1. NAME OF THE MEDICINAL PRODUCT

Kymriah

1.2×10^6 - 6×10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Kymriah (tisagenlecleucel) is a genetically modified autologous cell-based product containing T cells transduced *ex vivo* using a lentiviral vector expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked via a human CD8 hinge and transmembrane region to an intracellular signalling chain of human 4-1BB (CD137) co-stimulatory domain and CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of Kymriah contains tisagenlecleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one or more infusion bags overall containing a cell dispersion of 1.2×10^6 to 6×10^8 CAR-positive viable T cells in a cryopreservative solution.

The cellular composition and the final cell number varies between individual patient batches. In addition to T cells, natural killer (NK) cells may be present.

Each infusion bag contains 10-30 mL or 30-50 mL of cell dispersion.
The quantitative information of medicinal product, including the number of infusion bags (see section 6) to be administered, is presented on the batch specific documentation accompanying the medicinal product for treatment.

Excipients with known effect

This medicinal product contains 2.43 mg sodium per mL and 24.3 to 121.5 mg sodium per dose.
Each bag contains 11 mg dextran 40 and 82.5 mg dimethyl sulfoxide (DMSO) per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for intravenous infusion.

A colourless to slightly yellow dispersion in infusion bag/s.

4. CLINICAL PARTICULARS

Patient Information Brochure and Patient Alert Card
The marketing of Kymriah is subject to a risk management plan (RMP) including 'Patient information Brochure' and 'Patient Alert Card'. These materials emphasize important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review these materials before starting treatment.

Healthcare Professional Guides
This product is marketed with **Healthcare Professional Guides** (Prescriber's guide and Pharmacy /Cell Lab/Infusion Center training guides) providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

4.1 Therapeutic indications

Kymriah is indicated for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with CD19+ 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.
  Limitation of Use: Kymriah is not indicated for treatment of patients with primary or secondary central nervous system lymphoma.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

4.2 Posology and method of administration

Kymriah must be administered in a qualified treatment centre. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with the medicinal product.

In the event of cytokine release syndrome (CRS), at least one dose of tocilizumab and emergency equipment must be available per patient prior to infusion. The treatment centre must have access to additional doses of tocilizumab within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Ministry of Health website, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

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

Posology

Kymriah is intended for autologous use only (see section 4.4).

Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one or more infusion bags.

Dose in paediatric and young adult CD19+ B-cell ALL patients
The concentration of CAR-positive viable T cells is dependent on indication and patient body weight.

- For patients 50 kg and below: The dose is within a range of 0.2 to 5 $\times 10^6$ CAR-positive viable T cells per kg body weight.
- For patients above 50 kg: The dose is within a range of 0.1 to 2.5 $\times 10^8$ CAR-positive viable T cells (non-weight based).

Dose in adult DLBCL and FL patients
- The dose is within a range of 0.6 to 6.0 $\times$ 10^8 CAR-positive viable T cells (non-weight based).

See the accompanying batch specific documentation for additional information pertaining to dose.

Pre-treatment conditioning (lymphodepleting chemotherapy)

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

Lymphodepleting chemotherapy may be omitted if a patient is experiencing significant cytopenia, e.g.,

white blood cell (WBC) count ≤1 000 cells/µL within one week prior to infusion.

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

CD19+ 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 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 intravenous daily for 2 days) and etoposide (150 mg/m^2 intravenous daily for 3 days starting with the first dose of cytarabine).

DLBCL and FL
The recommended lymphodepleting chemotherapy regimen is:
- Fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine).

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

Pre-medication

To minimise 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 section 4.4).

Clinical assessment prior to infusion

Kymriah treatment should be delayed in some patient groups at risk (see section 4.4).

Monitoring after infusion

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome, neurological events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of cytokine release syndrome 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 (within 2 hours of travel) of a qualified clinical facility for at least 4 weeks following infusion.

Special populations

Elderly
CD19+ B-cell ALL
The safety and efficacy of Kymriah in this population have not been established.

DLBCL and FL
No dose adjustment is required in patients over 65 years of age.

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, active HBV, or active HCV infection. Leukapheresis material from these patients will not be accepted for Kymriah manufacturing. Screening for HBV, HCV, and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing.

Paediatric population
CD19+ B-cell ALL
No formal studies have been performed in paediatric patients below 3 years of age.

DLBCL and FL
The safety and efficacy of Kymriah in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Kymriah is for intravenous use only.

Preparation for infusion
Kymriah is intended for autologous use only. Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Kymriah infusion bags and accompanying documentation. The total number of infusion bags to be administered should also be confirmed with the patient specific information on the batch specific documentation (see section 4.4).

The timing of thaw of Kymriah and infusion should be coordinated (please refer to section 6.6).

Administration
Kymriah should be administered as an intravenous infusion through latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow.

If the volume of Kymriah to be administered is ≤20 mL, intravenous push may be used as an alternative method of administration.

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of Kymriah, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the medicinal product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the medicinal product.

Autologous use

Kymriah is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Kymriah must not be administered if the information on the product labels and batch

specific documentation do not match the patient's identity

Reasons to delay treatment

Due to the risks associated with tisagenlecleucel treatment, infusion should be delayed if a patient has any of the following conditions:
- 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 leukaemia burden or rapid progression of lymphoma following lymphodepleting chemotherapy.

Transmission of an infectious agent

Although Kymriah is tested for sterility and mycoplasma, a risk of transmission of infectious agents exists. Healthcare professionals administering Kymriah must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Blood, organ, tissue and cell donation

Patients treated with Kymriah must not donate blood, organs, tissues or cells for transplantation. This information is provided in the Patient Alert Card which should be given to the patient after treatment.

Active central nervous system (CNS) leukaemia or lymphoma

There is limited experience of use of Kymriah in patients with active CNS leukaemia and active CNS lymphoma. Therefore, the risk/benefit of Kymriah has not been established in these populations. Kymriah is not indicated for treatment of patients with primary or secondary central nervous system lymphoma.

Cytokine release syndrome

Cytokine release syndrome, including fatal or life-threatening events, has been frequently observed after Kymriah infusion (see section 4.8). In almost all cases, development of cytokine release syndrome occurred between 1 to 10 days (median onset 3 days) after Kymriah infusion in paediatric and young adult B-cell ALL patients, between 1 and 9 days (median onset 3 days) after Kymriah infusion in adult DLBCL patients and between 1 to 14 days (median onset 4 days) after Kymriah infusion in adult FL patients. The median time to resolution of cytokine release syndrome was 8 days in B-cell ALL patients, 7 days in DLBCL patients and 4 days in FL patients.

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

Risk factors for severe cytokine release syndrome 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 cytokine release syndrome following Kymriah infusion. High tumour burden prior to Kymriah infusion was identified as a risk factor for developing severe cytokine release syndrome in adult DLBCL patients.

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 cytokine release syndrome and may increase the risk of a fatal event.

Management of cytokine release syndrome associated with Kymriah
Cytokine release syndrome should be managed solely based on the patient's clinical presentation and according to the cytokine release syndrome management algorithm provided in Table 1. Anti-IL-6 based therapy such as tocilizumab has been administered for moderate or severe cytokine release syndrome associated with Kymriah. One dose of tocilizumab per patient must be on site and available for administration prior to Kymriah infusion. The treatment centre should have access to additional doses of tocilizumab within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Ministry of Health website, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

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 cytokine release syndrome.

