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KYMRIAH® 1.2 x 10^6 – 6 x 10^8 cells dispersion for IV infusion (tisagenlecleucel)

Kymriah healthcare professional training material

RMP 2022-007

This document has been determined by the Ministry of Health and the content therefore has been checked and approved on November 2022

Kymriah product and therapeutic indications

Kymriah is an immunocellular therapy containing tisagenlecleucel, autologous T-cells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR).

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.

Materials provided to healthcare professionals and patients

The following materials are provided in the Healthcare Professional information pack:

- Prescribing information (PI)
- Educational material: Pharmacy/Cell Lab/Infusion Centre Training Material
- Educational material: Healthcare Professional Training Material

The following materials are provided in the Patient information pack:

- Patient leaflet
- Patient Alert Card
  - The patient should carry the Patient Alert Card at all times and show it to any healthcare provider
- Educational material: Patient Information Brochure
  - Includes instructions for the patient and information for their healthcare professional

Kymriah Risk Management Plan (RMP): Key messages of additional risk minimisation measures

Controlled Distribution Program Objectives:

- To mitigate the safety risks associated with Kymriah treatment by ensuring that hospitals and their associated centres that dispense Kymriah infusion are specially qualified by Novartis
- Kymriah will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program, and have on-site, immediate access to tocilizumab.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.

Kymriah Risk Management Plan (RMP): Key messages of additional risk minimisation measures (continued)

Educational Program Objectives:

- **Pharmacy/Cell Lab/Infusion Centre Training Material:**
  - Inform about reception, storage, handling, thawing and preparation for infusion of Kymriah to mitigate a decrease in cell viability of Kymriah due to inappropriate handling of the product and subsequent potential impact on the efficacy/safety profile
- **Healthcare Professional Training Material:**
  - Mitigate the risk of severe or life-threatening CRS and neurological events by ensuring those, who prescribe, dispense, or administer Kymriah, are aware of how to manage the risks of CRS and neurological events
  - Encourage to spontaneously report AE(s) to Novartis or local Health Authorities
  - Counsel patients/guardians regarding:
    - Instances where Kymriah cannot be successfully manufactured and infusion cannot be provided, or the final manufactured product is Out-of-Specification (OOS)
    - The potential need for bridging chemotherapy and risk of progressive disease during manufacturing time, in addition to the risks of CRS and neurological events and actions to be taken

CRS, cytokine release syndrome.

Kymriah Risk Management Plan (RMP): Key messages of additional risk minimisation measures (continued)

Educational Program Objectives (continued):

- **Patient Information Brochure**
- Create awareness that there are instances where Kymriah cannot be successfully manufactured and infused, or final product is Out-of-Specification (OOS)
  - Inform about the potential need for bridging chemotherapy, associated adverse drug reactions, and the risk of progressive disease during the Kymriah manufacturing time
  - Educate patients/guardians on the risks of CRS and neurotoxicity, and when to seek medical attention
  - Inform about monitoring requirements and potential for hospitalisation following Kymriah infusion

CRS, cytokine release syndrome.

Reasons to delay Kymriah treatment

Delay Kymriah infusion if the patient has:

Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies

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Active uncontrolled infection

Active graft-versus-host-disease (GVHD)

Significant clinical worsening of leukaemia burden or rapid progression of lymphoma following lymphodepleting chemotherapy

Kymriah-associated cytokine release syndrome (CRS)

Cytokine release syndrome (CRS)

*CRS is a systemic inflammatory response associated with Kymriah cell expansion, activation and tumor cell killing

*CRS, including fatal or life-threatening events, has been frequently observed after Kymriah infusion.

