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# Risk Evaluation and Mitigation Strategy (REMS): Cytokine release syndrome and neurological toxicities

A REMS is a program required by the FDA to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of KYMRIAH outweigh its risks.

The purpose of the KYMRIAH REMS is to inform healthcare providers of the risks of cytokine release syndrome and neurological toxicities observed with KYMRIAH.

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This educational module contains information on selected KYMRIAH-associated adverse events, including cytokine release syndrome and neurological toxicities, observed in clinical trials ELIANA, JULIET, and ELARA for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse, adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma, and adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. The r/r FL indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.

# KYMRIAH Indication

- KYMRIAH (tisagenlecleucel), previously known as CTL019, is a CD19-directed genetically modified autologous T cell immunotherapy

- Indicated for the treatment of:
  - Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

  - Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
    - Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.

  - Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials(s).

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# KYMRIAH REMS Goals

- The goals of the KYMRIAH REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:
  - Ensuring that hospitals and their associated clinics that dispense KYMRIAH are specially certified and have on-site, immediate access to tocilizumab.
  - Ensuring those who prescribe, dispense, or administer KYMRIAH are aware of how to manage the risks of CRS and neurological toxicities.

# KYMRIAH REMS Materials

- KYMRIAH REMS Live Training Program Slides
  - Provides education on the risks of CRS and neurological toxicities
  - Addresses serious clinical manifestations, timing of events, monitoring and management, and importance of patient education
  - KYMRIAH REMS Program overview
- KYMRIAH REMS Program Patient Wallet Card
  - For patients and their guardians to keep with them at all times, reminds them of signs and symptoms that require immediate medical attention
  - Instructions to stay within 2 hours of treatment site for at least 4 weeks

# KYMRIAH REMS Materials, cont.

- KYMRIAH REMS Program Knowledge Assessment
  - Reinforces the messages about CRS and neurological toxicities, 10 questions, multiple choice
  - All staff involved in ordering, prescribing, or administering must successfully complete via email, in-person, fax, or online
- KYMRIAH REMS Program Hospital Enrollment Form
  - Must be completed by the authorized representative (via email, fax, or online) to certify the hospital
- KYMRIAH REMS Program Website
  - Holds all REMS educational tools for download/printing

# Site Certification

- To become certified* to dispense KYMRIAH, hospitals and their associated clinics must:
  - Designate an authorized representative to complete the certification process by submitting the completed KYMRIAH REMS Program Hospital Enrollment Form on behalf of the hospital and their associated clinics
  - Ensure the authorized representative oversees implementation and compliance with KYMRIAH REMS Program requirements

***Completion of the enrollment form and knowledge assessment does not guarantee your hospital will be certified to administer KYMRIAH. Please contact 1-844-4KYMRIAH(1-844-459-6742) for more information**

# Authorized Representative

- Completes KYMRIAH REMS Live training program and successfully completes KYMRIAH REMS Program Knowledge Assessment
- Ensures all relevant staff are trained and successfully complete knowledge assessment and maintain records of training
- Put processes and procedures in place to ensure that:
  - New staff is trained
  - Staff retrained if KYMRIAH has not been dispensed once annually from certification
  - Prior to dispensing KYMRIAH:
    - Verify 2 doses of tocilizumab are available onsite for each patient and ready for immediate administration
    - Provide patients and their guardians with KYMRIAH REMS Program Patient Wallet Card to inform them:
      - Signs and symptoms of CRS and neurological toxicities that require immediate medical attention.
      - Importance of staying within 2 hours of the certified hospital and their associated clinic for at least 4 weeks after receiving KYMRIAH treatment, unless otherwise indicated by the doctor.

# Conditions of Certification

- Recertify in the KYMRIAH REMS Program if the hospital and their associated clinics designate a new authorized representative.
- Report any adverse events suggestive of CRS or neurological toxicities.
- Maintain documentation that all processes and procedures are in place and are being followed for the KYMRIAH REMS Program and provide that documentation upon request to Novartis or a third party acting on behalf of Novartis.
- Comply with audits by Novartis or a third party acting on behalf of Novartis to ensure that all training, processes and procedures are in place and are being followed for the KYMRIAH REMS Program.
- Dispense KYMRIAH only after verifying that a minimum of two doses of tocilizumab are available on-site for each patient for administration within 2 hours.