Table 1 Cytokine release syndrome management algorithm

<table>
<tr><th>Cytokine release syndrome severity</th><th>Symptomatic treatment</th><th>Tocilizumab</th><th>Corticosteroids</th></tr>
<tr><td>Mild symptoms requiring symptomatic treatment only, e.g.
- low fever
- fatigue
- anorexia</td><td>Exclude other causes (e.g. infection) and treat specific symptoms with, for example, antipyretics, anti-emetics, analgesics, etc. If neutropenic, administer antibiotics per local guidelines</td><td>Not applicable</td><td>Not applicable</td></tr>
<tr><td>Symptoms requiring moderate intervention:
- high fever
- hypoxia
- mild hypotension</td><td>Antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed. Treat other organ toxicities as per local guidance</td><td rowspan="3">If no improvement after symptomatic treatment, administer tocilizumab intravenously over 1 hour:
- 8 mg/kg (max. 800 mg) if body weight ≥30 kg
- 12 mg/kg if body weight <30 kg
If no improvement, repeat every 8 hours (max total of 4 doses)*</td><td rowspan="3">If no improvement within 12-18 hours of tocilizumab, administer a daily dose of 2 mg/kg intravenously methylprednisolone (or equivalent) until vasopressor and oxygen no longer needed, then taper*</td></tr>
<tr><td>Symptom requiring aggressive intervention:
- hypoxia requiring high-flow oxygen supplementation or
- hypotension requiring high-dose or multiple vasopressors</td><td>High-flow oxygen
Intravenous fluids and high-dose vasopressor(s)
Treat other organ toxicities as per local guidelines</td></tr>
<tr><td>Life-threatening symptoms:
- haemodynamic instability despite intravenous fluids and vasopressors
- worsening respiratory distress
- rapid clinical deterioration</td><td>Mechanical ventilation
Intravenous fluids and high-dose vasopressor(s)
Treat other organ toxicities as per local guidelines</td></tr>
<tr><td colspan="4">* If no improvement after tocilizumab and steroids, consider other anti-cytokine and anti-T-cell therapies following institutional policy and published guidelines.</td></tr>
</table>

Alternative cytokine release syndrome management strategies may be implemented based on appropriate institutional or academic guidelines.

Neurological adverse reactions

Neurological events, in particular encephalopathy, confusional state or delirium, occur frequently with Kymriah and can be severe or life-threatening (see section 4.8). Other manifestations included depressed level of consciousness, seizures, aphasia and speech disorder. The majority of neurological events occurred within 8 weeks following Kymriah infusion and were transient. The median time to onset of the first neurological events occurring at any time following Kymriah infusion was 9 days in B-cell ALL, 6 days in DLBCL, and 9 days in FL. The median time to resolution was 7 days for B-cell ALL, 13 days for DLBCL, and 2 days for FL. Neurological events can be concurrent with cytokine release syndrome, following resolution of cytokine release syndrome or in the absence of cytokine release syndrome.

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, in some cases with late onset, occurred frequently in patients after Kymriah infusion (see section 4.8). 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 cytokine release syndrome.
The possibility of opportunistic infections of the central nervous system should be considered in patients with neurological adverse events and appropriate diagnostic evaluations should be performed.

Febrile neutropenia was frequently observed in patients after Kymriah infusion (see section 4.8) and may be concurrent with cytokine release syndrome. 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. 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 infusion and should be managed according to standard guidelines. The majority of patients who had cytopenias at day 28 following Kymriah treatment resolved to Grade 2 or below within three months after treatment for paediatric ALL and DLBCL patients, and within six months for FL patients. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen cytokine release syndrome symptoms and are not recommended during the first 3 weeks after Kymriah infusion or until cytokine release syndrome 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.

Hypogammaglobulinaemia

Hypogammaglobulinaemia and agammaglobulinaemia 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.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise 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, hepatic, pulmonary or cardiac function were excluded from the studies. These patient are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Prior stem cell transplantation

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 GVHD. Leukapheresis for Kymriah manufacturing should be performed at least 12 weeks after allogeneic SCT.

Serological testing

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

Screening for HBV, HCV and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing. 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. While activity of tisagenlecleucel has been observed, data are currently too limited to make an adequate assessment of the benefit-risk profile in these patients. Kymriah is not recommended if the patient has relapsed with CD19-negative leukaemia after prior anti-CD19 therapy.

Interference with virological 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.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) and dextran 40 in Kymriah. All patients should be observed closely during the infusion period.

Long-term follow-up

Patients are expected to be enrolled in a registry in order to better understand the long-term safety and efficacy of Kymriah.

Sodium and potassium content

This medicinal product contains 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 (39 mg) per dose, i.e. essentially “potassium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic or pharmacodynamic drug interaction studies with tisagenlecleucel have been performed in either the paediatric or adult population. The co-administration of agents known to

inhibit T-cell function has not been formally studied. Administration of low-dose 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.

Live vaccines

The safety of immunisation with live vaccines during or following Kymriah treatment has not been studied. As a precautionary measure, 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Pregnancy status for females of child-bearing age 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.

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

Pregnancy

There are no data from the use of tisagenlecleucel in pregnant women. No animal studies have been conducted with tisagenlecleucel to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3). It is not known whether tisagenlecleucel has the potential to be transferred to the foetus via the placenta and could cause foetal toxicity, including B-cell lymphocytopenia. Kymriah is not recommended during pregnancy and in women of childbearing potential not using contraception.

Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Kymriah therapy should be discussed with the treating physician. Pregnant women who have received Kymriah may have hypogammaglobulinaemia. Assessment of immunoglobulin levels is indicated in newborns of mothers treated with Kymriah.

Breast-feeding

It is unknown whether tisagenlecleucel cells are excreted in 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 the breast-fed infant.

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

Fertility

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

4.7 Effects on ability to drive and use machines

Kymriah has major influence on the 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 and must refrain from driving or operating heavy or potentially dangerous machines for 8 weeks following Kymriah infusion.

4.8 Undesirable effects

Summary of the safety profile

Safety assessment was based on a total of 424 patients (with paediatric and young adult B-cell ALL, DLBCL and FL) who received Kymriah in three multicentre pivotal clinical studies.

B-cell ALL
The adverse reactions described in this section were characterised in 212 patients infused with Kymriah in the pivotal clinical study CCTL019B2202 and in the supportive studies CCTL019B2205J and CCTL019B2001X.

The most common non-haematological adverse reactions were cytokine release syndrome (75%), infections (70%), hypogammaglobulinaemia (49%), pyrexia (43%) and decreased appetite (28%).

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

Grade 3 and 4 adverse reactions were reported in 86% of patients. The most common Grade 3 and 4 non-haematological adverse reaction was cytokine release syndrome (37%).

The most common Grade 3 and 4 haematological laboratory abnormalities were white blood cells decreased (97%), lymphocytes decreased (94%), neutrophils decreased (96%), platelets decreased (70%) and haemoglobin decreased (46%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (78% of patients) compared to after 8 weeks post-infusion (49% of patients).