-In paediatric and young adult patients with r/r B-cell ALL (ELIANA study, n=79): 77% of patients developed CRS of any grade (Penn grading criteria) and 48% developed grade 3 or 4 CRS

-In adult patients with r/r DLBCL (JULIET study, n=115): 57% of patients developed CRS of any grade (Penn grading criteria) and 23% developed grade 3 or 4 CRS

-In adult patients with r/r FL (ELARA study, n=97): 50% of patients developed CRS of any grade (Lee grading criteria) and no patients developed grade 3 or 4 CRS

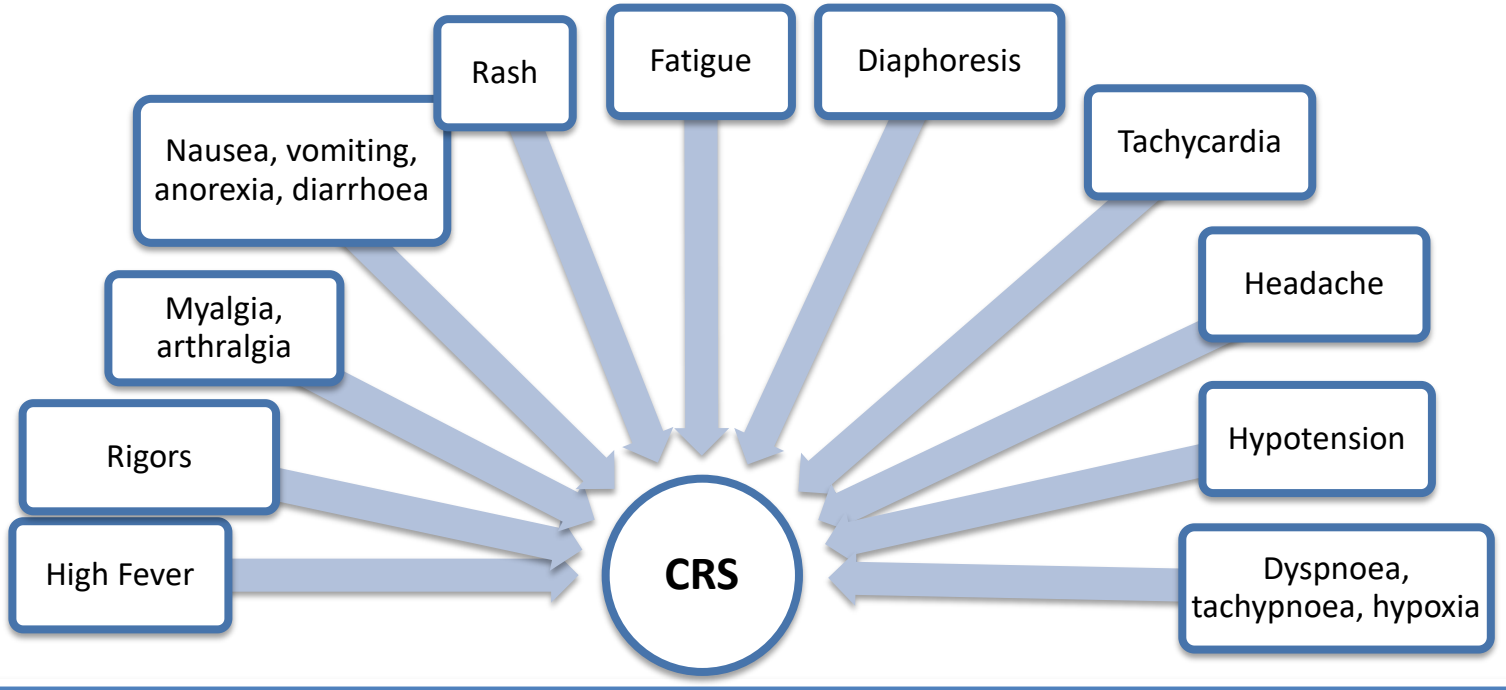
* In almost all cases, development of CRS after Kymriah infusion occurred between 1 to 10 days (median onset 3 days) in paediatric and young adult B-cell ALL patients, between 1 and 9 days (median onset 3 days) in adult DLBCL patients, and between 1 to 14 days (median onset 4 days) in adult FL patients

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

Patients with CRS may require admission to the intensive care unit for supportive care

ALL; acute lymphoblastic leukaemia; r/r DLBCL , relapsed or refractory diffuse large B-cell lymphoma ; FL, follicular lymphoma; r/r, relapsed/refractory

CRS signs and symptoms: patient presentation



Diagnosis based on clinical signs and symptoms[1-3]

CRS, cytokine release syndrome.

