Risk Evaluation and Mitigation Strategy (REMS) Document

Kymriah (tisagenlecleucel) REMS Program

I. Administrative Information

Application Number: BLA 125646
Application Holder: Novartis Pharmaceuticals Corporation
Initial REMS Approval: 8/2017
Most Recent REMS Update: 05/2022

II. 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 cytokine release syndrome and neurological toxicities.

III. REMS Requirements

Novartis must ensure that hospitals and their associated clinics, and patients comply with the following requirements:

1. Hospitals and their associated clinics that dispense Kymriah must:

   To become certified to dispense

   1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).

   2. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the hospital and their associated clinics.

   3. Have the authorized representative take the Live Training Program provided by the REMS Program.

   4. Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS Program.

   5. Have the authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form and submitting it to the REMS program.

   6. Train all relevant staff involved in prescribing, dispensing, or administering of Kymriah on the REMS Program requirements using the Live Training Program.

   7. Have all relevant staff involved in prescribing, dispensing, or administering successfully complete the Knowledge Assessment.
8. Establish processes and procedures to ensure new staff involved in the prescribing, dispensing, or administration of Kymriah are trained and complete the Knowledge Assessment.

9. Establish processes and procedures to verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).

10. Establish processes and procedures to provide patients with the Patient Wallet Card.

| Before infusion | 11. Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours) through the processes and procedures established as a requirement of the REMS Program. |
| Before discharge | 12. Provide the patient with the Patient Wallet Card through the processes and procedures established as a requirement of the REMS Program. |

To maintain certification to dispense, if there is a change in authorized representative

| 13. Have the new authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form. |

To maintain certification to dispense, if Kymriah has not been dispensed at least once annually from the date of certification in the REMS Program

| 14. Train all relevant staff involved in prescribing, dispensing, or administering of Kymriah on the REMS Program requirements using the Live Training Program. |
| 15. Have all relevant staff involved in prescribing, dispensing, or administering successfully complete the Knowledge Assessment. |
At all times | 16. Report any adverse events suggestive of cytokine release syndrome or neurological toxicities to the REMS Program.

| 17. Maintain records of staff training. |

| 18. Maintain records that all processes and procedures are in place and are being followed. |

| 19. Comply with audits carried out by Novartis or a third party acting on behalf of Novartis to ensure that all processes and procedures are in place and are being followed. |

| 2. Patients who are dispensed Kymriah: |

| Before discharge | 1. Receive the Patient Wallet Card. |
Novartis must provide training to hospital staff who prescribe, dispense, or administer Kymriah.

The training includes the following educational materials: Live Training Program and Knowledge Assessment. The training must be provided in-person or live webcast.

To support REMS Program operations, Novartis must:

1. Ensure Kymriah is only distributed to certified hospitals and their associated clinics.

2. Establish and maintain a REMS Program website, www.Kymriah-REMS.com. The REMS Program website must include the option to print the PI, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website.

3. Make the REMS Program website fully operational and all REMS materials available through website or call center.

4. Establish and maintain a REMS Program call center for REMS participants at 1-844-459-6742.

5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.

6. Ensure hospitals and their associated clinics are able to enroll in the REMS Program in person, online, fax, and phone.

7. Notify hospitals and their associated clinics after they become certified in the REMS Program.

To ensure REMS participants’ compliance with the REMS Program, Novartis must:

8. Verify annually that the designated authorized representative for certified hospitals and associated clinics remains the same. If different, the hospital and their associated clinics must re-certify with a new authorized representative.

9. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Kymriah distribution and dispensing; certification of hospitals and their associated clinics, and audits of REMS participants. These records must be readily available for FDA inspections.

10. Monitor hospitals and their associated clinics on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.

11. Maintain an ongoing annual audit plan of hospitals and their associated clinics.

12. Audit all hospitals and their associated clinics no later than 180 calendar days after the hospital places its first order of Kymriah to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Certified hospitals and their associated clinics must also be included in Novartis’ ongoing annual audit plan.

13. Take reasonable steps to improve implementation of and compliance with the requirements in the Kymriah REMS Program based on monitoring and evaluation of the Kymriah REMS Program.
IV. REMS Assessment Timetable

Novartis must submit REMS Assessments to the FDA at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS (8/30/2017). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Novartis must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Kymriah REMS:

**Enrollment Forms:**

Health Care Setting:

1. Hospital Enrollment Form

**Training and Educational Materials**

Patient:

2. Patient Wallet Card

Health Care Setting:

3. Live Training Program
4. Knowledge Assessment

**Other Materials**

5. REMS Program website
Kymriah is only available through the Kymriah Risk Evaluation and Mitigation Strategy (REMS) Program. Hospitals and their associated clinics that dispense Kymriah must be certified in the Kymriah REMS Program. In order to become specially certified to dispense Kymriah, hospitals and associated clinics must designate an Authorized Representative to:

• Complete the certification process by completing this Kymriah REMS Program Hospital Enrollment Form on behalf of the hospital and their associated clinics.
• Oversee implementation and compliance with the Kymriah REMS Program requirements as outlined below.

Please complete all required fields below and submit this enrollment form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com. You will receive a confirmation via E-mail.

