HCP Training: Kymriah® 1.2 x 10^6 – 6 x 10^8 cells dispersion for IV infusion (tisagenlecleucel)

Kymriah healthcare professional training material

NOVARTIS | Reimagining Medicine

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 B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

Materials provided to healthcare professionals and patients

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

- Singapore Package Insert
- 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 Alert Card
  - The patient should carry the Patient Alert Card at all times and show it to any healthcare provider
- Educational material: Patient Educational Leaflet
  - Includes instructions for the patient or guardian/caregiver 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, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat cytokine release syndrome (CRS)

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
- Caution on possible development of secondary malignancies or recurrence of their cancer
- Encourage reporting of adverse events (AEs) suspected to be associated with the use of Kymriah to Novartis or the local Health Authority
- 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)

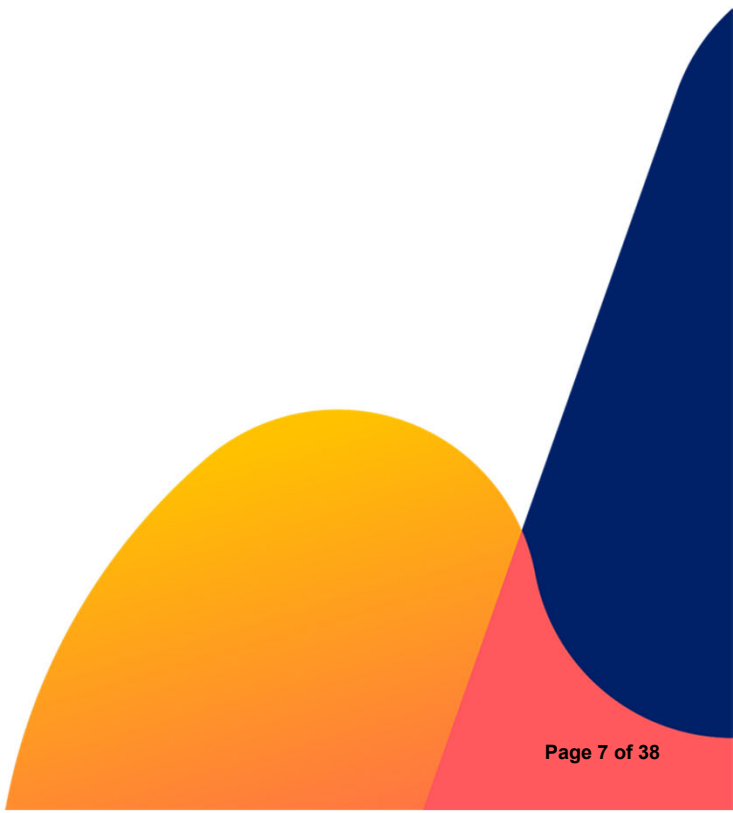
Educational Program Objectives (continued):

Patient Educational Leaflet

- 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

Active uncontrolled infection

Active graft-versus-host disease (GVHD)