References: 1. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. **2.** Smith LT, Venella K. *Clin J Oncol Nurs*. 2017;21(2):29-34. **3.** Kymriah PI as approved by the MOH.

CRS-induced organ toxicity and associated adverse reactions

Hepatic	• Hepatic failure: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinaemia
Renal	• Acute kidney injury and renal failure, may require dialysis
Respiratory	• Respiratory failure, pulmonary oedema, may require intubation and mechanical ventilation
Cardiac	• Arrhythmia • Cardiac failure
Vascular	• Hypotension • Capillary leak syndrome
Haematological disorders including cytopenias >28 days following Kymriah infusion	• Leukopenia, neutropenia, thrombocytopenia, and/or anaemia • **Note:** 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 or until CRS has resolved

CRS, cytokine release syndrome.

CRS-induced organ toxicity and associated adverse

Coagulopathy with hypofibrinogenaemia	• Disseminated intravascular coagulation (DIC) with low fibrinogen levels • May result in haemorrhage
Haemophagocytic lymphohistiocytosis / macrophage activation syndrome (HLH/MAS)	• **Note:** Severe CRS and HLH/MAS may have overlapping pathologies, clinical manifestations, and laboratory profile • **Note:** When HLH or MAS occur as a result of Kymriah, treat per CRS management algorithm • If no improvement after tocilizumab and steroids, consider other anti-cytokine and anti-T cell therapies following institutional policy and published guidelines.

CRS, cytokine release syndrome.

Risk factors for severe CRS that could be established in ALL, DLBCL and FL

Patients up to and including 25 years of age with r/r B-cell ALL	
Pre-infusion tumour burden	▪ High pre-infusion tumour burden, uncontrolled or accelerating tumour burden following lymphodepleting chemotherapy can be associated with severe CRS ▪ Prior to administration of Kymriah, efforts should be made to lower and control the patient's tumour burden
Infection	▪ Active infection may increase the risk of severe CRS ▪ Infections may also occur during CRS and may increase the risk of fatal events ▪ Prior to administration of Kymriah, provide appropriate prophylactic and therapeutic treatment for infections, and ensure complete resolution of any existing infection
Onset of fever	▪ Early onset of fever can be associated with severe CRS
Onset of CRS	▪ Early onset of CRS can be associated with severe CRS

Adult patients with r/r DLBCL	
Pre-infusion tumour burden	▪ High tumour burden can be associated with severe CRS

Adult patients with r/r FL
No risk factors for severe CRS were established for adult patients with r/r FL as no patients developed severe CRS in the ELARA clinical study.

ALL, acute lymphoblastic leukaemia; CRS, cytokine release syndrome;
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; r/r, relapsed/refractory.

Monitoring of CRS

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurological events and other toxicities
- Physicians should consider hospitalization for the first 10 days post-infusion or at the first signs/symptoms of CRS and/or neurological events
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion
- Patients should be instructed to remain within proximity (i.e., within 2 hours' travel) of a qualified clinical facility for at least 4 weeks following infusion

CRS, cytokine release syndrome.

Management of CRS

CRS should be managed based upon clinical presentation and according to the Kymriah CRS management algorithm as described in the PI and in the following slides

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

Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered

CRS, cytokine release syndrome; PI, Prescribing Information

Management of CRS (continued)

-Anti-IL-6 based therapy such as tocilizumab* has been administered for moderate or severe CRS associated with Kymriah.
One dose of tocilizumab per patient must be on site and available for administration prior to Kymriah infusion; the treatment centre must have access to additional doses of tocilizumab within 8 hours to manage CRS according to the CRS management algorithm per local prescribing information

- 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.

