis

Haematology laboratory abnormalities are presented in Table 3.

Table 3 B-cell ALL: Haematology laboratory abnormalities post-Kymriah infusion[1] based on CTCAE (N=104)

Laboratory parameter	All Grades (%)	Grades 3 and 4 (%)
White Blood Cells decreased	100	96
Haemoglobin decreased	100	50
Platelets decreased	95	77
Neutrophils decreased	98	96
Lymphocytes decreased	98	93

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

Diffuse Large B-Cell Lymphoma

The adverse reactions described in this section were identified in 111 patients, infused with Kymriah, in one global multi-centre study, i.e. the ongoing pivotal clinical study CCTL019C2201.

The most common non-haematological adverse reactions were CRS (58%), infections (54%), pyrexia (35%), diarrhoea (32%), nausea (29%), hypotension (26%) and fatigue (26%).

The most common haematological laboratory abnormalities were lymphocytes decreased (100%), haemoglobin decreased (99%), white blood cells decreased (98%), neutrophils decreased (97%), and platelet decreased (95%).

Grade 3 and Grade 4 adverse reactions were reported in 89% of patients. The most common Grade 3 and Grade 4 non-haematological adverse reaction was infections (32%) and CRS (22%).

The most common (>40%) Grade 3 and Grade 4 haematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (81%), white blood cell count decreased (77%), haemoglobin decreased (59%), and platelet count decreased (55%).

Grade 3 or 4 adverse events were more often observed within the initial 8 weeks post-infusion (85% of patients) compared to after 8 weeks post-infusion (49% of patients).

Eight fatalities not related to disease progression occurred following Kymriah infusion, all after 30 days from infusion. Of those, there were 2 deaths due to multiple organ dysfunction syndrome and one death each due to cerebral haemorrhage, chronic kidney disease, duodenal ulcer haemorrhage, neuroendocrine carcinoma, pulmonary haemorrhage and sepsis.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials Table 4 are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of

decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 4 Percentage of patients with adverse drug reactions in clinical trials[1]

Adverse drug reactions	C2201, N=111			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Infections and infestations[a)]				
Infections - pathogen unspecified	44	19	5	Very common
Bacterial infectious disorders	10	7	-	Very common
Fungal infectious disorders	10	5	1	Very common
Viral infectious disorders	8	2	-	Common
Blood and lymphatic system disorders				
Febrile neutropenia	16	13	3	Very common
Disseminated intravascular coagulation	3	2	-	Common
Histocytosis haematophagic	1	-	-	Common
Immune system disorders				
Cytokine release syndrome	58	14	8	Very common
Hypogammaglobulinaemia[b)]	15	4	-	Very common
Immunodeficiency	2	1	-	Common
Metabolism and nutrition disorders				
Hypokalaemia	23	8	-	Very common
Hypomagnasaemia	17	-	-	Very common
Hypophosphataemia	17	14	-	Very common
Decreased appetite	12	4	-	Very common
Hyponatraemia	8	5	1	Common
Hypocalcaemia	5	-	-	Common
Hyperglycaemia	5	2	-	Common
Hypoalbuminaemia	5	3	-	Common
Tumor lysis syndrome	1	1	-	Common
Psychiatric disorders				
Anxiety	11	1	-	Very common
Delirium[c)]	5	3	-	Common
Nervous system disorders				
Headache[d)]	23	1	-	Very common
Encephalopathy[e)*]	16	7	5	Very common
Dizziness [f)]	12	2	-	Very common
Paraesthesia[g)]	6	-	-	Common
Tremor	5	-	-	Common
Speech disorders[h)]	5	1	-	Common

Adverse drug reactions	C2201, N=111			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Neuralgia	3	1	-	Common
Seizure[i]	3	1	-	Common
Ischemic cerebral infarction	1	1	-	Common
Cardiac disorders				
Tachycardia[j)]	14	3	-	Very common
Arrhythmia[k)]	6	2	-	Common
Cardiac failure[l)]	1	-	1	Common
Vascular disorders				
Hypotension	26	6	3	Very common
Hypertension	3	2	-	Common
Capillary leak syndrome	1	-	-	Common
Respiratory, thoracic and mediastinal disorders				
Dyspnoea[m)]	21	5	2	Very common
Cough[n)]	18	-	-	Very common
Hypoxia	8	3	1	Common
Pleural effusion	5	2	-	Common
Gastrointestinal disorders				
Diarrhoea	32	1	-	Very common
Nausea	29	1	-	Very common
Constipation	16	1	-	Very common
Vomiting	9	1	-	Common
Abdominal pain[o)]	9	2	-	Common
Dry mouth	5	-	-	Common
Stomatitis	5	-	-	Common
Abdominal distension	4	2	-	Common
Hepatobiliary disorders				
Hyberbiliburinaemia	3	3	-	Common
Skin and subcutaneous tissue disorders				
Night sweats	5	-	-	Common
Petechiae	5	-	-	Common
Pruritus	5	-		Common
Rash[p)]	8	-		Common
Hyperhydrosis	4	-	-	Common
Pruritus	4	-	-	Common
Erythema	2	1	-	Common
Musculoskeletal and connective tissue disorders				
Arthralgia	10	-	-	Very common
Back pain	5	1		Common