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

The most common non-haematological adverse reactions were cytokine release syndrome (57%), infections (58%), pyrexia (35%), diarrhoea (31%), nausea (29%), fatigue (27%) and hypotension (25%).

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

Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (34%) and cytokine release syndrome (23%).

The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (82%), white blood cell count decreased (78%), haemoglobin decreased (59%) and platelet count decreased (56%).

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

FL
The adverse reactions described in this section were characterised in 97 patients infused with Kymriah in one global multicentre international study, i.e. the ongoing pivotal clinical study CCTL019E2202.

The most common non-haematological adverse reactions (>25%) were cytokine release syndrome (50%), infections (50%) and headache (26%).

The most common haematological laboratory abnormalities were decreased haemoglobin (94%), decreased lymphocytes (92%), decreased white blood cells (91%), decreased neutrophils (89%) and decreased platelets (89%).

Grade 3 and 4 adverse reactions were reported in 75% of patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (16%).

The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (87%), white blood cell count decreased (74%), neutrophil count decreased (71%), platelet count decreased (26%) and haemoglobin decreased (25%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (70%) compared to after 8 weeks post-infusion (40%).

Tabulated list of adverse drug reactions

The adverse reactions described in this section were identified in 79, 115 and 97 patients in the ongoing multicentre pivotal clinical studies (CCTL019B2202, CCTL019C2201 and CCTL019E2202), as well as 64 and 69 patients in the supportive studies (CCTL019B2205J and CCTL019B2001X). Adverse drug reactions from these clinical studies (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, using the following convention: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions observed in clinical studies

Infections and infestations[1)]	
Very common:	Infections - pathogen unspecified, viral infections, bacterial infections
Common:	Fungal infections
Blood and lymphatic system disorders	
Very common:	Anaemia, febrile neutropenia, neutropenia, thrombocytopenia
Common:	Leukopenia, pancytopenia, coagulopathy, lymphopenia
Uncommon:	B-cell aplasia
Immune system disorders	
Very common:	Cytokine release syndrome, hypogammaglobulinaemia[2)]
Common:	Infusion-related reaction, graft-versus-host disease[3)], haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders	
Very common:	Decreased appetite, hypokalaemia, hypophosphataemia
Common:	Hypomagnesaemia, hypoalbuminaemia[4)], hyperglycaemia, hyponatraemia, hyperuricaemia[5)], hypercalcaemia, tumour lysis syndrome, hyperkalaemia, hyperphosphataemia[6)], hypernatraemia, hyperferritinaemia[7)], hypocalcaemia
Uncommon:	Hypermagnesaemia
Psychiatric disorders	
Common:	Anxiety, delirium[8)], sleep disorder[9)]

Nervous system disorders	
Very common:	Headache[10)], encephalopathy[11)]
Common:	Dizziness[12)], peripheral neuropathy[13)], tremor[14)], motor dysfunction[15)], seizure[16)], speech disorders[17)], neuralgia[18)]
Uncommon:	Ischaemic cerebral infarction, ataxia[19)], immune effector cell-associated neurotoxicity syndrome**
Eye disorders	
Common:	Visual impairment[20)]
Cardiac disorders	
Very common:	Tachycardia[21)]
Common:	Cardiac failure[22)], cardiac arrest, atrial fibrillation
Uncommon:	Ventricular extrasystoles
Vascular disorders	
Very common:	Haemorrhage[23)], hypotension[24)], hypertension
Common:	Thrombosis[25)], capillary leak syndrome
Uncommon:	Flushing
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough[26)], dyspnoea[27)], hypoxia
Common:	Oropharyngeal pain[28)], pulmonary oedema[29)], nasal congestion, pleural effusion, tachypnoea
Uncommon:	Acute respiratory distress syndrome, lung infiltration
Gastrointestinal disorders	
Very common:	Diarrhoea, nausea, vomiting, constipation, abdominal pain[30)]
Common:	Stomatitis, abdominal distension, dry mouth, ascites
Hepatobiliary disorders	
Common:	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Very common:	Rash[31)]
Common:	Pruritus, erythema, hyperhidrosis, night sweats
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, musculoskeletal pain[32)]
Common:	Myalgia
Renal and urinary disorders	
Very common:	Acute kidney injury[33)]
General disorders and administration site conditions	
Very common:	Pyrexia, fatigue[34)], oedema[35)], pain[36)]
Common:	Influenza-like illness, asthenia, multiple organ dysfunction syndrome, chills
Investigations	
Very common:	Lymphocyte count decreased*, white blood cell count decreased*, haemoglobin decreased*, neutrophil count decreased*, platelet count decreased*, hepatic enzyme increased[37)]
Common:	Blood bilirubin increased, weight decreased, blood fibrinogen decreased, international normalised ratio increased, fibrin D dimer increased, activated partial thromboplastin time prolonged, prothrombin time prolonged

1) Infections and infestations presented reflect high-level group terms.
2) Hypogammaglobulinaemia includes blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinaemia, immunodeficiency, immunodeficiency common variable and immunoglobulins decreased.
3) Graft-versus-host disease (GvHD) includes GvHD, GvHD in gastrointestinal tract, GvHD in skin
4) Hypoalbuminaemia includes blood albumin decreased, hypoalbuminaemia
5) Hyperuricaemia includes blood uric acid increased, hyperuricaemia
6) Hyperphosphataemia includes blood phosphorus increased, hyperphosphataemia
7) Hyperferritinaemia includes hyperferritinaemia, serum ferritin increased

8) Delirium includes agitation, delirium, hallucination, hallucination visual, irritability and restlessness.
9) Sleep disorder includes insomnia, nightmare and sleep disorder.
10) Headache includes headache and migraine.
11) Encephalopathy includes automatism, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, memory impairment, mental status changes, metabolic encephalopathy, somnolence and thinking abnormal. Encephalopathy is a dominant feature of immune effector cell-associated neurotoxicity syndrome (ICANS), along with other symptoms.
12) Dizziness includes dizziness, presyncope and syncope.
13) Peripheral neuropathy includes dysaesthesia, hyperaesthesia, hypoaesthesia, neuropathy peripheral, paraesthesia and peripheral sensory neuropathy.
14) Tremor includes dyskinesia and tremor.
15) Motor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy.
16) Seizure includes generalised tonic-clonic seizures, seizure and status epilepticus.
17) Speech disorders includes aphasia, dysarthria and speech disorders.
18) Neuralgia includes neuralgia and sciatica.
19) Ataxia includes ataxia and dysmetria.
20) Visual impairment includes vision blurred and visual impairment.
21) Tachycardia includes sinus tachycardia, supraventricular tachycardia, tachycardia
22) Cardiac failure includes cardiac failure, cardiac failure congestive, left ventricular dysfunction and right ventricular dysfunction.
23) Haemorrhage includes anal haemorrhage, blood blister, blood urine present, catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, cystitis haemorrhagic, disseminated intravascular coagulation, duodenal ulcer haemorrhage, ecchymosis, epistaxis, eye contusion, gastrointestinal haemorrhage, gingival bleeding, haemarthrosis, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, heavy menstrual bleeding, injection site haematoma, intermenstrual bleeding, large intestinal haemorrhage, lip haemorrhage, melaena, mouth haemorrhage, mucosal haemorrhage, oral blood blister, periorbital haematoma, peritoneal haematoma, petechiae, pharyngeal haemorrhage, postprocedural haemorrhage, pulmonary haemorrhage, purpura, rectal haemorrhage, retinal haemorrhage, stoma site haemorrhage, subcutaneous haematoma, subdural haematoma, subdural haemorrhage, tooth socket haemorrhage, tracheal haemorrhage, traumatic haematoma, tumour haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.
24) Hypotension includes hypotension and orthostatic hypotension.
25) Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis.
26) Cough includes cough, productive cough and upper-airway cough syndrome.
27) Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory distress and respiratory failure.
28) Oropharyngeal pain includes oral pain and oropharyngeal pain.
29) Pulmonary oedema includes acute pulmonary oedema and pulmonary oedema.
30) Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain.
31) Rash includes dermatitis, dermatitis acneiform, dermatitis contact, rash, rash maculo-papular, rash papular and rash pruritic.
32) Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, neck pain, non-cardiac chest pain.
33) Acute kidney injury includes acute kidney injury, anuria, azotaemia, blood creatinine abnormal, blood creatinine increased, blood urea increased, renal failure, renal tubular dysfunction and renal tubular necrosis.
34) Fatigue includes fatigue and malaise.
35) Oedema includes face oedema, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema peripheral, periorbital oedema and peripheral swelling.
36) Pain includes pain and pain in extremity.
37) Hepatic enzyme increased includes alanine aminotransferase increased, aspartate