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

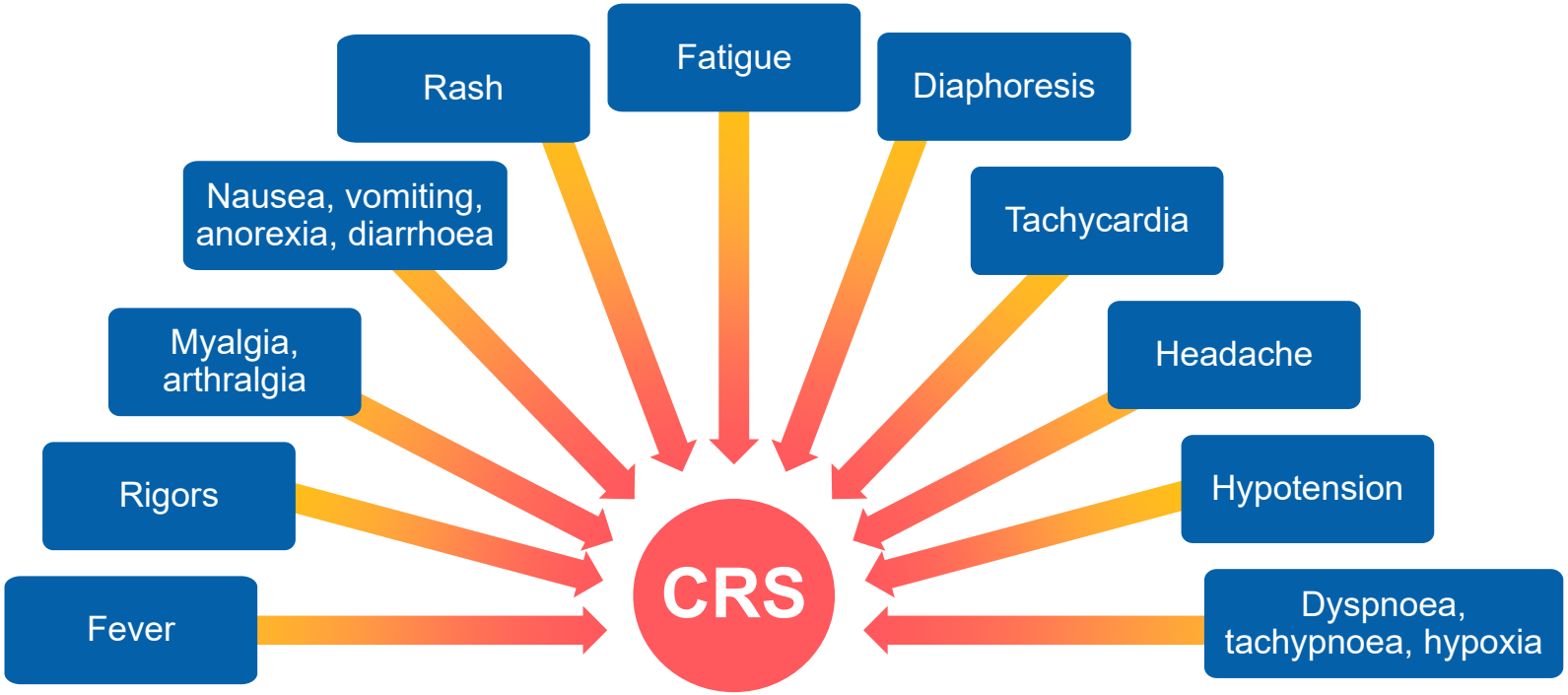
Kymriah-associated cytokine release syndrome (CRS)

Cytokine release syndrome (CRS)

- **CRS is a systemic inflammatory response associated with Kymriah cell expansion, activation and tumour 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. In some cases, onset of CRS occurred after that period.**
- **Patients should be closely monitored for signs or symptoms of CRS and patients and caregivers should be informed about potential late onset of signs or symptoms and instructed accordingly.**
- **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; DLBCL, 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 [summary of product characteristics]. Nuremberg, Germany: Novartis Pharma GmbH; 2022.

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	• Tachycardia • Atrial fibrillation • Ventricular extrasystoles • 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 reactions (continued)

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 profiles • **Note:** When HLH or MAS occurs as a result of Kymriah, treat per CRS management algorithm. For late-onset, tocilizumab-refractory HLH/MAS, 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, and hospitalisation should be considered for the first 10 days after infusion.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Physicians should consider hospitalisation at the first signs/symptoms of CRS and/or neurological events.
- 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 Singapore Package Insert 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 CRS 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.

Management of CRS (continued)

- **Anti-IL-6–based therapy such as tocilizumab* has been administered for mild or moderate or severe CRS associated with Kymriah and a minimum of 2 doses of tocilizumab per patient must be on site and available for administration prior to Kymriah infusion. Treatment centre should have timely 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, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS
- **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 moderate or severe 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**

CRS, cytokine release syndrome; IL, interleukin.
*Kymriah continues to expand and persist despite administration of tocilizumab and corticosteroids.

Kymriah CRS management algorithm

CRS Severity*	Symptomatic Treatment	Tocilizumab	Corticosteroids
Grade 1: • Fever# ≥ 38°C not attributable to any other cause • No hypoxia • No hypotension	Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms. If neutropenic, administer broad spectrum antibiotics and G-CSF. In patients with persistent (>3 days) or refractory fever, consider managing as per Grade 2 CRS.	Not applicable	Not applicable

CRS, cytokine release syndrome; G-CSF, granulocyte-colony stimulating factor.

*Monitor complete blood cell count (CBC), comprehensive metabolic panel (CMP), magnesium, phosphorus, c-reactive protein (CRP), lactate dehydrogenase (LDH), uric acid, fibrinogen, prothrombin time (PT)/partial thromboplastin time (PTT), and ferritin. Consider screening for cytomegalovirus infection (CMV) and Epstein-Barr virus (EBV). For patients with fever, assess for infection with blood and urine cultures, and a chest radiograph. If patient is neutropenic, follow institutional neutropenic fever guidelines. For grade 2 or higher, patients should be monitored with continuous cardiac telemetry and pulse oximetry. Perform cardiac monitoring in patients who experience at least grade 2, clinically significant arrhythmia, and additionally as clinically indicated. Consider chest or abdominal computed tomography (CT) imaging, brain magnetic resonance imaging (MRI), and/or lumbar puncture.
#Fever is not required to grade subsequent CRS severity in patients who receive antipyretics or anticytokine therapy (steroids or tocilizumab). Instead, CRS grading is driven by hypotension and/or hypoxia.