Adverse drug reactions	C2201, N=111			Frequency category (all grades)
	All grades %	Grade 3 %	Grade 4 %	
Myalgia	5	-	-	Common
Renal and urinary disorders				
Acute kidney injury[q)]	17	4	3	Very common
General disorders and administration site conditions				
Pyrexia	35	5	-	Very common
Fatigue	26	6	-	Very common
Oedema[r)]	23	2	-	Very common
Pain[s)]	14	3	-	Very common
Chills	13	-	-	Very common
Influenza-like illness	7	-	-	Common
Asthenia	7	-	-	Common
Multiple organ dysfunction syndrome	3	-	3	Common
Investigations				
Weight decreased	11	3	-	Very common
Aspartate aminotransferase increased	5	-	1	Common
Blood alkaline phosphatase increased	5	1	-	Common
Fibrin d-dimer increased	5	1	-	Common
Serum ferritin increased	5	1	-	Common

[1)]The frequency of ADRs observed is the crude incidence rate[a)] Infections and infestations presented reflect high level group terms.

[b)] Hypogammaglobulinemia includes hypogammaglobulinaemia, blood immunoglobulin G decreased, immunodeficiency common variable, immunoglobulins decreased.

[c)] Delirium includes agitation, delirium and irritability.

[d)] Headache includes headache and migraine.

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

[f)] Dizziness includes dizziness, presyncope and syncope.

[g)] Paraesthesia includes paraesthesia, hyperaesthesia and hypoaesthesia.

[h)] Speech disorder includes speech disorder, dysarthria and aphasia.

[i)] Seizure includes seizure and status epilepticus[j)] Tachycardia includes sinus tachycardia and tachycardia.

[k)] Arrhythmia includes atrial fibrillation and supraventricular tachycardia.

[l)] Cardiac failure includes cardiac failure congestive.

[m)] Dyspnoea includes dyspnoea, dyspnoea exertional,respiratory distress and respiratory failure.

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

[o)] Abdominal pain includes abdominal pain, abdominal discomfort and abdominal pain upper.

[p)] Rash includes rash, rash maculo-papular, rash papular and rash pruritic.

[q)] Acute kidney injury includes acute kidney injury and blood creatine increased.

[r)] Oedema includes oedema peripheral, generalised oedema, localised oedema and face oedema.

[s)] Pain includes pain and pain in extremity.

**With reported sequelae of secondary cerebral oedema.*

Haematology laboratory abnormalities are presented in Table 5.

Table 5 DLBCL: Haematology laboratory abnormalities post-Kymriah infusion[1] based on CTCAE (N=106)

Laboratory parameter	All Grades (%)	Grades 3 and 4 (%)
White Blood Cells decreased	98	77
Haemoglobin decreased	99	59
Platelets decreased	95	55
Neutrophils decreased	97	81
Lymphocytes decreased	100	95

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

Description of selected adverse drug reactions

Cytokine release syndrome (CRS)

In the ongoing clinical studies in paediatric and young adult B-cell ALL (N=104), CRS reactions classified based on the PENN Grading system for CRS (Porter et al 2015) were reported in 81% of patients (44% with Grade 3 or 4) with a median time to onset of 3 days and a median CRS duration of 8 days.

In the ongoing clinical study in DLBCL (N=111), CRS was reported in 58% of patients, (22% with Grade 3 or 4), with a median time to onset of 3 days and a median duration of 7 days.

Of the 84 patients with r/r ALL who had CRS, 35 (42%) received tocilizumab. Ten (12%) patients received two doses of tocilizumab, 6 (7%) patients received three doses of tocilizumab, and 19 (23%) patients received addition of corticosteroids (e.g., methylprednisolone).

Of the 64 patients with r/r DLBCL who had CRS, 17 (27%) received systemic tocilizumab or corticosteroids. Six (9%) patients received a single dose of tocilizumab, 10 (16%) patients received two doses of tocilizumab, and 11 (17%) patients received corticosteroids in addition to tocilizumab. One patient with r/r DLBCL received corticosteroids for CRS without concomitant tocilizumab.

For clinical management of CRS, see Special Warnings and Precautions for Use and Table 1. Neurological events have occurred in the context of CRS. The timing has been prior to the onset of CRS, during and shortly after the resolution of CRS, and rarely has recurred after apparent resolution of the event.

Febrile neutropenia and infections

Severe febrile neutropenia (Grade 3 or 4) was observed in 36% of paediatric and young adult B-cell ALL patients and 15% of DLBCL patients. See Special Warnings and Precautions for Use for the management of febrile neutropenia before Kymriah and after Kymriah infusion.

In B-cell ALL patients severe infections (Grade 3 or 4), which can be life-threatening or fatal, occurred in 38% of patients after Kymriah infusion. The overall incidence was 67% (bacterial 25%, viral 33%,

unspecified 48%, and fungal 13%) (see Special Warnings and Precautions for Use). 44% of the patients experienced an infection of any type by 8 weeks after Kymriah infusion.

In DLBCL patients severe infections (Grade 3 or 4), which can be life-threatening or fatal, occurred in 32% of patients. The overall incidence was 54% (bacterial 10%, viral 8%, unspecified 44%, and fungal 10%) (see Special Warnings and Precautions for Use). 34% of the patients experienced an infection of any type within 8 weeks.