-Due to the known lympholytic effect of corticosteroids*:
- -Do not use corticosteroids for premedication except in the case of a life-threatening emergency
- -Avoid the use of corticosteroids after infusion except in cases of life-threatening emergencies or in line with the CRS management algorithm

-Tumour necrosis factor (TNF) antagonists are not recommended for the management of Kymriah-associated CRS

*Kymriah continues to expand and persist despite administration of tocilizumab and corticosteroids.

CRS, cytokine release syndrome; IL, interleukin

Kymriah CRS management algorithm

CRS Severity	Symptomatic Treatment	Tocilizumab	Corticosteroids
Mild symptoms requiring symptomatic treatment only, e.g. ▪ low fever ▪ fatigue ▪ anorexia	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	Not applicable	Not applicable

CRS, cytokine release syndrome.

Kymriah CRS management algorithm (continued)

CRS Severity	Symptomatic Treatment	Tocilizumab	Corticosteroids
Symptoms requiring moderate intervention: ▪ high fever ▪ hypoxia ▪ mild hypotension	Antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed Treat other organ toxicities as per local guidance	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)*	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*
Symptom requiring aggressive intervention: ▪ hypoxia requiring high-flow oxygen supplementation or ▪ hypotension requiring high-dose or multiple vasopressors	High-flow oxygen Intravenous fluids and high-dose vasopressor(s) Treat other organ toxicities as per local guidelines		
Life-threatening symptoms: ▪ haemodynamic instability despite intravenous fluids and vasopressors ▪ worsening respiratory distress ▪ rapid clinical deterioration	Mechanical ventilation Intravenous fluids and high-dose vasopressor(s) Treat other organ toxicities as per local guidelines		

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

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

CRS, cytokine release syndrome.

Definition of high-dose vasopressors[1-3]

	Dose to be given for ≥3 hours	
Vasopressor	**Weight-based dosing[a]**	**Flat dosing[b]**
Norepinephrine monotherapy	≥ 0.2 mcg/kg/min	≥ 20 mcg/min
Dopamine monotherapy	≥ 10 mcg/kg/min	≥ 1000 mcg/min
Phenylephrine monotherapy	≥ 2 mcg/kg/min	≥ 200 mcg/min
Epinephrine monotherapy	≥ 0.1 mcg/kg/min	≥ 10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 0.1 mcg/kg/min[d]	Vasopressin + norepinephrine equivalent (NE) ≥ 10 mcg/min[c]
If on combination vasopressors (not vasopressin)	NE of ≥ 0.2 mcg/kg/min[d]	NE of ≥ 20 mcg/min[c]

[a] Weight-based dosing was extrapolated by dividing the flat dosing of a vasopressor by 100.
[b] If institutional practice is to use flat dosing.
[c] Vasopressin and Septic Shock Trial (VASST) norepinephrine equivalent equation:
NE dose (flat dosing) = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷ 10][3]
[d] Vasopressin and Septic Shock Trial (VASST) norepinephrine equivalent equation, adapted for weight-based dosing from Russell JA et al.:
NE dose (weight-based dosing) = [norepinephrine (mcg/kg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/kg/min)] + [phenylephrine (mcg/kg/min) ÷ 10][3]

References: 1. Lee DW et al. *Blood*. 2014;124(2):188-195. Erratum in: *Blood*. 2015;126(8):1048. **2.** Porter DL et al. *Sci Transl Med*. 2015;7(303):303ra139. https://stm.sciencemag.org/content/suppl/2015/08/31/7.303.303ra139.DC1. Accessed March 30, 2020. **3.** Russell JA et al. *N Engl J Med*. 2008;358(9):877-887. https://www.nejm.org/doi/suppl/10.1056/NEJMoa067373/suppl_file/nejm_russell_877sa1.pdf. Accessed March 30, 2020.