# KYMRIAH Boxed Warning

**WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES**

- **Cytokine Release Syndrome (CRS), including fatal or life- threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed.**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS.**

# KYMRIAH-associated Cytokine Release Syndrome

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# Cytokine Release Syndrome (CRS)

- CRS, including fatal or life-threatening reactions, was the most common adverse event in the KYMRIAH pivotal clinical trials in pediatric and young adult patients with r/r ALL, adult patients with r/r DLBCL, and r/r FL
- In clinical trials, CRS was effectively managed in the majority of patients based on a CRS management algorithm
- Patients with CRS may require admission to the intensive care unit for supportive care

# CRS in Pediatric and young adult patients up to 25 years of age with r/r B-cell ALL

- In the KYMRIAH pivotal clinical trial in pediatric and young adult patients with r/r B-cell ALL (ELIANA Study)
  - 77% (61/79) of patients developed CRS of any grade (Penn grading system); 48% (38/79) developed CRS ≥ grade 3
- The median time to onset of CRS was 3 days (range: 1-22 days); 1 patient with onset after Day 10
- The median time to resolution of CRS was 8 days (range: 1-36 days)
- Of the patients who developed CRS, 51% (31/61) received tocilizumab:
  - 16% (10/61) received two doses, 5% (3/61) received three doses of tocilizumab
  - 28% (17/61) received addition of corticosteroids (e.g. methylprednisolone)



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# Risk Factors for severe CRS in patients up to 25 years of age with r/r B-cell ALL

| | |
|---|---|
| **Pre-infusion tumor burden** | • High pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy were associated with severe CRS<br>• Efforts should be made to lower and control the patient's tumor burden prior to KYMRIAH administration |
| **Infection** | • Infections occur concurrently with CRS, may increase the risk of fatal events<br>• Prior to administration of KYMRIAH, provide appropriate prophylactic and therapeutic treatment for infection, and ensure complete resolution of any existing infection |
| **Onset of fever** | • Early onset of fever can be associated with severe CRS |
| **Inflammatory processes** | • Active inflammatory processes may increase the risk of severe CRS |