Hematopoietic cytopenias not resolved by day 28

In paediatric and young B-cell ALL patients, Grade 3 and 4 cytopenias beyond 28 days were reported based on laboratory findings and included neutropenia (59%), leukopenia (58%), lymphopenia (47%), thrombocytopenia (46%), and anaemia (11%). In adult patients with DLBCL Grade 3 and 4 cytopenias beyond 28 days were reported based on laboratory findings and included thrombocytopenia (41%), lymphopenia (28%), neutropenia (24%), leukopenia (21%) and anaemia (14%).

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

Neurological events

The majority of these events occurred within 8 weeks following infusion and were transient. In paediatric and young adult B-cell ALL patients, manifestations of encephalopathy and/or delirium occurred in 38% of patients (11% Grade 3 or 4) within 8 weeks after Kymriah infusion. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 21% of patients (12% were Grade 3 or 4) within 8 weeks after Kymriah infusion.

The other most common neurological event was headache (35% in paediatric and young adult B-cell ALL patients and 23% in DLBCL patients).

Special populations

B-cell ALL: Based on covariate analysis on data collected in clinical trials there do not appear to be any special populations. There are no data in the elderly or those with renal or hepatic impairment as these populations were not enrolled in the trials of children and young adults. There is very limited data in patients less than 3 years of age.

DLBCL: There are no data in the young patients below the age of 18 years or those with renal or hepatic impairment as these populations were not enrolled in the trials of adult DLBCL. Clinical benefit and tolerability in elderly patients above the age of 65 years (23% of study population) were comparable to that in the overall population.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 BIOLOGICAL PROPERTIES

5.1 BIODYNAMIC PROPERTIES

Mechanism of action

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

Biodynamic effects

Cardiac electrophysiology

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

Clinical trials

Acute Lymphoblastic Leukemia (ALL)

The safety and efficacy of Kymriah treatment in patients with relapsed and refractory (r/r) paediatric and young adults B-cell ALL, were evaluated in three open-label, single-arm, studies (160 patients in total). All patients had leukapheresis products collected and cryopreserved prior to or during study entry.

Pivotal study B2202 used tisagenlecleucel exclusively sourced from the Novartis registered manufacturing facility. A small number of tisagenlecleucel batches (3/29) were manufactured at Novartis for study B2205J and no batches came from Novartis for study B2101J. A formal comparability study of Novartis-made tisagenlecleucel batches and other manufacturing sites has not taken place.

<u>CCTL019B2202 (Study 1)</u>

The pivotal study (B2202) is a multicenter, single-arm phase II study in paediatric and young adult patients with r/r B-cell acute lymphoblastic leukaemia. Of 92 patients enrolled, 75 received infusion with Kymriah; for 7 patients (8%) Kymriah could not be manufactured; reasons for discontinuation prior to Kymriah infusion included death (n=7; 8%) or adverse events (n=3; 3%) while awaiting Kymriah manufacturing in the clinical study.

The 75 infused patients included 43 males and 32 females of median age 11 years (range: 3-23 years). Seventy-seven percent of patients were White, 8% were Asian, and 15% were of other races. Six (8%)

had primary refractory disease, 40 (53%) had one prior stem cell transplantation, 6 patients (8%) had two stem cell transplantations. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 daily for 2 days) followed by a single dose of KYMRIAH. Among the 75 patients who received Kymriah infusion, a total of 65 and 72 received bridging chemotherapy and lymphodepleting chemotherapy respectively after enrollment and prior to the Kymriah infusion (see Table 6).

Table 6 Study B2202: Baseline population information

	N=75 **n (%)**
Age (years)	
Mean (standard deviation)	12.0 (5.28)
Median (minimum – maximum)	11.0 (3 – 23)
Age category (years) - n (%)	
<10 years	31 (41.3)
≥10 years and <18 years	31 (41.3)
≥18 years	13 (17.3)
Sex - n (%)	
Male	43 (57.3)
Female	32 (42.7)
Disease status (%)	
Primary refractory[1]	6 (8.0)
Relapsed disease[2]	69 (92.0)
Prior stem-cell transplantation - n (%)	
0	29 (38.7)
1	40 (53.3)
2	6 (8.0)
[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), within 3 months post infusion, as determined by Independent Review Committee (IRC) assessment. Secondary endpoints included duration of remission (DOR) and the proportion of patients who achieved complete remission (CR) or complete remission with incomplete blood count (Cri) with minimal residual disease (MRD) <0.01% by flow cytometry (MRD-negative). The ORR at 3 months was 81% (61/75). The median time from Kymriah infusion to the data cut-off date was 13.11 months (range: 2.1 to 23.5). See Table 7 and Figure 1 and Figure 2 for efficacy results from this study. Fifty-seven of 61 responders achieved CR/CRi by the Day 28 assessment. ORR was consistent across all subgroups. Seven patients who received Kymriah infusion went to transplant while in remission. Seventy six percent of patients were hospitalized at the time of infusion and 24% were not hospitalized at the time of Kymriah infusion.

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 13.5 at Month 3 and 16.9 at Month 6 and 27.2 at Month 12, and the mean change from baseline in the EQ VAS score was 16.5 at Month 3 and 15.9 at Month 6 and 24.7 at Month 12, indicating overall clinically meaningful improvement in HRQoL following Kymriah infusion.