	aminotransferase increased, blood alkaline phosphatase increased, hepatic enzyme increased, transaminases increased.
*	Frequency is based on laboratory values. Patients are counted only for the worst grade observed post baseline.
**	Abbreviated as ICANS. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.

Description of selected adverse drug reactions

Cytokine release syndrome
In the clinical studies in paediatric and young adult B-cell ALL (N=212), cytokine release syndrome was reported in 75% of patients (37% with Grade 3 or 4; 0.5% [1 patient] with fatal outcome).

In the ongoing clinical study in DLBCL (N=115), cytokine release syndrome was reported in 57% of patients (23% with Grade 3 or 4).
In the ongoing clinical study in FL (N=97), cytokine release syndrome was reported in 50% of patients. No Grade 3 or 4 events were reported.

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

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

For clinical management of cytokine release syndrome, see section 4.4 and Table 1.

Infections and febrile neutropenia
In B-cell ALL patients severe infections (Grade 3 and higher), which can be life-threatening or fatal, occurred in 36% of patients after Kymriah infusion. The overall incidence (all grades) was 70% (unspecified 55%, viral 31%, bacterial 24% and fungal 12%) (see section 4.4). 41% of the patients experienced an infection of any type within 8 weeks after Kymriah infusion.

In DLBCL patients severe infections (Grade 3 and higher), 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 4.4). 37% of the patients experienced an infection of any type within 8 weeks.

In FL patients severe infections (Grade 3 or 4), occurred in 16% of patients. The overall incidence (all grades) was 50% (unspecified 36%, viral 17%, bacterial 6%, and fungal 2%) (see section 4.4). 19% of the patients experienced an infection of any type within 8 weeks.

Severe febrile neutropenia (Grade 3 or 4) was observed in 26% of paediatric and young adult B-cell ALL patients, 17% of DLBCL patients and 12% of FL patients. See section 4.4 for the management of febrile neutropenia before and after Kymriah infusion.

Prolonged cytopenias
Cytopenias are very common based on prior chemotherapies and Kymriah therapy.

All paediatric and young adult B-cell ALL patients had a Grade 3 or 4 cytopenia at some time after

Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 after Kymriah infusion based on laboratory findings included decreased count of white blood cells (50%), neutrophils (56%), lymphocytes (43%), and thrombocytes (32%) and decreased haemoglobin (11%).

All adult DLBCL patients had Grade 3 and 4 cytopenias at some time after Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 based on laboratory findings included decreased count of thrombocytes (39%), lymphocytes (29%), neutrophils (25%), and white blood cells (21%) and decreased haemoglobin (14%).
In adult patients with FL, 99% had Grade 3 and 4 cytopenias at any time post Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 after Kymriah infusion based on laboratory findings included a decreased count of lymphocytes (23%), thrombocytes (17%), neutrophils (16%), white blood cells (13%) and decreased haemoglobin (3%).

Neurological adverse reactions
The majority of neurotoxic events occurred within 8 weeks following infusion and were transient.

In paediatric and young adult B-cell ALL patients, serious neurological adverse reactions including manifestations of encephalopathy and/or delirium occurred in 32% of patients (10% were Grade 3 or 4) within 8 weeks after Kymriah infusion. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 20% of patients (11% were Grade 3 or 4) within 8 weeks after Kymriah infusion. In FL patients, these occurred in 9% of patients (1% Grade 3 or 4) within 8 weeks after Kymriah infusion. Among the neurotoxic events in FL patients, immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 4% of patients (1% Grade 3 or 4), all within 8 weeks of Kymriah infusion.

Hypogammaglobulinaemia
Hypogammaglobulinaemia was reported in 49% of patients treated with Kymriah for r/r ALL,17% of patients with r/r DLBCL and 17% of patients with r/r FL.

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

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 paediatric and young adult ALL (B2202, B2205J, B2001X, 84.0%), adult DLBCL (C2201, 93.9%) and adult FL (E2202, 66.0%) patients.

Treatment-induced anti-mCAR19 antibodies were found in 40.5% of paediatric and young adult ALL (B2202), 8.7% of adult DLBCL and 28.7% of adult FL patients. Pre-existing and treatment-induced antibodies were not associated with an impact on clinical response nor did they have an impact on the expansion and persistence of tisagenlecleucel. There is no evidence that the presence of pre-existing and treatment-induced anti-mCAR19 antibodies impacts the safety or effectiveness of Kymriah.

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

Post-marketing experience

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 studies. 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 unknown: Anaphylactic reaction/infusion related reaction, neurotoxicity.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
And to Novartis using the following email address: Safetydest.israel@novaris.com

4.9 Overdose

Overdose has not been reported.
In case of overdose, the potential risk is an increased probability of developing CRS including severe CRS. For close monitoring, see section 4.2; for symptoms and management of CRS, see section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XL04

Mechanism of action

Tisagenlecleucel is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. The CAR is comprised of a murine single chain antibody fragment which recognises 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 anti-tumour activity, while 4-1BB enhances the expansion and persistence of tisagenlecleucel. Upon binding to CD19-expressing cells, the CAR transmits a signal promoting T-cell expansion and persistence of tisagenlecleucel.

Clinical efficacy and safety

Acute lymphoblastic leukaemia (ALL)
The safety and efficacy of Kymriah treatment in paediatric and young adult patients up to and including 25 years of age, with relapsed or refractory (r/r) B-cell ALL were evaluated in a total of 203 patients in one pivotal (B2202, N=79) and two supportive (B2205J, N=64, and B2101J, N=60) open-label, single-arm phase I/II studies. All patients had leukapheresis products collected and cryopreserved prior to or during study entry.