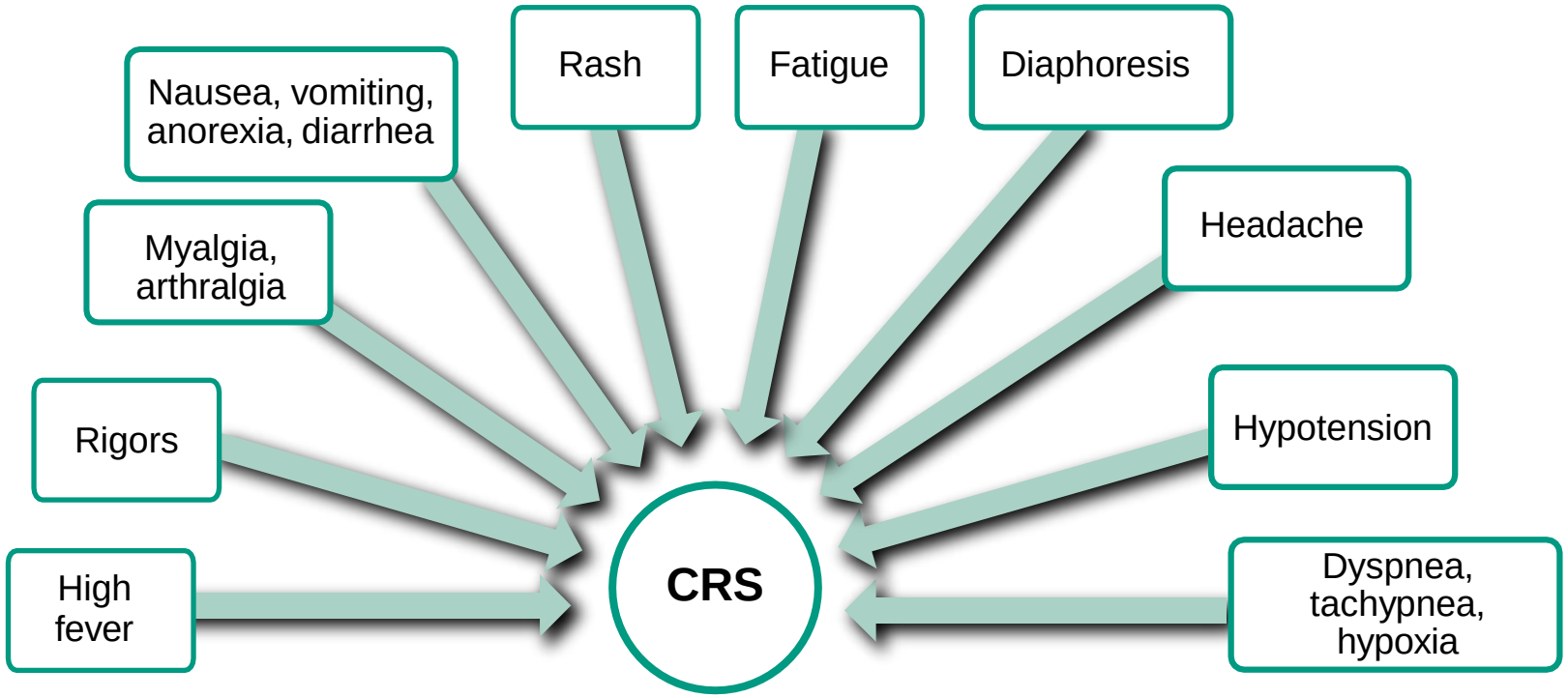
# CRS in adult patients with r/r DLBCL

- In the KYMRIAH pivotal clinical trial in adult patients with r/r DLBCL (JULIET Study)
  - 74% (85/115) of patients developed CRS of any grade (Penn grading system); 23% (26/115) developed CRS ≥ grade 3
- The median time to onset of CRS was 3 days (range: 1-51 days); 1 patient with onset after Day 10.
- The median time to resolution of CRS was 7 days (range: 2-30 days).
- Of the patients who developed CRS, 22% (19/85) received tocilizumab or corticosteroids:
  - 8% (7/85) received one dose of tocilizumab and 13% (11/85) received two doses of tocilizumab
  - 13% (11/85) of patients received corticosteroids in addition to tocilizumab
  - One (1/85) patient received corticosteroids for CRS, without concomitant tocilizumab

# CRS in adult patients with r/r FL

- In the KYMRIAH pivotal clinical trial in adult patients with r/r FL (ELARA Study)
  - 53% (51/97) of patients developed CRS; all were Grade 1 or 2 (Lee grading system)
- The median time to onset of CRS was 4 days (range: 1-14 days)
- The median time to resolution of CRS was 4 days (range: 1-13 days).
- Of the patients who developed CRS:
  - 29% (15/51) received systemic anticytokine treatment with tocilizumab
  - 6% (3/51) received 3 dosages of tocilizumab
  - 8% (4/51) received 2 dosages of tocilizumab
  - 16% (8/51) received 1 dosage of tocilizumab
  - 4% (2/51) received corticosteroids in addition to tocilizumab

# CRS signs and symptoms




***Diagnosis based on clinical symptoms and events***



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# CRS: associating events and organ dysfunction

| | |
|---|---|
| **Liver** | • Hepatic dysfunction: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinemia |
| **Renal** | • Renal insufficiency, may require dialysis |
| **Respiratory** | • Respiratory failure, pulmonary edema |
| **Cardiac** | • Transient cardiac insufficiency<br>• Transient arrhythmia |
| **Cytopenias lasting > 28 days** | • Avoid myeloid growth factors, particularly GM-CSF, during the first 3 weeks after KYMRIAH infusion or until CRS has resolved |

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# CRS: associating events and organ dysfunction, cont.

**Coagulopathy with hypofibrinogenemia**

- May accompany severe CRS
- Prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT), and low fibrinogen
- May result in bleeding
- Monitor coagulation panel (platelet count, PT/PTT and fibrinogen), replace as needed

# Delay KYMRIAH infusion if the patient has:

- Unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension)
- Active uncontrolled infection
- Active graft versus host disease (GVHD)
- Worsening of leukemia burden following lymphodepleting chemotherapy

# CRS: Management

- Management of CRS is based solely upon clinical presentation
- Monitor patients for signs or symptoms of CRS 2-3 times during the first week following KYMRIAH infusion at the REMS-certified healthcare facility. Monitor patients for at least 4 weeks after treatment with KYMRIAH
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time
- At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab an/or corticosteroids as indicated
- Evaluate for and treat other causes of fever, hypoxia, and hypotension (e.g. infection)
- CRS should be managed according to the KYMRIAH CRS management algorithm. Alternative CRS management strategies may be implemented based on appropriate institutional or academic guidance
- Interleukin-6 (IL-6) receptor antagonist, tocilizumab, is recommended for the management of moderate or severe CRS associated with KYMRIAH
- Before KYMRIAH infusion, verify two doses of tocilizumab are available on site for each patient and ready for immediate administration
- Due to the known lympholytic effect of corticosteroids do not use corticosteroids for premedication