Table 7 B2202: Efficacy results in paediatric and young adult patients with relapsed/refractory B-cell Acute Lymphoblastic Leukaemia (ALL)

Primary Endpoint	**N=75**
Overall Remission Rate (ORR) [1,2], n (%)	61 (81.3)
95% CI	(70.7, 89.4)
	p<0.0001
CR [3], n (%)	45 (60.0)
CRi [4], n (%)	16 (21.3)
NR[5], n (%)	6 (8.0)
Not evaluable, n (%)	8 (10.7)
Key Secondary Endpoint	**N=75**
CR or CRi with MRD negative bone marrow [6,7], n (%)	61 (81.3)
95% CI	(70.7, 89.4)
	p<0.0001
Duration of remission (DOR)[8]	**N=61**
% event free probability at 6 months	79.5
Median (months) (95% CI)	Not reached (8.6, NE[9])
Other Secondary Endpoint	**N=75**
Overall survival (OS)	
% survival probability at 6 months	90.3
% survival probability at 12 months	76.4
Median (months) (95% CI)	19.1 (15.2, 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, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion.
[5] NR = No Response
[6] MRD (minimal residual disease) negative was defined as MRD by flow cytometry <0.01%.
[7] Norminal one-sided exact p-value based on H0: Rate of MRD negative remission ≤ 15% vs. Ha: > 15%.
[8] DOR was defined as time since onset of CR or CRi to relapse or death due to underlying indication, whichever is earlier (N=61)
[9] NE= Not estimable

Figure 1 B2202: Duration of remission (DOR)

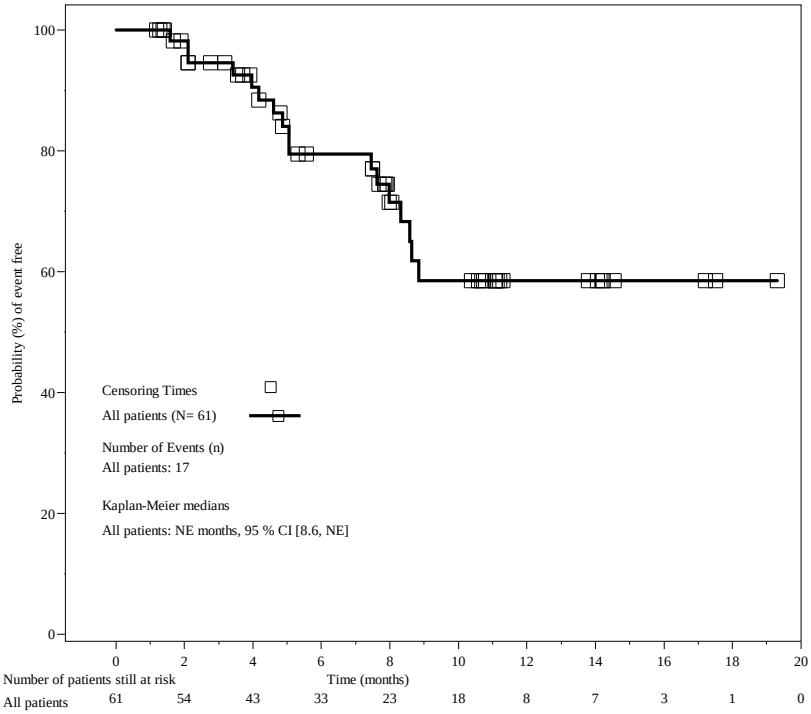
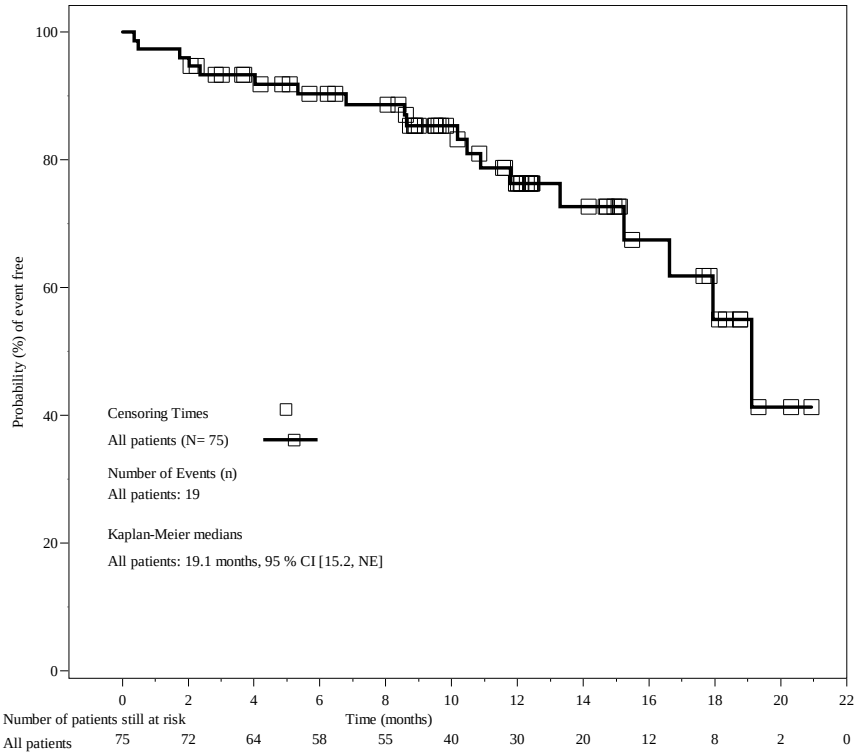


Figure 2 B2202: Overall Survival (OS)



CCTL019B2205J (Study 2) and CCTL019B2101J (Study 3)

The supportive study B2205J is a phase II, single arm, multicentre trial in 29 paediatric and young adult patients 3 to 25 years of age with r/r B-cell acute lymphoblastic leukaemia. Eligibility criteria, dosing, and disease assessment criteria were similar to B2202.