The pivotal study B2202 (ELIANA) is a multicentre, single-arm phase II study in paediatric and young adult patients with r/r B-cell ALL. Of 97 patients enrolled in the main cohort, 79 received infusion with Kymriah; for 8 patients (8%) Kymriah could not be manufactured; reasons for discontinuation prior to Kymriah infusion included death (n=7; 7%) or adverse events (n=3; 3%) while awaiting Kymriah manufacturing in the clinical study. The median duration of study follow-up defined as the time from Kymriah infusion to the date of completion or discontinuation from follow-up prior to the data cut-off date was 28.5 months (range: 0.4-65.5). The median time from Kymriah infusion to the data cut-off date was 79.4 months (range: 59.7-90.3).

Key baseline information for enrolled and infused patients is presented in Table 3. The majority of patients (69/79, 87%) received bridging therapy while waiting for Kymriah. A total of 76 out of 79 patients (96%) who received Kymriah infusion also received lymphodepleting chemotherapy after

enrolment and prior to infusion of a single dose of Kymriah (see section 4.2 for condition of lymphodepleting chemotherapy).

Table 3 Study B2202: Baseline information across the enrolled and the infused patient population

	Enrolled N=97 n (%)	**Infused N=79 n (%)**
Age (years)		
Mean (standard deviation)	12 (5.48)	12 (5.38)
Median (minimum – maximum)	11 (3 – 27)	11 (3 – 24)
Age category (years) - n (%)		
<10 years	40 (41.2)	32 (40.5)
≥10 years and <18 years	40 (41.2)	33 (41.8)
≥18 years	17 (17.5)	14 (17.7)
Sex - n (%)		
Male	54 (55.7)	45 (57.0)
Female	43 (44.3)	34 (43)
Disease status - n (%)		
Primary refractory[1]	8 (8.2)	6 (7.6)
Relapsed disease[2]	89 (91.8)	73 (92.4)
Prior stem-cell transplantation - n (%)		
0	39 (40.2)	31 (39.2)
1	50 (51.5)	42 (53.2)
2	8 (8.2)	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). See Table 4 for efficacy results from this study. ORR was consistent across all subgroups. Eight patients (10.1%) who achieved CR/CRi after Kymriah infusion went to haematopoietic stem cell transplant while in remission of which 6 of the patients (7.6%) proceeded to transplant within the first 6 months post-infusion while in remission. Kymriah was administered in a qualified Kymriah treatment centre in an inpatient and outpatient setting.

Table 4 Study B2202: Efficacy results in paediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukaemia (ALL)

Primary endpoint	**Enrolled patients N=97**	**Infused patients N=79**
Overall remission rate (ORR) within 3 months[1,2], n (%) 95% CI	**65 (67.0)** (56.7, 76.2) p<0.0001	**65 (82.3)** (72.1, 90.0) p<0.0001
CR[3], n (%)	49 (50.5)	49 (62.0)
CRi[4], n (%)	16 (16.5)	16 (20.3)
Key secondary endpoint	**N=97**	**N=79**
CR or CRi with MRD negative bone marrow[5,6], n (%) 95% CI	64 (66.0) (55.7, 75.3) p<0.0001	64 (81.0) (70.6, 89.0) p<0.0001
Duration of remission (DOR)[7]	**N=66**	**N=66**
% event free probability at 12 months	67.4	67.4
% event free probability at 30 months	56.2	56.2
Median (months) (95% CI)	46.8(17.8, NE[9])	46.8 (17.8, NE)
Other secondary endpoint	**N=97**	**N=79**
Overall survival (OS)[8]		
% survival probability at 36 months	52.8	63.5
Median (months) (95% CI)	47.9 (19.4, NE)	Not reached (45.6, NE)

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/μL and absolute neutrophil counts [ANC] >1 000/μL) 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 MRD (minimal residual disease) negative was defined as MRD by flow cytometry <0.01%.
6 Nominal one-sided exact p-value based on H0: Rate of MRD negative remission ≤15% vs. Ha: >15%.
7 DOR was defined as time since onset of CR or CRi to relapse or death due to underlying indication, whichever is earlier (N=66). One patient achieved remission after month 3.
8 OS was defined as time from date of Kymriah infusion to the date of death due to any cause for infused patients and from time of date of enrolment to the date of death due to any cause for enrolled patients.
9 Not estimable

The supportive study B2205J (ENSIGN) was a multicentre single-arm phase II study in paediatric and young adult patients with r/r B-cell ALL. The study had similar study design and enrolled comparable patient populations as the pivotal study B2202. The main difference between the two studies was the definition of the primary efficacy endpoint ORR, which was measured within 6 months after Kymriah infusion in study B2205J compared to 3 months in the pivotal study. Of 75 patients enrolled, 64 received infusion of Kymriah; for 5 patients (6.7%), Kymriah could not be manufactured and 6 patients (8.0%) died while awaiting Kymriah manufacturing in the clinical study. The median duration of study follow-up defined as the time from Kymriah infusion to the date of completion or discontinuation from follow-up prior to the data cut-off date in the final analyses was 12.2 months (range: 0.4-49.3). The median time from Kymriah infusion to the data cut-off date was 31.7 months (range: 17.6-56.0).

Among the patients infused, the median age was 12.5 years (range: 3 to 25), 34 (53.1%) were female and 30 (46.9%) were male, 10.9% had primary refractory disease, 89.1% had relapsed disease, and 43.8% of patients had at least one prior haematopoietic stem cell transplant. Baseline disease characteristics were similar in the enrolled patients with regard to age (median age 13.0 years, range: 3 to 25), gender (46.7% female and 53.3% male), primary refractoriness (10.7%), and prior transplant history (42.7%). The majority of infused patients (57/64, 89.1%) received bridging chemotherapy while waiting for Kymriah. A total of 60 out of 64 patients (93.8%) who received Kymriah infusion also received lymphodepleting chemotherapy after enrolment and prior to infusion of a single dose of Kymriah.

Efficacy was established through the primary endpoint of ORR, which included best overall response as CR or CRi that were maintained for at least 28 days within 6 months post-infusion, as determined by IRC assessment, as well as secondary endpoints including DOR, proportion of patients who achieved CR or CRi with MRD-negative disease status, and OS. Among the patients infused, ORR was demonstrated in 45 patients (70.3%; 59.4% CR and 10.9% CRi). CR/CRi with MRD-negative bone marrow was reported in 43 patients (67.2%). The median DOR was not reached and the event-free probability at 12 months was 70.5%. The survival probability at 24 months was 54.7%, and the median OS was estimated as 29.9 months (95% CI: 15.1, 42.4). The OS results were confirmed in an updated OS analyses (i.e. median OS 29.9 months [95% CI: 15.2, NE] with 57.6% survival probability at 24 months; with a median follow-up for OS of 25.9 months), which included patients transitioned to a separate long-term follow-up study. Seven patients (10.9%) who achieved CR/CRi after Kymriah infusion proceeded to haematopoietic stem cell transplant while in remission during the study, of which 5 of the patients (7.8%) proceeded to transplant within the first 6 months post-infusion. Efficacy results reported for the enrolled patients (n=75) demonstrate an ORR of 60.0% (50.7% CR and 9.3% CRi; 57.3% with MRD-negative bone marrow). The reported overall survival in the enrolled population is in accordance with the infused population.

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

Patients with active CNS leukaemia
Of four patients with active CNS leukaemia (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 1-3 months of infusion. One patient died due to disease progression and the remaining three patients achieved a CR or CRi and remain alive 1.5-2 years after infusion.