Kymriah-associated neurological events

Neurological events

Neurological events, in particular encephalopathy, confusional state or delirium, occur frequently with Kymriah and can be severe or life-threatening. Other manifestations include a depressed level of consciousness, seizures, aphasia and speech disorder.

- In paediatric and young adult patients with r/r B-cell ALL (ELIANA study, n=79): manifestations of encephalopathy and/or delirium of all grades occurred in 39% of patients, and grade 3 or 4 were seen in 13% of patients within 8 weeks after infusion
- In adult patients with r/r DLBCL (JULIET study, n=115): manifestations of encephalopathy and/or delirium of all grades occurred in 20% of patients, and grade 3 or 4 were seen in 11% of patients within 8 weeks after Kymriah infusion
- In adult patients with r/r FL (ELARA study, n=97): manifestations of encephalopathy and/or delirium of all grades occurred in 9% of patients, and grade 3 or 4 were seen in 1% of patients within 8 weeks after Kymriah infusion

- ❑ Encephalopathy is a dominant feature of immune effector cell-associated neurotoxicity syndrome (ICANS), a new term coming into use during this study that was reported in 4% of patients at all grades and in 1% of patients at grade 3 or 4, all within 8 weeks of Kymriah infusion

ALL, acute lymphoblastic leukaemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma, , FL, follicular lymphoma

Neurological events (continued)

- The majority of neurological events occurred within 8 weeks following Kymriah infusion and were transient
  - Median time to onset*: 8 days in B-cell ALL, 6 days in DLBCL, and 9 days in FL
  - Median time to resolution: 7 days for B-cell ALL, 13 days for DLBCL, and 2 days for FL

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

ALL, acute lymphoblastic leukaemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma, FL, follicular lymphoma.

*Median time to onset of the first neurological events occurring at any time following Kymriah infusion.

Monitoring for neurological events

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurological events and other toxicities
- Physicians should consider hospitalisation for the first 10 days post-infusion or at the first signs/symptoms of CRS and/or neurological events
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion
- Patients/guardians should be instructed to remain within proximity (i.e., within 2 hours' travel) of a qualified clinical facility for at least 4 weeks following infusion

CRS, cytokine release syndrome.

Evaluation and management of neurological adverse events

*Patients should be diagnostically worked-up for neurologic events and managed depending on the underlying pathophysiology and in accordance with local standard of care

*Evaluation and grading of neurological events may include: a neurologic assessment and evaluation of neurologic domains such as level of consciousness, motor symptoms, seizures, and signs of elevated intracranial pressure/cerebral oedema[1]

*Patients should be monitored for infections, with late occurrence in some cases. Patients with neurological adverse events should be diagnostically worked up for opportunistic infections of the central nervous system (CNS) and should be managed depending on the underlying pathophysiology and in accordance with local standard of care

*If the neurological event is concurrent with CRS, please refer to the CRS management algorithm for treatment recommendations

*Consider anti-seizure medications (e.g. levetiracetam) for patients at high risk (prior history of seizure) or administer in the presence of seizure

*For encephalopathy, delirium or associated events: appropriate treatment and supportive care should be implemented as per local standard of care. In worsening events, consider a short course of steroids

Reference: 1. Lee DW, et al. Biol Blood Marrow Transplant. 2019;25(4):625-638.

Kymriah-Infections

Infections

- Infections commonly occur in patients due to several underlying pathomechanisms due to underlying disease and immunocompromised condition following preceding anti-cancer treatment such as chemotherapy and radiation, or lymphodepleting chemotherapy.

- Serious infections were observed in patients after tisagenlecleucel infusion, in some cases with late onset, some of which were life threatening or fatal. Infections are classified as an important identified risk due to the observed severity and seriousness

    - In B-cell ALL patients: Overall incidence (all grades) –72%, Severe infections (Grade 3 and higher) - 48% of patients after Kymriah infusion. 43% of the patients experienced an infection of any type within 8 weeks after Kymriah infusion.