The supportive study B2101J was a single arm, single site phase I/II trial in 56 paediatric and young adult patients 1 to 24 years of age with CD19+ B cell malignancies and was similar to B2205J.

Table 8 B2205J and B2101J: Efficacy results in paediatric and young adult patients with relapsed/refractory B-cell Acute Lymphoblastic Leukaemia (ALL)

	B2205J N=29	**B2101J N=56 [1]**
Overall Remission Rate (ORR) [2, 3], n (%)	**20 (69.0)**	**53 (94.6)**
95% CI	(49.2, 84.7)	(85.1, 98.9)
	p<0.0001	
CR [4], n (%)	18 (62.1)	42 (75.0)
CRi [5], n (%)	2 (6.9)	11 (19.6)
NR[6]	7 (24.1)	3 (5.4)
Not evaluable	2 (6.9)	0
CR or CRi with MRD negative bone marrow [7], n (%)	18 (62.1)	50 (89.3)
95% CI	(42.3, 79.3)	(78.1,96.0)
Duration of remission (DOR) [8]	**N=20**	**N=53**
% event free probability at 6 months	66.4	73.2
Median (months) (95% CI)	Not reached (5.4, NE[9])	33.4 (8.0, NE[9])
Overall survival (OS)	**N=29**	**N=56**
% survival probability at 6 months	75.7	85.7
Median (months) (95% CI)	Not reached (6.9, NE[9])	37.9 (22.7, NE[9])

[1] Non-CNS-3 B-ALL patients
[2] Requires remission status to be maintained for at least 28 days without clinical evidence of relapse in Study B2205J. Did not require maintenance of remission status in Study B2101J
[3] One-sided exact p-value threshold 0.0052 (adjusted for interim) for Study B2205J. The null hypothesis of ORR ≤20% was rejected
[4] 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
[5] CRi (complete remission with incomplete blood count recovery) was defined as <5% of blasts in the bone marrow, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion
[6] NR= No response
[7] MRD (minimal residual disease) negative was defined as MRD by flow cytometry <0.01%
[8] DOR was assessed in CR/CRi patients (N=20 in Study B2205J, N=53 in Study B2101J) and defined as time since onset of CR or CRi to relapse or death due to underlying indication, whichever is earlier
[9] NE= Not estimable

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 (111 DLBCL patients in total).

CCTL019C2201

The pivotal study (C2201) is a multicentre, single-arm phase II study in adult patients with relapsed or refractory DLBCL. Of 165 patients enrolled, 111 patients received infusion with Kymriah (4 infusions were pending at the time of analysis); Twelve out of 165 patients did not receive Kymriah due to manufacturing failure. Other reasons for discontinuation prior to Kymriah infusion included death (n=16), physician decision/primary disease progression (n=16), adverse event (n=3), subject decision (n=3) or adverse events (n=2) while awaiting Kymriah manufacturing in the clinical trial.

Median age of infused patients was 56 years (range 22 to 76 years), 76% of patients had Stage III-IV disease, 51% had received 3 or more prior lines of treatment for DLBCL. Forty-nine percent of patients had received prior stem cell transplant. Fifty-five percent of patients were refractory to last line of treatment. All patients had leukapheresis starting material collected and cryopreserved prior to or during study entry. The majority of patients 102/111 received bridging therapy while waiting for Kymriah and 103/111 received lymphodepleting chemotherapy prior to Kymriah infusion. Kymriah was given as a single dose intravenous infusion.

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 9). The primary endpoint was assessed in 93 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 93 patients (Table 9) included in the primary analysis, the best ORR was 51.6% (48/93) with a 95% confidence interval (CI) of (41.0%, 62.1%). Thirty-seven patients (39.8%) achieved CR and 11 (11.8%) achieved PR. 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 53.1% and 50.0% in patients with ≤2 lines of therapies and >2 lines of therapies, respectively), prior SCT (ORR of 50.0% and 53.7% in patients without or with previous SCT, respectively), relapsed or refractory disease (ORR 64.4% and 39.6%, respectively) or biological factors such as cell of origin (ORR 52.5% in non-GCB and 48.0% in GCB subtype) and double-hit/triple hit lymphoma with Bcl-2 and c-myc expression (ORR of 50.0% in patients with double-hit/triple hit lymphoma).