Diffuse large B-cell lymphoma (DLBCL)
The safety and efficacy of Kymriah treatment in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) who received ≥2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous haematopoietic stem cell transplantation (HSCT), was evaluated in the multicentre, open-label, pivotal, single-arm phase II study C2201 (JULIET). Patients with T-cell rich/histiocyte-rich large B-cell lymphoma (THRBCL), primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), EBV-positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma were not enrolled in study C2201.

Of 167 patients enrolled in study C2201, 115 patients received infusion with Kymriah. Approximately 31% of patients discontinued the study prior to Kymriah infusion. For 13 patients (8%) Kymriah could not be manufactured. Other reasons for discontinuation prior to Kymriah infusion included death (n=16; 10%), physician decision/primary disease progression (n=16; 10%), patient decision (n=2; 1%), protocol deviation (n=1; 1%) or adverse events (n=4; 2%) while awaiting Kymriah manufacturing in the clinical study. The median duration of study follow-up defined as the time from Kymriah infusion to date of completion or discontinuation from follow-up prior to the data cut-off date in the final analysis was 7.7 months (range: 0.4-61.0). The median time from Kymriah infusion to the data cut-off date in the final analysis was 74.3 months (range: 58.1-86.6).

Key baseline information for enrolled and infused patients is presented in Table 5. All patients had

leukapheresis starting material collected and cryopreserved prior to or during study entry. The majority of patients (103/115, 90%) received bridging therapy for disease stabilisation. The type and duration of bridging therapy was left to the discretion of the physician. 107/115 patients (93%) received lymphodepleting chemotherapy prior to Kymriah infusion. Kymriah was given as a single-dose (0.6-6.0 × 10^8 CAR-positive viable T cells) intravenous infusion in a qualified Kymriah treatment centre in an inpatient and outpatient setting.

Table 5 Study C2201: Baseline information across the enrolled and the infused patient populations

	Enrolled N=167 n (%)	**Infused N=115 n (%)**
Age (years)		
Mean (standard deviation)	56 (12.9)	54 (13.1)
Median (minimum – maximum)	58 (22 - 76)	56 (22 - 76)
Age category (years) - n (%)		
<65 years	120 (71.9)	89 (77.4)
≥65 years	47 (28.1)	26 (22.6)
Sex - n (%)		
Male	105 (62.9)	71 (61.7)
Female	62 (37.1)	44 (38.3)
Prior haematopoietic stem cell transplant (SCT) - n (%)		
No	93 (55.7)	59 (51.3)
Yes	74 (44.3)	56 (48.7)
Stage III/IV disease at study entry - n (%)		
No	36 (21.6)	27 (23.5)
Yes	131 (78.4)	88 (76.5)
Number of prior lines of antineoplastic therapy – n (%)		
1	6 (3.6)	5 (4.3)
2	73 (43.7)	51 (44.3)
3	52 (31.1)	36 (31.3)
≥4	36 (21.6)	23 (20.0)
Disease status - n (%)		
Refractory to last line of therapy	98 (58.7)	63 (54.8)
Relapse to last line of therapy	69 (41.3)	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 Independent Review Committee (IRC) assessment as well as secondary endpoints including duration of response (Table 6).

Table 6 Study C2201: Efficacy results in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

	Enrolled patients N=167	**Infused patients N=115**
Primary endpoint[1]	**N=147**	**N=99**
Overall response rate (ORR) (CR+PR)[2], n (%) 95% CI	**54 (36.7)** (28.9, 45.1)	**54 (54.5)** (44.2, 64.6)
CR, n (%)	41 (27.9)	41 (41.4)
PR, n (%)	13 (8.8)	13 (13.1)
Response at month 3	N=147	N=99
ORR (%)	40 (27.2)	40 (40.4)
CR (%)	34 (23.1)	34 (34.3)
Response at month 6	N=147	N=99
ORR (%)	34 (23.1)	34 (34.3)
CR (%)	31 (21.1)	31 (31.3)
Duration of response (DOR)[3]	**N=54**	**N=54**
Median (months) (95% CI)	Not reached (10.0, NE[5])	Not reached (10.0, NE[5])
% relapse free probability at 12 months	63.4	63.4
% relapse free probability at 24 months	60.8	60.8
% relapse free probability at 36 months	60.8	60.8
% relapse free probability at 54 months	60.8	60.8
Other secondary endpoints	**N=167**	**N=115**
Overall survival (OS)[4]		
% survival probability at 12 months	41.0	48.2
% survival probability at 36 months	29.4	36.6
% survival probability at 60 months	25.5	31.7
Median (months) (95% CI)	8.2 (5.8, 11.7)	11.1 (6.6, 23.9)

[1] The primary endpoint was analysed on all patients whose Kymriah was manufactured at the Novartis US facility.
[2] ORR is the proportion of patients with best overall response (BOR) of CR or PR based on the Lugano response criteria (Cheson 2014); non-infused patients were assigned BOR=Unknown (i.e. non-responders).
[3] DOR was defined as time from achievement of CR or PR to relapse or death due to DLBCL, whichever occurs first.
[4] OS was defined as time from date of Kymriah infusion to the date of death due to any cause (N=115) and time from date of enrolment to the date of death due to any cause for enrolled patients (N=167).
[5] Not estimable.

Among 41 patients who achieved CR, 16 patients initially had an overall disease response of PR which improved to CR over time; most patients (13/16) achieved PR to CR conversion within 6 months post-tisagenlecleucel infusion. ORR was consistent across subgroups.

Follicular lymphoma (FL)
The safety and efficacy of Kymriah treatment in adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) were evaluated in an open label, multicentre, single-arm, phase II study (E2202, N=97).

The pivotal study E2202 (ELARA) included patients who were refractory to or relapsed within 6 months after completion of a second or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent), relapsed during or within 6 months after completion of anti-CD20 antibody maintenance therapy following at least two lines of therapy, or relapsed after autologous haematopoietic stem cell transplant (HSCT). The study excluded patients with active or serious infections, transformed lymphoma or other aggressive lymphomas, including patients with FL Grade 3b, those who had received prior allogeneic HSCT, or who had disease with active CNS involvement.

Of 98 patients who were enrolled and underwent leukapheresis, 97 patients received infusion with Kymriah. One patient achieved a complete response prior to infusion which was attributed to their prior last line of therapy and was subsequently discontinued from the study due to physician decision prior to infusion. All patients had leukapheresis products collected and cryopreserved prior to or during study entry. Kymriah was delivered for all enrolled patients. The median duration of study follow-up defined as the time from Kymriah infusion to date of completion or discontinuation from follow-up prior to the data cut-off date was 18.6 months (range: 1.8-29.9). The median time from Kymriah infusion to the data cut-off date was 20.8 months (range: 14.4-29.9). The study is still ongoing.

Of the 97 patients infused with Kymriah, 94 patients had measurable disease at baseline per Independent Review Committee (IRC) and are included in the efficacy analysis set (EAS).

Key baseline information for the enrolled set and EAS is presented in Table 7. Approximately half of the patients (44/94; 47%) received bridging therapy for disease stabilisation between leukapheresis and administration of Kymriah and all patients received lymphodepleting chemotherapy. For all infused patients, Kymriah was administered as a single dose intravenous infusion in a qualified treatment centre in an inpatient or outpatient (18%) setting.