    - In DLBCL patients: Overall incidence (all grades) - 58%, Severe infections (Grade 3 and higher)- 34% of patients. 37% of the patients experienced an infection of any type within 8 weeks.

    - In FL patients: Overall incidence (all grades) - 50%, Severe infections (Grade 3 and higher) –16% of patients. 19% of the patients experienced an infection of any type within 8 weeks.

Monitoring of Infection

- Prior to Kymriah infusion, infection prophylaxis should follow standard guidelines based on the degree of preceding immunosuppression

- Patients should be monitored daily for the first 10 days following infusion for potential CRS, neurological events and other toxicities.

Kymriah-

Hematopoietic cytopenias not resolved by day 28

Prolonged Cytopenias

- Grade 3 and 4 cytopenias not resolved by day 28 have been observed in patients infused with tisagenlecleucel and also with other CAR-T-cell therapies.
    - In paediatric and young adult B-cell ALL patients, Grade 3 and 4 cytopenias not resolved by day 28 were reported based on laboratory findings and included decreased count of white blood cells (57%), neutrophils (54%), lymphocytes (44%), thrombocytes (42%) and decreased haemoglobin (13%).
    - In adult DLBCL, patients, Grade 3 and 4 cytopenias not resolved by day 28 were reported based on laboratory findings and included decreased count of thrombocytes (39%), lymphocytes (29%), neutrophils (25%), white blood cells (21%) 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%).
    - 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.
- The etiology of these cytopenias may be either the underlying B-cell malignancy, the CAR-T-cell therapy itself, the lymphodepleting chemotherapy administered prior to the infusion or a combination.
- Prolonged neutropenia has been associated with increased risk of infection. It is classified as an important identified risk based on its potential severity and seriousness

Monitoring of Prolonged Cytopenias

- Patients should be monitored daily for the first 10 days following infusion for potential CRS, neurological events and other toxicities.

- 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 (i.e., within 2 hours' travel) of a qualified clinical facility for at least 4 weeks following infusion.

Management of Prolonged Cytopenias (Cont.)

- The risk can be managed with standard measures of observation, blood product support, growth factors and/or antibiotics as indicated.

- Since myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen CRS (if it occurs), these are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.

Kymriah-

Prolonged depletion of normal B-cells/ agammaglobulinemia

Prolonged depletion of normal B-cells/ agammaglobulinemia

Prolonged depletion of B-cells is an expected on-target toxicity of CD19-directed CAR-T-cell therapy. This may result in hypo- or agammaglobulinemia, potentially rendering the patients more susceptible to infections, especially with encapsulated organisms.
Viral reactivation such as herpes viruses may occur. Prolonged depletion of normal B-cells/Agammaglobulinemia is classified as an important identified risk given the potential of developing severe and serious events.

- Hypogammaglobulinaemia and agammaglobulinaemia can occur in patients with a complete remission after Kymriah infusion.

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

Management of Prolonged depletion of normal B-cells/ agammaglobulinemia (Cont.)

- Patients should be monitored daily for the first 10 days following infusion for potential CRS, neurological events and other toxicities.

- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.

Management of Prolonged depletion of normal B-cells/ agammaglobulinemia (Cont.)

- Patients should be instructed to remain within proximity (i.e., within 2 hours' travel) of a qualified clinical facility for at least 4 weeks following infusion.

- Immunoglobulin levels should be monitored after treatment with tisagenlecleucel. 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.

Physician to provide patient/guardian education

Patient/Guardian education

Physicians need to hand out 3 materials: the Kymriah Patient Leaflet, the Kymriah Patient Information Brochure and the Kymriah Patient Alert Card. Please review these materials with patients in detail

Patients/guardians should read and keep the Patient Leaflet. Please review and explain the Leaflet with patients, guardians, and caregivers

Patients/guardians should read and keep Kymriah Patient Information Brochure to remind them of the signs and symptoms of CRS and neurological events, in addition to other clinically important side effects that require immediate medical attention

Patients/guardians should read the Kymriah Patient Alert Card in its entirety. Patient should carry the card with them at all times and show it to all healthcare providers

CRS, cytokine release syndrome.