Table 9 C2201: Efficacy results in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are ineligible for autologous stem cell transplant (08-Dec-17 cut-off)

Primary Endpoint	**N=93**
Overall Response Rate (ORR) (CR+PR) [1], n (%) 95% CI	48 (51.6) (41.0, 62.1)
CR, n (%)	37 (39.8)
PR, n (%)	11 (11.8)
Response at Month 3 ORR (%) CR (%)	 35 (37.6) 30 (32.3)
Response at Month 6 ORR (%) CR (%)	N=92 30 (32.6) 27 (29.3)
Duration of response (DOR)[2]	N=48
Median (months) (95% CI) % relapse free probability at 9 months % relapse free probability at 12 months	Not reached (10.0, NE[5]) 67.4 65.1
Other Secondary Endpoints	N=111
Overall survival (OS)[3] Median (months) (95% CI) % survival probability at 9 months % survival probability at 12 months	 11.7 (6.6, NE[4]) 54.8 49.0

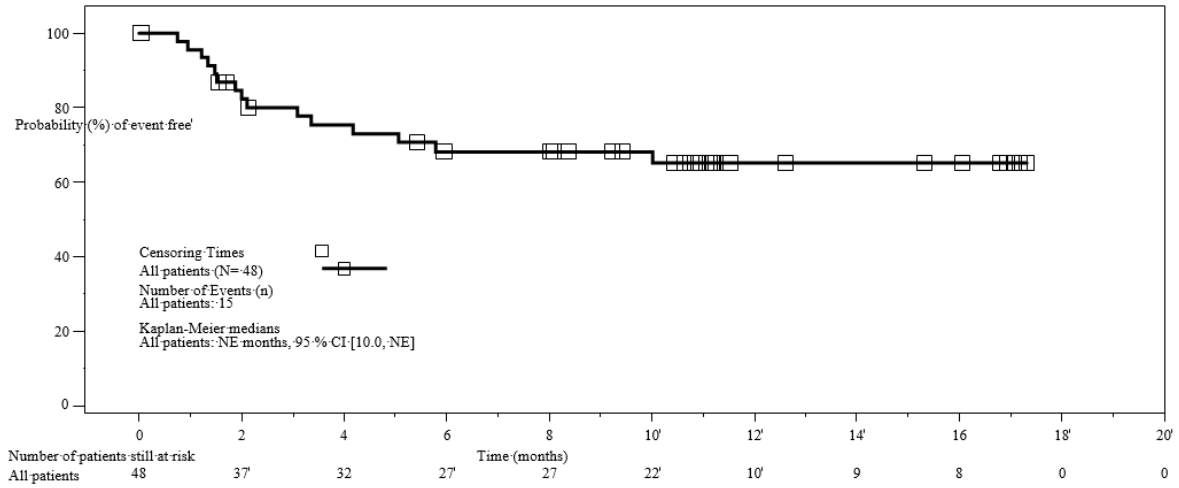
[1] ORR was calculated based on the first 93 patients who received Kymriah manufactured at the Novartis U.S. facility and have completed at least 3 months follow up, or discontinued earlier

[2] DOR was defined as time from achievement of CR or PR, whichever occurs first, to relapse or death due to DLBCL (N=48)

[3] OS was defined as time from date of Kymriah infusion to the date of death due to any cause (N=111)

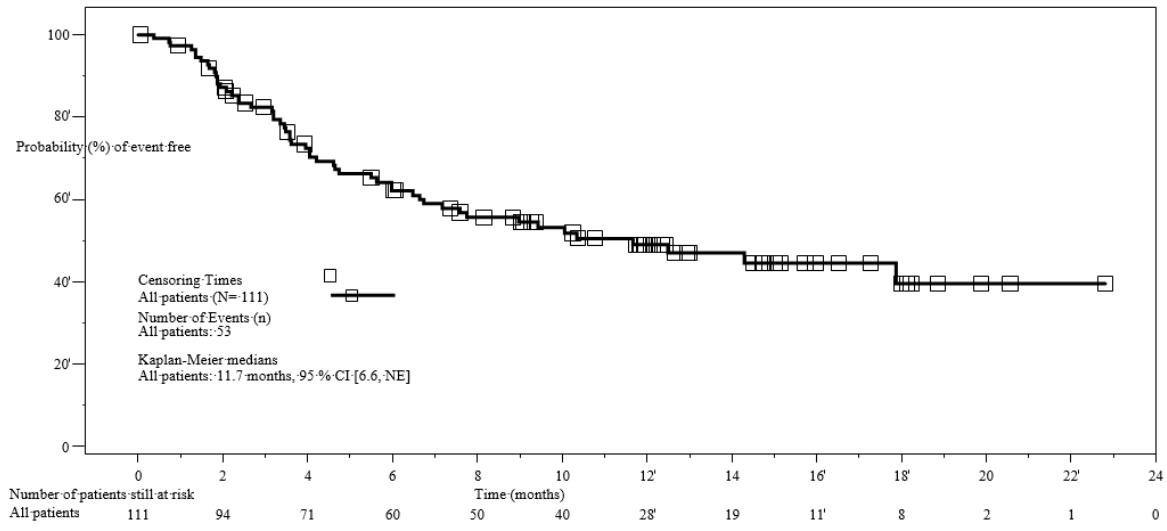
[4] Not estimable

Figure 3 **Kaplan-Meier plot of duration of response (DOR) censoring HSCT by IRC assessment for main cohort patients (Efficacy Analysis Set) – 08-Dec-17 cut-off**



- Efficacy analysis set (EAS) = All patients who receive CTL019 infusion at least 3 months prior to data-cut date.
- Only patients who achieved best overall response (BOR) of CR or PR are included.
- Time is relative to onset of response, 1 month=30.4375 days.

Figure 4 **Kaplan-Meier plot of overall survival (OS) (Full analysis set) – 08-Dec-17 cut-off**



- Full analysis set (FAS) = All patients who received an infusion of CTL019
- Time is relative to first CTL019 infusion date, 1 month=30.4375 days.