Table 7 Study E2202: Baseline information across the enrolled and the EAS patient populations

	Enrolled N=98 n (%)	**EAS* N=94 n (%)**
Age (years)		
Mean (standard deviation)	56.5 (10.34)	56.4 (10.54)
Median (minimum – maximum)	57.5 (29-73)	57.0 (29-73)
Age category (years) – n (%)		
<65 years	74 (75.5)	70 (74.5)
≥65 years	24 (24.5)	24 (25.5)
Sex – n (%)		
Male	65 (66.3)	64 (68.1)
Female	33 (33.7)	30 (31.9)
Stage III/IV disease at study entry – n (%)	84 (85.7)	81 (86.2)
High FLIPI score[1] – n (%)	59 (60.2)	57 (60.6)
Bulky disease at baseline[2] – n (%)	62 (63.3)	61 (64.9)
Number of prior lines of antineoplastic therapy – n (%)		
2	24 (24.5)	24 (25.5)
3	21 (21.4)	19 (20.2)
4	25 (25.5)	24 (25.5)
≥5	28 (28.6)	27 (28.7)
Median (minimum – maximum)	4.0 (2.0 -13.0)	4.0 (2.0 - 13.0)
Disease status – n (%)		
Refractory to last line of therapy	76 (77.6)	74 (78.7)
Relapse to last line of therapy	17 (17.3)	17 (18.1)
Double refractory[3] – n (%)	67 (68.4)	65 (69.1)
Progression of disease within 24 months (POD24)[4] – n (%)	61 (62.2)	61 (64.9)
Prior haematopoietic stem cell transplant (HSCT) – n (%)	36 (36.7)	35 (37.2)
Prior PI3K inhibitor – n (%)	21 (21.4)	19 (20.2)

* Infused patients who had measurable disease at baseline per Independent Review Committee (IRC) and are included in the efficacy analysis set.

1 FLIPI includes 5 labelled prognostic factors; FLIPI = sum (where prognostic factor = 'Yes'); Low: 0-1 criteria met; intermediate: 2 criteria met; high: 3 or more met.

2 Bulky disease defined per IRC as imaging showing any nodal or extra nodal tumour mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm.

3 Double refractory is defined as patients who failed to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen.

4 POD24: subjects with primary refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb containing treatment.

Efficacy was evaluated through the primary endpoint of complete response rate (CRR), recorded from infusion until progressive disease or start of new therapy. CRR was determined by IRC based on Lugano classification criteria (Cheson 2014). Secondary endpoints included overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS). Median time from enrolment to infusion was 46 days (range: 23 to 127). The first disease assessment was scheduled to be performed at month 3 post-infusion.

Table 8 Study E2202: Efficacy results in adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of therapy

	Enrolled patients N=98	**EAS patients* N=94**
Complete response rate (CRR)[1], per IRC		
n (%)	67 (68.4)	65 (69.1)
95% CI	(58.2, 77.4)	(58.8, 78.3)
Overall response rate (ORR)[2], per IRC		
n (%)	84 (85.7)	81 (86.2)
Duration of response (DOR)[3], per IRC	**N=84**	**N=81**
Median (months) (95% CI)	NE (20.9, NE)	NE (15.6, NE)
% event-free probability at 9 months (95% CI)	75.9 (64.8, 83.9)	76.2 (64.9, 84.3)

CI=Confidence interval, NE=Not estimable

* Infused patients who had measurable disease at baseline per Independent Review Committee (IRC) and are included in the efficacy analysis set.

1 The primary endpoint was CRR per IRC based on Lugano response criteria (Cheson 2014) and defined as the proportion of patients with a best overall response (BOR) of complete response (CR). The non-infused patient was treated as a non-responder.

2 ORR was defined as the proportion of patients with a BOR of CR or partial response (PR). The non-infused patient was treated as a non-responder.

3 DOR was defined as time from achievement of CR or PR to relapse or death due to FL, whichever occurs first.

All responders achieved their first response (CR or PR) at the first disease assessment performed post-infusion, at 3 months. Of the 65 patients who eventually achieved a CR, 15 patients (16%) initially had a PR. The majority of patients converted from PR to CR within 6 months post-infusion. No patient who received Kymriah infusion went to transplant while in response (CR or PR).

The probability for a patient to remain in response (DOR) ≥9 months was 76% (95% CI: 64.9, 84.3), while the probability for a patient who achieved a CR to remain in response ≥9 months was 87% (95% CI: 75.6, 93.3).

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

Special populations

There are not enough data to determine whether there are any differences in efficacy or safety between different age subgroups, although the clinical benefit and safety experience in elderly patients with DLBCL and FL above the age of 65 years (23% and 24.7% of the study population for DLBCL and FL, respectively) were comparable to the overall population.

5.2 Pharmacokinetic properties

Following infusion of Kymriah into paediatric and young adult r/r B-cell ALL, r/r DLBCL and r/r FL patients, tisagenlecleucel typically exhibited an initial rapid expansion followed by a slower bi-exponential decline. High inter-subject variability was associated with the *in vivo* exposure metrics ($AUC_{0\text{-}28d}$ and C_{max}) across all indications.

Cellular kinetics in paediatric and young adult B-cell ALL patients

A summary of cellular kinetic parameters of tisagenlecleucel in paediatric and young adult B-cell ALL patients is provided in Table 9 below. The maximal expansion (C_{max}) was approximately 1.5-fold

higher in CR/CRi patients (n=114) compared with non-responding (NR) patients (n=10) as measured by qPCR. Delayed and lower expansion was observed in NR patients compared to CR/CRi patients.

Table 9 Cellular kinetic parameters of tisagenlecleucel in paediatric and young adult r/r B-cell ALL (Studies B2202 and B2205J)

Parameter	Summary statistics	Responding patients (CR/CRi) N=114	Non-responding patients (NR) N=12
C_{max} (copies/μg)	Geometric mean (CV%), n	32 900 (173.8), 114	21 900 (80.7), 10
T_{max}‡ (day)	Median [min;max], n	9.85 [5.70; 54.8], 114	20.1 [12.6; 62.7], 10
$AUC_{0\text{-}28d}$ (copies/μg*day)	Geometric mean (CV%), n	286 000 (194.9), 114	232 000 (104.5), 8
$T_{½}$ (day)	Geometric mean (CV%), n	40.0 (436.8), 72	3.78 (222.0), 4
T_{last} (day)	Median [min;max], n	190 [17.8; 1 860], 114	28.8 [13.9; 888], 11

Cellular kinetics in adult DLBCL patients

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

Table 10 Cellular kinetic parameters of tisagenlecleucel in r/r DLBCL patients

Parameter	Summary statistics	Responding patients (CR and PR) N=44	Non-responding patients (SD/PD/Unknown) N=71
C_{max} (copies/μg)	Geometric mean (CV%), n	6 070 (256.8), 44	5 000 (391.7), 67
T_{max} (day)	Median [min;max], n	9.02 [5.78; 27.7], 44	8.84 [0.994; 26.7], 67
$AUC_{0\text{-}28d}$ (copies/μg*day)	Geometric mean (CV%), n	63 000 (177.7), 43	52 300 (321.4), 62
$T_{½}$ (day)	Geometric mean (CV%), n	151 (487.5), 31	11.6 (196.2), 49
T_{last} (day)	Median [min;max], n	930 [17.1; 1 830], 44	41.9 [0.994; 1 480], 67

Cellular kinetics in FL patients

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

The geometric mean $AUC_{0\text{-}28d}$ value of responders was 2.9 fold higher compared to non-responders, while the geometric mean C_{max} value was 2.1 fold higher in responders compared to non-responders.

