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

▼ *This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions along with the batch ID of the medicine should be reported to HPRA Pharmacovigilance at www.hpra.ie. Adverse events can also be reported to Novartis preferably at www.novartis.com/report, by emailing drugsafety.dublin@novartis.com or by calling (01) 2080 612.*

**Kymriah healthcare professional training material**

NOVARTIS | Reimagining Medicine

**Novartis Ireland Ltd.,**
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Merrion Road, Dublin 4, D04 A9N6

**HPRA approved September 16th 2025**

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# 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:**

- Summary of Product Characteristics (SmPC)
- 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:**

- Package 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 Educational Leaflet
  - 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 European Medicines Agency shortage catalogue, prior to infusion 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
  - Inform about adverse event (AE) reporting in the respective registry for cellular therapy, while encouraging to spontaneously report the same 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 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.

# Important Notice for Thawing and Infusion

- 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.

Please refer to 'Pharmacy/Cell Lab/Infusion Centre Training Material for further guidance on Preparation, Thawing and Administration of Kymriah.

# 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

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# Kymriah-associated cytokine release syndrome (CRS)

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# 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.



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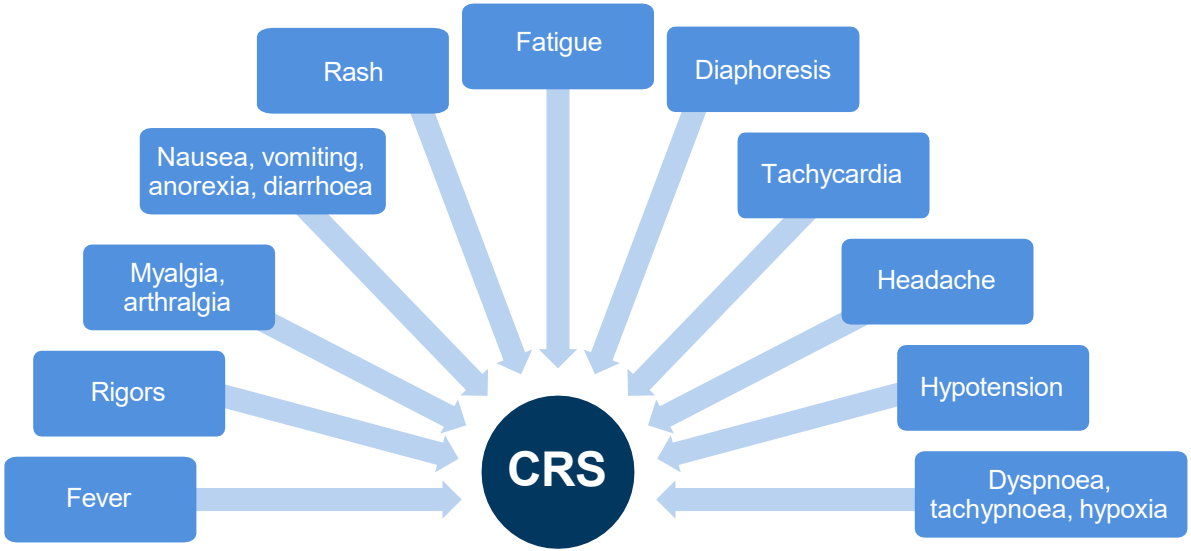
# CRS signs and symptoms: patient presentation




*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** | ▪ Arrhythmia<br>▪ Cardiac failure |
| **Vascular** | ▪ Hypotension<br>▪ Capillary leak syndrome |
| **Haematological disorders including cytopenias >28 days following Kymriah infusion** | ▪ Leukopenia, neutropenia, thrombocytopenia, and/or anaemia<br>▪ **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<br>▪ 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<br>▪ **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<br>▪ 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<br>▪ Infections may also occur during CRS and may increase the risk of fatal events<br>▪ 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

- In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion, for signs and symptoms of potential CRS, neurological events and other toxicities.
- After the first week 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 SmPC 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; SmPC, summary of product characteristics.

# 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 European Medicines Agency shortage catalogue, prior to infusion 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 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 |
|---|---|---|---|
| Mild symptoms requiring symptomatic treatment only, e.g.<br>▪ low fever<br>▪ fatigue<br>▪ anorexia | Exclude other causes (e.g. infection) and treat specific symptoms with, for example, antipyretics, anti-emetics, analgesics, etc.<br>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:<br>▪ high fever<br>▪ hypoxia<br>▪ mild hypotension | Antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed<br>Treat other organ toxicities as per local guidance | If no improvement after symptomatic treatment administer tocilizumab intravenously over 1 hour:<br>▪ 8 mg/kg (max. 800 mg) if body weight ≥30 kg<br>▪ 12 mg/kg if body weight <30 kg<br>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:<br>▪ hypoxia requiring high-flow oxygen supplementation or<br>▪ hypotension requiring high-dose or multiple vasopressors | High-flow oxygen<br>Intravenous fluids and high-dose vasopressor(s)<br>Treat other organ toxicities as per local guidelines | | |
| Life-threatening symptoms:<br>▪ haemodynamic instability despite intravenous fluids and vasopressors<br>▪ worsening respiratory distress<br>▪ rapid clinical deterioration | Mechanical ventilation<br>Intravenous fluids and high-dose vasopressor(s)<br>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

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# 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*: 9 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

- In the first week following infusion, patients should be monitored 2 to 3 times, or more frequently at the physician's discretion for signs and symptoms of potential CRS, neurological events and other toxicities.
- After the first week 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.

# Evaluation and management of neurological 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 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.

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

# Secondary malignancies of T-cell origin

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# 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.
- Healthcare professionals should report all new secondary malignancies (subsequent neoplasm) to Novartis 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
  - Eligible patients should be offered enrollment in a non-interventional post authorization safety study to facilitate testing of the secondary malignancies of T-cell origin.
  - For all other patients (including not eligible, decline consent or site declines to participate in the study) with a reported secondary T cell malignancy, the current Novartis Secondary Malignancy Guidance Document and Process will be followed.



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# Physician to provide patient/guardian education

# Patient/Guardian education

| |
|---|
| Physicians need to hand out 3 materials: the Kymriah Package Leaflet, the Kymriah Patient Educational Leaflet and the Kymriah Patient Alert Card. Please review these materials with patients in detail |
| Patients/guardians should read and keep the Package Leaflet. Please review and explain the 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 |

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 2 to 3 times during the first week after treatment, or more frequently, 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: Registry and adverse event reporting

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# Registry and adverse event reporting

- Healthcare providers should offer their patients enrolment into the CAR-T Registries for cellular therapy conducted by EBMT following Kymriah treatment, for adequate follow-up of safety and efficacy, for up to 15 years following infusion
- Healthcare providers should report AEs in the EBMT registry for cellular therapy and, in parallel, providers are encouraged to spontaneously report the same AEs with regard to Kymriah treatment.
- This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions along with the batch ID of the medicine should be reported to HPRA Pharmacovigilance at www.hpra.ie. Adverse events can also be reported to Novartis preferably at www.novartis.com/report, by emailing drugsafety.dublin@novartis.com or by calling (01) 2080 612.
- Importantly, when reporting adverse events, healthcare providers should always include the individual Kymriah Batch-identification number
- If you have a question about the product, please contact Medical Information at medinfo.dublin@novartis.com

AEs, adverse events; CAR-T, chimeric antigen receptor T cell; 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)
- Patients treated with such an OOS product should be offered enrolment into the registries for cellular therapy for 15-year long-term follow-up

# Thank you

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