5.2 CELLULAR KINETICS

Following infusion of Kymriah into paediatric and young adult r/r B-cell ALL and r/r DLBCL patients, Kymriah typically exhibited an initial rapid expansion followed by a slower bi-exponential decline.

Cellular kinetics in paediatric B-cell ALL patients

A summary of cellular kinetic parameters of tisagenlecleucel is provided in Table 10 below.

The maximal expansion (Cmax) was approximately 2-fold higher in CR/CRi patients (n=79) compared with non-responding (NR) patients (n=10) as measured by qPCR. Transgene persistence has been

detected up to 784 days in peripheral blood (B2101J) and up to 617 days in responding patients in the in pooled studies B2202 and B2205J). Together these data, signify the potential role of expansion and persistence for eliciting a clinical response.

Table 10 Cellular kinetic parameters of tisagenlecleucel in paediatric and young adult r/r B-cell ALL (B2202, B2205J)

Parameter	Summary Statistics	Responding Patients N=80	Non-Responding Patients N=11
C_{max} (copies/µg)	Geometric mean (CV%),n	32,700 (163.4), 79	19,500 (123.7), 10
$T_{max‡}$ (day)	Median [min;max], n	9.83 [0.0111;27.8], 79	20.0 [0.0278;62.7], 10
AUC_{0-28d} (copies/µg*day)	Geometric mean (CV%), n	300,000 (193.4), 78	210,000 (111.7), 8
$T_{½}$ (day)	Geometric mean (CV%), n	21.7 (196.8), 65	2.70 (154.4), 3

‡A total of 5patients had an early T_{max} (<1 days), the next lowest T_{max} occurs at 5.7 days. Early T_{max} may not be representative of the true maximal expansion, rather the amount of transgene present in the catheter from which sample was collected.

Cellular kinetics in DLBCL patients

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

Tisagenlecleucel undergoes significant *in vivo* expansion following infusion and demonstrated persistence of the CAR transgene up to 693 days in responding patients (CR/PR) with shorter persistence in non-responding patients up to 374 days.

AUC_{0-28d} and C_{max} were similar between responder (CR and PR) and non-responder patients (SD, PD, and patients with unknown response status) based on clinical response at month 3. The geometric mean estimate for expansion (C_{max}) in DLBCL patients was observed to be lower than that in paediatric ALL patients (geometric mean C_{max} (%CV): 5,530 (303.3) copies/microgram, n=86, Study C2201; 35,800 (157.4) copies/microgram, n=72, Study B2202).

A trend for longer half-life was noted in responding patients compared to non-responding patients geometric mean T1/2: 91.3 days in responders, and 15.4 days in non-responders.

Table 11 Cellular kinetic parameters of tisagenlecleucel in r/r DLBCL patients by clinical response at month 3

Parameter	Summary Statistics	Responding Patients (CR and PR) N=35	Non-Responding Patients (SD/PD/Unknown) N=58
C_{max} (copies/µg)	Geometric mean (CV%), n	6210 (226.1), 35	5100 (372.6), 51
T_{max} (day)	Median [min;max], n	9.83 [5.78;16.8], 35	8.86 [3.04;27.7],51
AUC_{0-28d} (copies/µg*day)	Geometric mean (CV%), n	64300 (156.1), 33	64800 (301.1), 42
$T_{½}$ (day)	Geometric mean (CV%), n	91.3 (200.7), 22	15.4 (156.0), 34
T_{last}	Median [min;max], n	289 [18.0; 693], 35	57.0 [16.0; 374], 48

Absorption

Not applicable. Kymriah is a T-cell immunocellular therapy and is administered via intravenous infusion.

Distribution

In paediatric and young adult B-cell ALL patients, Kymriah has been shown to be present in the blood as well as bone marrow beyond 2 years (study B2101J). 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, demonstrating high trafficking to bone marrow (Studies B2202 and B2205J). In addition, Kymriah also traffics and persists in cerebrospinal fluid in paediatric 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 2 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.

Excretion

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

Linearity/non-linearity

Dose and cellular kinetic parameters are independent, thus there is no apparent relationship with AUC_{0-28d} and C_{max} with dose.

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 scatter plots of cellular kinetic parameters versus age revealed no relevant relationship between cellular kinetic parameters ($AUC_{0\text{-}28d}$ and C_{max}) with age. The $AUC_{0\text{-}28d}$ in patients with ≥65 years of age was observed to be 49.1% and 64.0% lower than patients ≥40 to <65 years and <40 years, respectively. However, the data should be interpreted with caution due to the high inter-individual variability associated with the parameter.

Gender

Gender is not a significant characteristic influencing tisagenlecleucel expansion in B-cell ALL and DLBCL patients.

Race/ethnicity

The majority of patients treated with Kymriah are Caucasian, therefore, there is limited evidence that race/ethnicity impact the expansion of Kymriah in paediatric and young adult ALL and DLBCL patients. In Studies B2202 and B2205J there were 79.8% of Caucasian, 7.7% of Asian and 12.5% of other ethnicities.

In Study C2201, there were 88% Caucasian, 5% Asian, 4% Black or African American patients and three patients (3%) of unknown race.

Body weight

In DLBCL patients, across the weight ranges (38.4 to 186.7 kg), the scatter plots of qPCR cellular kinetic parameters versus weight revealed no apparent relationship between cellular kinetic parameters with weight.