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

Parameter	Summary statistics	Responding patients (CR and PR) N=81	Non-responding patients (SD/PD) N=12
C_{max} (copies/micrograms)	Geometric mean (CV%), n	6 280 (331), 67	3 000 (1 190), 8
T_{max} (day)	Median [min;max], n	9.92 [2.62; 28.0], 67	13.0 [7.73; 16.0], 8
AUC_{0-28d} (copies/micrograms*day)	Geometric mean (CV%), n	57 500 (261), 66	20 100 (18 100), 7
$T_{½}$ (day)	Geometric mean (CV%), n	43.8 (287), 43	24.4 (180), 6
T_{last} (day)	Median [min;max], n	191 [19.9; 558], 73	107 [18.7; 366], 10

Biodistribution

In paediatric and young adult B-cell ALL patients, tisagenlecleucel has been shown to be present in the blood and bone marrow for up to 5 years and 6 months, respectively. The blood to bone marrow partitioning of tisagenlecleucel in bone marrow was 50% of that present in blood at day 28 while at both months 3 and 6 it distributes at 67% (Studies B2202 and B2205J). Tisagenlecleucel also traffics and persists in cerebrospinal fluid in paediatric and young adult B-cell ALL patients (Study B2101J) for up to 1 year.

In adult DLBCL patients (Study C2201), tisagenlecleucel has been detected for up to 5 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 both responder and non-responder patients.
In adult FL patients (Study E2202), tisagenlecleucel has been detected for up to 18 months in peripheral blood and up to month 3 in bone marrow for complete responder patients. The blood to bone marrow partitioning in bone marrow was nearly 54% of that present in blood at month 3 in both responder and non-responder patients.

Elimination

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

Linearity/non-linearity

There is no apparent relationship between dose and AUC_{0-28d} or C_{max}.

Special populations

Elderly
The scatter plots of cellular kinetic parameters versus age (22 to 76 years in DLBCL patients and 29 to 73 years in FL patients) revealed no relevant relationship between cellular kinetic parameters (AUC_{0-28d} and C_{max}) with age.

Gender
Gender has not been identified as a significant characteristic influencing tisagenlecleucel expansion in B-cell ALL, DLBCL and FL patients. In Study B2202, there were 43% female and 57% male patients, in Study C2201 38% female and 62% male patients and in Study E2202 34% female and 66% male patients who received Kymriah. Further, in Study E2202, the geometric means of the exposure parameters (C_{max} and AUC_{0-28d}) were shown to be 111% and 106% higher, respectively, in female patients compared to male patients. Although the interpretation of expansion in relation to gender is difficult due to overlapping ranges and high inter-subject variability.

Race/ethnicity
There is limited evidence that race/ethnicity impact the expansion of Kymriah in paediatric and young adult ALL, DLBCL and FL patients. In Study B2202 there were 73.4% Caucasian, 12.7% Asian and 13.9% other ethnic patients. In Study C2201 there were 85% Caucasian, 9% Asian, 4% Black or African American patients, and 3 patients (3%) of unknown race. In Study E2202, there were 75% Caucasian, 13% Asian, 1% Black or African American patients, and 10% of unknown race.

Body weight
In ALL, DLBCL and FL patients, across the weight ranges (ALL; 14.4 to 137 kg; DLBCL: 38.3 to 186.7 kg; FL: 44.3 to 127.7 kg), the scatter plots of qPCR cellular kinetic parameters versus weight revealed no apparent relationship between cellular kinetic parameters with weight.

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

5.3 Preclinical safety data

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

Carcinogenicity and mutagenicity

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

In vitro expansion studies with CAR-positive T cells (Kymriah) from healthy donors and patients showed no evidence for transformation and/or immortalisation 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 harbouring 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Albumin
Dextrose
Dextran 40 for injection
Sodium chloride
Sodium gluconate
Sodium acetate

N-acetyltryptophanate
Sodium
Caprylate
Potassium chloride
Magnesium chloride
DMSO
Aluminium
Dimethyl sulfone
Potassium
5'-hydroxymethylfurfural
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

The medicinal 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.

6.4 Special precautions for storage

Kymriah must be stored and transported ≤ -120°C, in the vapour phase of liquid nitrogen, and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Do not re-freeze after thawing.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Ethylene vinyl acetate (EVA) infusion bag with polyvinyl chloride (PVC) tubing and a luer spike interconnector closed by a luer-lock cap containing either 10–30 mL (50 mL bags) or 30–50 mL (250 mL bags) cell dispersion.

Each infusion bag is placed into a protective layer.

One individual treatment dose comprises 1 to 3 infusion bags.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

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

This medicinal product contains human blood cells. Healthcare professionals handling Kymriah must take appropriate precautions (wearing gloves and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Kymriah infusion bags and accompanying documentation. The total number of infusion bags to be administered should also be confirmed with the patient specific information on the batch specific documentation accompanying the medicinal product.

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

Inspection and thawing of the infusion bag(s)

Do not thaw the product until it is ready to be used.

The infusion bag should be placed inside a second sterile bag during thawing to protect ports from contamination and avoid spills in the unlikely event of the bag leaking. Kymriah should be thawed at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. The bag should be removed immediately from the thawing device and kept at room temperature (20°C-25°C) until infusion. If more than one infusion bag has been received for the treatment dose (refer to the batch certificate for number of bags constituting one dose), the next bag should only be thawed after the contents of the preceding bag have been infused.

Kymriah should not be manipulated. For example, Kymriah should not be washed (spun down and resuspended in new media) prior to infusion.

The infusion bag(s) should be examined for any breaks or cracks prior to thawing. If the infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local procedures on handling of biological waste.

Administration

Kymriah intravenous infusion should be administered by a healthcare professional experienced with immunosuppressed patients and prepared to manage anaphylaxis. In the event of cytokine release syndrome (CRS), ensure that at least one dose of tocilizumab per patient and emergency equipment are available prior to infusion. Hospitals must have access to additional doses of tocilizumab within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Ministry of Health website, ensure that suitable alternative measures to treat cytokine release syndrome are available on site.

The patient's identity should be matched with the patient identifiers on the infusion bag. Kymriah is intended solely for autologous use and must not, under any circumstances, be administered to other patients.

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

If the volume of Kymriah to be administered is ≤20 mL, intravenous push may be used as an alternative method of administration.

Measures to take in case of accidental exposure

In case of accidental exposure local guidelines on handling of human-derived material should be followed. Work surfaces and materials which have potentially been in contact with Kymriah must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Kymriah (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

7. REGISTRATION HOLDER AND IMPORTER AND ITS ADDRESS

Novartis Israel Ltd., POB 7126 , Tel Aviv.

8. REGISTRATION NUMBER(S)

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