# Kymriah CRS grading and management

| CRS Grade [a] | Symptomatic treatment | Tocilizumab | Corticosteroids |
|---|---|---|---|
| **Grade 1**<br>Mild symptoms requiring symptomatic treatment only (e.g., low grade fever, fatigue, anorexia, etc.) | Exclude other causes (e.g., infection) and treat specific symptoms (e.g., with antipyretics, antiemetics, analgesics, etc.) | In patients with persistent (>3 days) or refractory fever, consider managing as Grade 2 CRS [b] | Not applicable |
| **Grade 2**<br>Symptoms require and respond to moderate intervention<br>Oxygen requirement <40% or<br>Hypotension responsive to fluids or low dose of one vasopressor or<br>Grade 2 organ toxicity | Antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed | Administer tocilizumab [c] 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 after first dose, repeat every 8 hours (limit to a maximum total of 3 dosages in 24 hours period; maximum total of 4 doses) | If no improvement within 24 hours of tocilizumab, administer a daily dose of 2 mg/kg methylprednisolone intravenously (or equivalent) until vasopressor and oxygen no longer needed, then taper<br>If not improving, manage as appropriate grade below |
| **Grade 3**<br>Symptoms require and respond to aggressive intervention<br>Oxygen requirement ≥40% or<br>Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis | High-flow oxygen<br>Intravenous fluids, and high-dose or multiple vasopressors<br>Treat other organ toxicities as per local guidelines | Per Grade 2<br>If not improving, consider alternative therapy [d] | Per Grade 2<br>If not improving, manage as Grade 4 |
| **Grade 4**<br>Life-threatening symptoms<br>Requirement for ventilator support or<br>Grade 4 organ toxicity (excluding transaminitis) | Mechanical ventilation<br>Intravenous fluids and high-dose vasopressor(s)<br>Treat other organ toxicities as per local guidelines | Per Grade 2<br>If not improving, consider alternative therapy [d] | Administer methylprednisolone 1,000 mg intravenously one to two times per day for 3 days.<br>If not improving, consider methylprednisolone 1,000 mg intravenously two to three times a day or alternate therapy [d]. Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate |

[a] Lee at al. 2014
[b] Santomasso et al. 2021
[c] Refer to tocilizumab Prescribing Information for details.
[d] Alternative therapy includes anti-cytokine and anti-T cell therapies as per institutional policy and published guidelines such as (but not limited to) anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

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# CRS grading scales for CAR-T cell therapy

| Grade | Penn Grading Scale[1,2] | 2014 NCI Consensus (Lee) Grading Scale[3] | ASTCT Grading Scale[4] |
|---|---|---|---|
| 1 | • Mild reaction treated with supportive care only | • Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgias, malaise) | • Fever (temperature ≥ 38°C)<br>• No hypotension and/or hypoxia |
| 2 | • Moderate reaction requiring IV therapies or parenteral nutrition<br>• Mild signs of organ dysfunction (creatinine ≤ grade 2 or LFTs ≤ grade 3)<br>• Hospitalization for CRS or febrile neutropenia | • Symptoms require and respond to moderate intervention<br>• Oxygen requirement < 40% or hypotension responsive to fluids or low-dose pressors or grade 2 organ toxicity | • Fever (temperature ≥ 38°C)<br>• Hypotension not requiring vasopressors<br>• Hypoxia requiring low-flow (≤ 6 L/min) nasal cannula or blow-by |
| 3 | • More severe reaction requiring hospitalization<br>• Moderate signs of organ dysfunction (grade 3 creatinine or grade 4 LFTs) related to CRS<br>• Hypotension treated with IV fluids[a] or low-dose pressors<br>• Hypoxemia requiring oxygenation, BiPAP, or CPAP | • Symptoms require and respond to aggressive intervention<br>• Oxygen requirement ≥ 40% or hypotension requiring high-dose or multiple pressors or grade 3 organ toxicity or grade 4 transaminitis | • Fever (temperature ≥ 38°C)<br>• Hypotension requiring vasopressors with or without vasopressin<br>• Hypoxia requiring high-flow (> 6 L/min) nasal cannula, facemask, nonrebreather mask, or Venturi mask |
| 4 | • Life-threatening complications, including hypotension requiring high-dose vasoactives or hypoxemia requiring mechanical ventilation | • Life-threatening symptoms<br>• Requirement for ventilator support or grade 4 organ toxicity (excluding transaminitis) | • Fever (temperature ≥ 38°C)<br>• Hypotension requiring multiple vasopressors (excluding vasopressin)<br>• Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation) |
| 5 | • Death related to AE | • Death related to AE | • Death related to AE |

ASTCT, American Society for Transplantation and Cellular Therapy; AE, adverse event; BiPAP, bilevel positive airway pressure; CAR, chimeric antigen receptor; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; IV, intravenous; LFT, liver function test; NCI, National Cancer Institute.