Kymriah CRS management algorithm (continued)

CRS Severity*	Symptomatic Treatment	Tocilizumab	Corticosteroids
Grade 2: • Fever[#] ≥ 38°C not attributable to any other cause Plus • Hypoxia requiring low-flow oxygen supplementation And/or • Hypotension not requiring vasopressors	Continue supportive care as per Grade 1 and include IV fluid bolus and/or supplemental oxygen as needed	Administer tocilizumab 8 mg/kg i.v. over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours if no improvement in signs and symptoms of CRS, limit to a maximum of three doses in a 24-hour period, with a maximum of four doses total. Manage per Grade 3 if no improvement within 24 hours of starting tocilizumab	If no improvement in hypotension after two fluid boluses and after one to two doses of tocilizumab, may consider dexamethasone 10 mg i.v. (or equivalent) every 12 hours for one to two doses and then reassess.

CRS, cytokine release syndrome.

*Monitor complete blood cell count (CBC), comprehensive metabolic panel (CMP), magnesium, phosphorus, c-reactive protein (CRP), lactate dehydrogenase (LDH), uric acid, fibrinogen, prothrombin time (PT)/partial thromboplastin time (PTT), and ferritin. Consider screening for cytomegalovirus infection (CMV) and Epstein-Barr virus (EBV). For patients with fever, assess for infection with blood and urine cultures, and a chest radiograph. If patient is neutropenic, follow institutional neutropenic fever guidelines. For grade 2 or higher, patients should be monitored with continuous cardiac telemetry and pulse oximetry. Perform cardiac monitoring in patients who experience at least grade 2, clinically significant arrhythmia, and additionally as clinically indicated. Consider chest or abdominal computed tomography (CT) imaging, brain magnetic resonance imaging (MRI), and/or lumbar puncture.
[#]Fever is not required to grade subsequent CRS severity in patients who receive antipyretics or anticytokine therapy (steroids or tocilizumab). Instead, CRS grading is driven by hypotension and/or hypoxia.

Kymriah CRS management algorithm (continued)

CRS Severity*	Symptomatic Treatment	Tocilizumab	Corticosteroids
Grade 3: • Fever[#] ≥ 38°C not attributable to any other cause And/or • Hypoxia requiring high- flow oxygen supplementation Plus • Hypotension requiring a vasopressor with or without vasopressin	Continue as per Grade 2 and include vasopressor as needed. Admit patient to intensive care unit (ICU). Assess cardiac function (echocardiogram) and conduct hemodynamic monitoring.	Tocilizumab as per Grade 2 if maximum dose is not reached within 24-hour period.	Dexamethasone 10 mg i.v. every 6 hours (or equivalent) and rapidly taper once symptoms improve. Manage per Grade 4 if refractory.

CRS, cytokine release syndrome.

*Monitor complete blood cell count (CBC), comprehensive metabolic panel (CMP), magnesium, phosphorus, c-reactive protein (CRP), lactate dehydrogenase (LDH), uric acid, fibrinogen, prothrombin time (PT)/partial thromboplastin time (PTT), and ferritin. Consider screening for cytomegalovirus infection (CMV) and Epstein-Barr virus (EBV). For patients with fever, assess for infection with blood and urine cultures, and a chest radiograph. If patient is neutropenic, follow institutional neutropenic fever guidelines. For grade 2 or higher, patients should be monitored with continuous cardiac telemetry and pulse oximetry. Perform cardiac monitoring in patients who experience at least grade 2, clinically significant arrhythmia, and additionally as clinically indicated. Consider chest or abdominal computed tomography (CT) imaging, brain magnetic resonance imaging (MRI), and/or lumbar puncture.
[#]Fever is not required to grade subsequent CRS severity in patients who receive antipyretics or anticytokine therapy (steroids or tocilizumab). Instead, CRS grading is driven by hypotension and/or hypoxia.

Kymriah CRS management algorithm (continued)

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

CRS, cytokine release syndrome; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure.

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

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

[^]Noting limited experience with other agents, alternate options may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, and antithymocyte globulin. Alternative CRS management strategies may be implemented based on appropriate institutional or academic guidelines.

Definition of high-dose vasopressors[1-3]

Vasopressor	Dose to be given for ≥3 hours	
	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; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; r/r, relapsed/refractory.