Patient/Guardian education (continued)

Counsel patients/guardians on the possibility that Kymriah may not be successfully manufactured and infusion cannot be provided if the final manufactured product is Out-of-Specification (OOS) and does not pass release tests. In some instances, a second manufacturing of Kymriah may be attempted. In case of OOS, the final product may be still provided as per physician's request, if supported by a positive benefit-risk assessment
Counsel patients/guardians on potential need for bridging therapy to stabilise the underlying disease while awaiting manufacturing and associated drug adverse reactions
Counsel patients/guardians on the risk of progressive disease during the Kymriah manufacturing time
Counsel patients/guardians that before getting Kymriah, a short course of lymphodepleting chemotherapy for conditioning may be given
Advise patients/guardians of the risk of CRS and neurological events and to contact their healthcare provider if experiencing signs and symptoms associated with CRS and neurological events

CRS, cytokine release syndrome.

Patient/Guardian education (continued)

Patients/guardians should plan to stay within the proximity (i.e., within 2 hours' travel) of the qualified treatment centre for at least 4 weeks after receiving Kymriah treatment, unless otherwise indicated by the doctor

Instruct patients/guardians to return to the hospital daily for at least 10 days to allow monitoring for CRS, neurological events and other toxicities and potential need for hospitalisation for side effects

Patients/guardians should be advised to measure the patient's temperature twice a day for 3-4 weeks after administration of Kymriah. If their temperature is elevated, they should see their doctor immediately

Due to the potential of Kymriah to cause problems such as altered or decreased consciousness, confusion, and seizures in the 8 weeks following infusion, patients should not drive, use machines, or take part in activities that require alertness

Patients/guardians should be advised that patient should not donate blood, organs, tissues or cells

CRS, cytokine release syndrome.

Kymriah:
Adverse event reporting

Adverse event reporting

•Healthcare providers are encouraged to spontaneously report AE(s)
•Adverse reactions may be reported to the Ministry of Health by means of the online form for reporting adverse reactions located at: https://sideeffects.health.gov.il
•You may also report to the Registration Holder Novartis Israel LTD. at: safetydesk.israel@novartis.com

•Importantly, when reporting adverse events, healthcare providers should always include the individual Kymriah Batch-identification number printed on the front of the Kymriah Patient Alert Card

•For further information, please refer to the PI.

PI, Prescribing Information; AEs, adverse events; CAR-T, chimeric antigen receptor T cell; CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Society for Blood and Marrow Transplantation.

Manufacturing failure and Out-of-Specification product

Overview of the Out-of-Specification product release process

- In some cases, it may either not be possible to manufacture Kymriah or the release criteria may not be met due to patient-intrinsic factors or manufacturing failure

- In instances where the product cannot be manufactured or if the manufactured product is Out-of-Specification (OOS), the treating healthcare professional will be informed as early as possible by Novartis in accordance with Section 11.5 of Volume 4 of the Good Manufacturing Practice (GMP) guideline specific to Advanced Therapy Medicinal Products (ATMPs), so the appropriate measures for the safety of the patient can be taken

- In the case a Kymriah batch proves to be OOS, Novartis will conduct an assessment of the anticipated efficacy and safety risks pertaining to this particular quality defect. The risk assessment will take into consideration prior clinical experience with Kymriah infusion in clinical trials and commercial setting as available and published literature. Importantly, the assessment does not provide infusion recommendations but is meant to inform the treating physician of the anticipated risks associated with a potential infusion of such a batch

- The Novartis risk assessment will be communicated to the treating physician to allow the physician to perform an independent evaluation of risk-benefit of this batch and either request the product to be provided for infusion or consider any alternatives, such as other anti-cancer treatment or re-manufacturing of a new batch (if feasible taking into account the medical status of the patient)

Thank you