[a] Defined as multiple fluid boluses for blood pressure support.


[1] Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139;

[2] Fitzgerald JC, et al. *Crit Care Med*. 2017;45(2):e125-e131;

[3] Lee D, et al. *Blood*. 2014;124(2):188-195;

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

# Definition of high-dose vasopressors 1-3

| | Dose ≥ 3 hours | |
|---|---|---|
| **Vasopressor** | **Weight-based dosing [a]** | **Flat dosing (if this is institutional practice)** |
| Norepinephrine monotherapy | ≥ 0.2 µg/kg/min | ≥ 20 µg/min |
| Dopamine monotherapy | ≥ 10 µg/kg/min | ≥ 1000 µg/min |
| Phenylephrine monotherapy | ≥ 2 µg/kg/min | ≥ 200 µg/min |
| Epinephrine monotherapy | ≥ 0.1 µg/kg/min | ≥ 10 µg/min |
| If no vasopressin | High dose if vasopressin + norepinephrine equivalent of ≥ 0.1 µg/kg/min (using VASST formula) [b] | Vasopressin + norepinephrine equivalent of ≥ 10 µg/min [c] |
| If no combination vasopressors (not vasopressin) | Norepinephrine equivalent of ≥ 0.2 µg/kg/min [b] | Norepinephrine equivalent of ≥ 20 µg/min (using VASST formula) [c] |

VASST Vasopressor Equivalent Equation

[a] Weight-based dosing was extrapolated by dividing the flat dosing of a vasopressor by 100.

[b] Norepinephrine-equivalent dose [body weight adjusted dosing (µg/kg/min dosing)] = [norepinephrine (µg/kg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/kg/min)] + [phenylephrine (µg/kg/min) ÷ 10] [3]

[c] Norepinephrine-equivalent dose [flat dosing (µg/min)] = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10][3]

References

1. Lee DW et al. 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 toxicities

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# Neurological toxicities

- Neurological toxicities, which may be severe or life-threatening can occur following treatment with KYMRIAH
- Major manifestations of neurological toxicities observed with KYMRIAH include encephalopathy and delirium
- The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion and were transient
- In KYMRIAH pivotal clinical trials, neurological toxicities, occurred after KYMRIAH infusion as follows:
  - In pediatric and young adult patients with r/r ALL (ELIANA Study): seen in 71% (56/79) of patients, with ≥ grade 3 in 22% (17/79) of patients
  - In adult patients with r/r DLBCL (JULIET Study): seen in 60% (69/115) of patients, with ≥ grade 3 in 19% (22/115) of patients
  - In adult patients with r/r FL (ELARA Study): seen in 43% (42/97) of patients, with ≥ Grade 3 in 6% (6/97)
- All patients with r/r ALL and the majority of patients with r/r DLBCL and r/r FL were treated with supportive care alone.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIAH are trained about the management of neurological toxicities.

# Neurological toxicities, cont.

| | |
|---|---|
| **Monitoring** | • Monitor patients for neurological events |
| **Types of neurological toxicities** | • Early: concurrent with CRS and high fevers during the development and at the time of maximal grade of CRS<br>• Delayed onset: as CRS is resolving or following the resolution of CRS<br>• In the absence of CRS |
| **Onset and duration** | • The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion<br>• The majority of events were transient |
| **Clinical presentation** | • Major manifestations of neurological toxicities observed with KYMRIAH include encephalopathy, delirium or related events<br>• Anxiety, dizziness, headache, peripheral neuropathy, and sleep disorders were the other most common neurological toxicities<br>• Other related manifestations: seizures, and aphasia<br>• The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS |



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# Neurological toxicities, cont.

| | |
|---|---|
| **Diagnostic work-up** | • Neurological work-up should be considered, as appropriate, to exclude other causes for neurological symptoms |
| **Management** | • Supportive care should be given for KYMRIAH-associated neurological toxicities |
| **Patients / guardians education** | • Patients/guardians:<br>  • Should be advised about the risk and symptoms of neurological toxicities that they may experience<br>  • Should carry the KYMRIAH patient wallet card to remind them of the signs and symptoms of neurological toxicities that require immediate attention<br>  • Should contact their healthcare professional if experiencing signs and symptoms of neurological toxicities<br>  • Refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving KYMRIAH. |