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
  - In some cases, onset of neurological events occurred after that period
- **Neurological events can be concurrent with CRS, following resolution of CRS, or in the absence of CRS**
- **Patients should be monitored for neurological events and patients and caregivers should be informed about the potential late onset of events and instructed accordingly**

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, and hospitalisation should be considered for the first 10 days after infusion.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Physicians should consider hospitalisation at the first signs/symptoms of CRS and/or neurological events.
- 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 events

- To reduce the risk of or manage neurological toxicities (including ICANS), patients treated with Kymriah may receive supportive treatment based on the most recent American Society of Clinical Oncology (ASCO) guideline, and/or appropriate local institutional / academic guidelines
- 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 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

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

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

Secondary malignancies of T-cell origin

Secondary malignancies of T-cell origin

- Patients treated with Kymriah may develop secondary malignancies or relapse of their leukemia or lymphoma.
- Secondary malignancies of T-cell origin have been reported within weeks and up to several years following administration of CAR T-cell medicines, including Kymriah. Risk factors including anticancer therapies (chemotherapy, radiation therapy, and HSCT) prior to or post-Kymriah infusion are associated with the development of new malignancies. Additionally, historical or concurrent other malignancies suggest high genomic instability.
- Patients should be monitored life-long for secondary malignancies, including those of T-cell origin. Healthcare professionals should report all new secondary malignancies (subsequent neoplasm) to Novartis (patientsafety.sg@novartis.com or +65 6019 6483) for patients treated with Kymriah and arrangements should be made for testing of archived tumor samples and/or DNA extracted and saved from blood from the patient, when feasible
  - For all patients with a reported secondary T cell malignancy, the current Novartis Secondary Malignancy Guidance Document and Process will be followed.

Physician to provide patient/guardian education

Patient/Guardian education

Physicians need to hand out 2 materials: the Kymriah Patient Educational Leaflet and the Kymriah Patient Alert Card. Please review these materials with patients in detail

Please review and explain the Patient Educational Leaflet with patients, guardians, and caregivers

Patients/guardians should read and keep Kymriah Patient Educational Leaflet 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
Caution risk of developing secondary malignancies, including those of T-cell origin

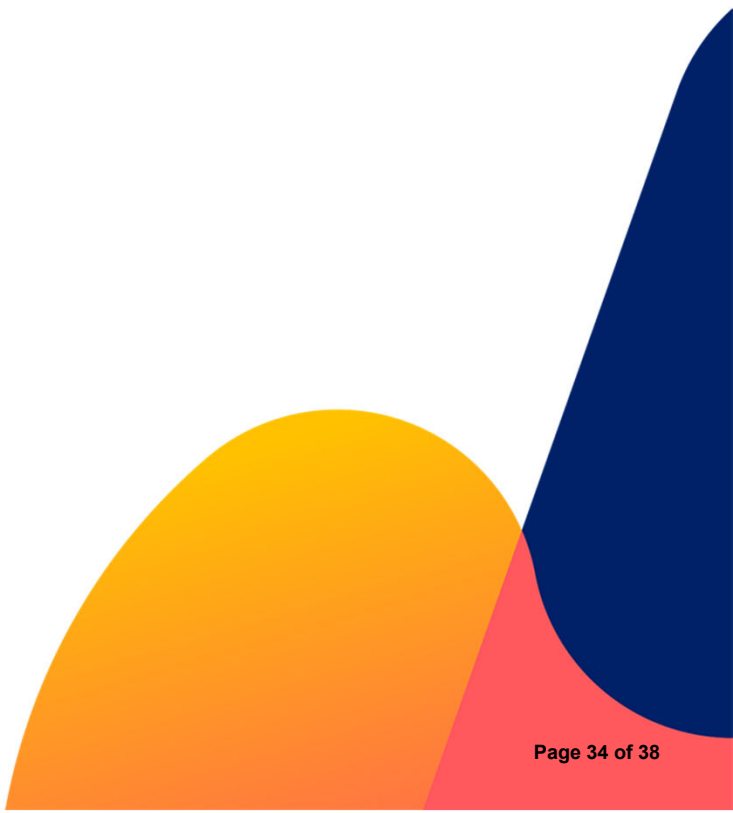
CRS, cytokine release syndrome.

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 the first 10 days to allow monitoring for CRS, neurological events and other toxicities and inform them about the potential need for hospitalisation for the first 10 days post-infusion or at the first signs/symptoms of CRS and/or neurological events
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



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Adverse event reporting

- Adverse reactions associated with Kymriah can be reported to Novartis at https://www.novartis.com/report or by calling Novartis at +65 6019 6483, or to your local Health Authority at Vigilance and Compliance Branch, Health Products Regulation Group, Health Sciences Authority at Tel: 6866 1111, or report online at https://www.hsa.gov.sg/adverse-events

- Importantly, when reporting adverse events, healthcare providers should always include the individual Kymriah Batch ID

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 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)

For Healthcare Professionals only

Please visit https://www.novartis.com.sg/product-list/kymriah to access or download Package Insert. Alternatively, please scan this code for more information about this medicine

Thank you

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This document has been approved by HSA as of 17-07-2025.

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