Renal impairment

Kymriah is a cell based product, and based on the mechanism of action renal impairment is not expected to impact tisagenlecleucel expansion and cellular kinetics; hence no formal renal impairment studies were performed.

Prior Transplantation

Prior transplantation did not impact the expansion/persistence of tisagenlecleucel in paediatric and young adult patients or adult DLBCL patients.

Hepatic impairment

Kymriah is a cell based product, and based on the mechanism of action hepatic impairment is not expected to impact tisagenlecleucel expansion and cellular kinetics; hence no formal hepatic impairment studies were performed.

Immunogenicity

Cell based therapeutics carry the potential for immunogenicity. Humoral immunogenicity of tisagenlecleucel was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. In paediatric and young adult ALL, the majority of patients (84.6%) tested positive for pre-dose anti-mCAR19, however, the pre-existing antibodies were not associated with an impact on clinical response nor have an impact on the expansion and persistence of tisagenlecleucel. Additionally treatment induced anti-mCAR19 antibodies were detected in 34.6 % of patients in the SCP pool. The treatment induced anti-mCAR19 antibodies did not impact cellular kinetics or clinical response.

In Study C2201, the majority of patients (91.4%) tested positive for pre-infusion humoral immunogenicity by the detection of anti-mCAR19 antibodies and 5% of patients had treatment-induced anti-mCAR19 antibodies detected. Anti-mCAR19 antibodies, both pre-existing and treatment-induced, were not associated with any apparent impact on clinical response nor have an impact on the in vivo initial expansion and persistence (Cmax and AUC0-28d) of tisagenlecleucel.

Cellular immunogenicity assessment was performed in paediatric and young adult ALL patients and r/r DLBCL patients to test for mCAR19 peptide-activated responses by stimulated intracellular interferon-gamma production. The cellular immunogenicity responses did not correlate with *in vivo* expansion and persistence and Month 3 response, for CD4 and CD8 T cell responses, for patients in both the indications.

As with any immunogenicity assay, the detection of anti-mCAR19 antibodies is highly dependent on assay sensitivity and specificity. Furthermore, the observed pre- and post-dose anti-mCAR19 may be influenced by several factors, including assay specifications, sample handling, timing of sample collection, prior therapy, administration of intravenous immunoglobulin or other concomitant medications as well as underlying disease. In addition, 90% of healthy volunteer samples screened during assay development were positive for anti-mCAR19 antibodies.

Active Central Nervous System (CNS) Leukaemia or Lymphoma

There is limited experience for use of Kymriah in patients with active CNS leukaemia and active CNS lymphoma. Therefore risk/benefit of Kymriah has not been established in this population.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Conventional genotoxicity assays have not been performed with tisagenlecleucel, and are not appropriate for cell therapy products. 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 harbouring integration sites of concern. However, a risk for insertional mutagenesis in mature T cells leading to oncogenic transformation cannot be excluded.

Carcinogenicity

Standard rodent carcinogenicity studies have not been performed with tisagenlecleucel. *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 after cell injection.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The cryo-media solution contains:

- Potassium 0.082 g/L
- Magnesium 0.012 g/L
- Sodium 2.43 g/L
- Aluminium 40.0 microgram/L
- Acetate 0.549 g/L
- Chloride 2.15 g/L
- Dextran 40 11.000 g/L
- Glucose 21.906 g/L
- Albumin (HSA) 52.400 g/L
- Dimethyl sulfoxide (DMSO) 82.500 g/L
- Dimethyl sulfone 0.03g/L
- D-gluconic acid 1.543 g/L
- Acetytriptophan 1.079 g/L
- Hydroxymethylfurfural 0.097mg/L
- Caprylate 0.630 g/L

This medicinal product contains 2.43 mg sodium per mL and 24.3 to 121.5 mg sodium per dose, equivalent to 1 to 6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains potassium, less than 1 mmol (39mg) per dose, ie essentially "potassium free."

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Store between 20 - 25°C	30 minutes
Store at 2°C to 8°C (Refrigerate. Do not freeze).	1 hour

6.5 NATURE AND CONTENTS OF CONTAINER

Container

Ethylene vinyl acetate (EVA) infusion bags with polyvinyl chloride (PVC) tubing and a luer spike interconnector closed by a luer-lock cap. Target volume 10 mL to 50 mL.

Pack size

Single dose unit.

6.6 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 cells.

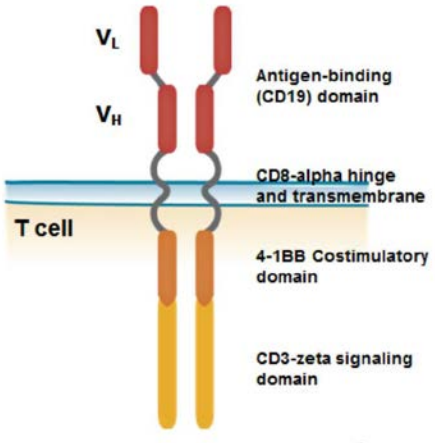
Kymriah products should be transported within the facility in closed, break-proof, leak-proof containers.

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.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The CAR-19 protein is comprised of a murine single chain antibody fragment, a CD8 hinge and transmembrane region, a 4-1BB (CD137) and CD3-zeta signalling domain



CAS number

Not established.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not determined.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 Dec 2018

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	N/A

Internal document code: kym131218i based on CDS 08-Feb-2018