# Kymriah ICANS grading and management

| ICANS Grade[a] | No concurrent CRS | Concurrent CRS |
|---|---|---|
| **Grade 1**<br>ICE score [b]: 7-9 with no depressed level of consciousness | Offer supportive care with intravenous hydration and aspiration precautions | Administer tocilizumab at any grade CRS, as per dosage recommendation in Table 1. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose [c] |
| **Grade 2**<br>ICE score [b]: 3-6<br>and/or<br>Mild somnolence awaking to voice | Supportive care as above<br>Consider dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours) until the event is Grade 1 or less. If improving, taper corticosteroids | Administer tocilizumab at any grade CRS, as per dosage recommendation in Table 1. If refractory to tocilizumab past the first dose, administer dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours) until the event is Grade 1 or less, then taper corticosteroids |
| **Grade 3**<br>ICE score [b]: 0-2*<br>and/or<br>Depressed level of consciousness awakening only to tactile stimulus<br>and/or<br>Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention<br>and/or<br>Focal or local edema on neuroimaging | Administer dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours) | Administer tocilizumab at any grade CRS, as per dosage recommendation in Table 1. Administer dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours). Continue corticosteroids until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4 |
| **Grade 4**<br>ICE score [b]: 0* (patient is unarousable and unable to perform ICE)<br>and/or<br>Stupor or coma<br>and/or<br>Life-threatening prolonged seizure (>5 minutes) or repetitive clinical or electrical seizures without return to baseline in between<br>and/or<br>Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing's triad | Consider mechanical ventilation for airway protection<br>Administer high-dose methylprednisolone intravenously 1,000 mg one to two times per day for 3 days<br>If not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy [d]<br>Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate<br>Treat seizures, status epilepticus, and cerebral edema as per institutional guidelines | Administer tocilizumab at any grade CRS, as per dosage recommendation in Table 1. Administer methylprednisolone 1000 mg intravenously one to two times per day for 3 days.<br>If not improving, consider methylprednisolone 1,000 mg intravenously two to three times per day or alternate therapy [d]. Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate.<br>Treat seizures, status epilepticus, and cerebral edema as per institutional guidelines |

[a] ASTCT criteria for grading NT (Lee et al 2019); NCI CTCAE criteria for grading NT used in clinical trials.
[b] ICE Assessment Tool: (1) Orientation: orientation to year, month, city, and hospital: 4 points. (2) Naming: ability to name three objects (e.g., point to clock, pen, and button): 3 points. (3) Following commands: ability to follow simple commands (e.g., show me 2 fingers or close your eyes and stick out your tongue): 1 point. (4) Writing: ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point. (5) Attention: ability to count backward from 100 by 10: 1 point.
[c] Santomasso et. al. 2021
[d] Alternate therapy may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, antithymocyte globulin, or intrathecal hydrocortisone (50 mg) plus methotrexate (12 mg)
*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

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# Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)

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# HLH/MAS

- HLH/MAS occurred in 6% (5/79) of patients with r/r ALL. All HLH events occurred during ongoing CRS and resolved.
  - Time to onset ranged from 3 – 18 days
- HLH/MAS occurred in 2% (2/115) of patients with r/r DLBCL. All HLH events occurred during ongoing CRS and resolved.
  - Times to onset were Day 7 and Day 10
- 1% (1/97)patient with r/r FL developed HLH > 1 year after receiving KYMRIAH with a fatal outcome. The patient did not have CRS during or immediately preceding HLH.
- Presenting signs and symptoms of HLH/MAS are similar to those of CRS and infections
- Treatment of HLH/MAS should be administered per institutional standards

# Patients / Guardians Education

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# Patients/Guardians education

Advise patients/guardians of the risks of CRS and neurological toxicities and to contact their healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities

Patients/guardians should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving KYMRIAH treatment, unless otherwise indicated by the doctor

Patients/guardians should carry KYMRIAH patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention

Refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving KYMRIAH

# Reporting Adverse Events

Healthcare providers are encouraged to report suspected adverse events of Kymriah® to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at www.report.novartis.com or by calling 1-888-669-6682.

- When reporting adverse events, healthcare providers should always include the individual Kymriah Batch-identification number.

For further information, please visit www.KYMRIAH-REMS.com or call 1-844-4KYMRIAH(1-844-459-6742)

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