If you have any questions, require additional information, or need further copies of any of the Kymriah REMS Program documents, please visit the REMS program website at www.Kymriah-REMS.com, or call the Kymriah REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742).

Authorized Representative Responsibilities

On behalf of my hospital/associated clinics, I understand and agree to comply with the following Kymriah REMS Program requirements:

• I must complete the Kymriah REMS Live Training Program and successfully complete the Kymriah REMS Program Knowledge Assessment.
• Those participating in Kymriah clinical trials and/or the pre-approval safety training will be exempt from the live training but will be required to review the REMS materials on the REMS website.
• I must submit this completed Kymriah REMS Program Hospital Enrollment Form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
• I must submit the completed Kymriah REMS Program Knowledge Assessment form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
• I will oversee implementation and compliance with the Kymriah REMS Program.
• I will ensure that my hospital and associated clinics will establish processes and procedures that are subject to monitoring by Novartis Pharmaceuticals Corporation (NPC), or a third party acting on behalf of NPC to help ensure compliance with the requirements of the Kymriah REMS Program, including the following, before administering Kymriah:
  a. Ensuring all relevant staff involved in the prescribing, dispensing or administering of Kymriah are trained on the REMS Program requirements and successfully complete the Kymriah REMS Program Knowledge Assessment, and maintain records of staff training.
  b. Performing routine re-education of all staff involved in the prescribing, dispensing or administering of Kymriah and maintaining records of re-training if Kymriah has not been dispensed at least once annually from the date of certification in the Kymriah REMS Program.
  c. Prior to dispensing Kymriah, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on site for each patient and are ready for immediate administration (within 2 hours).
  d. Before discharge, provide patients and their legal guardians the Patient Wallet Card.
As a condition of certification, the certified hospital must:

- Ensure that if the hospital designates a new authorized representative, the new authorized representative must review the Kymriah REMS Live Training Program, complete the Kymriah REMS Program Knowledge Assessment, complete a new Kymriah REMS Program Hospital Enrollment Form and submit the forms via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
- Report any adverse events suggestive of cytokine release syndrome or neurological toxicities of Kymriah to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at https://psi.novartis.com or 1-888-669-6682.
- Dispense Kymriah to patients only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
- Maintain documentation of all processes and procedures for the Kymriah REMS Program and provide 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.

**Hospital Information (All Fields Required)**

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Name</td>
<td></td>
</tr>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>City</td>
<td></td>
</tr>
<tr>
<td>State</td>
<td></td>
</tr>
<tr>
<td>Zip Code</td>
<td></td>
</tr>
<tr>
<td>Phone</td>
<td></td>
</tr>
<tr>
<td>Fax</td>
<td></td>
</tr>
</tbody>
</table>

**Authorized Representative Information (All Fields Required)**

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Name</td>
<td></td>
</tr>
<tr>
<td>Last Name</td>
<td></td>
</tr>
<tr>
<td>Credentials</td>
<td></td>
</tr>
<tr>
<td>DO</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td></td>
</tr>
<tr>
<td>R.Ph</td>
<td></td>
</tr>
<tr>
<td>NP/PA</td>
<td></td>
</tr>
<tr>
<td>Other (please specify)</td>
<td></td>
</tr>
<tr>
<td>Phone</td>
<td></td>
</tr>
<tr>
<td>Fax</td>
<td></td>
</tr>
<tr>
<td>E-mail</td>
<td></td>
</tr>
</tbody>
</table>

**Next Steps**

1. Please complete all required fields above and submit this enrollment form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com. You will receive a confirmation via E-mail.
2. Completion of this form does not guarantee your hospital will be certified to administer Kymriah.
3. NPC will assess and provide confirmation of certification via E-mail after processing this enrollment form and a successfully completed Kymriah REMS Program Knowledge Assessment form.
4. Product orders cannot be placed until hospital certification is complete.
PATIENT WALLET CARD

Have This Card With You At All Times
Show It To Any Doctor That Sees You And When You Go To The Hospital

You should plan to stay within 2 hours of the location where you received your treatment for at least 4 weeks after getting Kymriah. Your healthcare provider will check to see if your treatment is working and help you with any side effects that occur.
INFORMATION FOR THE HEALTHCARE PROVIDER

This patient has received Kymriah (CAR-T cell) therapy

Following Kymriah treatment, Cytokine Release Syndrome (CRS) can happen. It may include neurological toxicities.

Please contact his/her treating oncologist in the following situations:

• before giving steroids or cytotoxic medications
• if the patient has a serious infection
• before the patient undergoes an invasive procedure

Date received Kymriah: __________________________

Oncologist Name (for Kymriah therapy): __________________________

Phone Number: __________________________

Kymriah 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 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. r/r FL 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 benefits in confirmatory trial(s).

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

KYMRIAH
(tisagenlecleucel) Suspension for Intravenous Use
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 KYMRIAHS outweigh its risks.

The purpose of the KYMRIAHS REMS is to inform healthcare providers of the risks of cytokine release syndrome and neurological toxicities observed with KYMRIAHS.
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).
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 KYMRIAHI 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 KYMRIAHI 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 KYMRIAHI REMS Program.
• Dispense KYMRIAHI only after verifying that a minimum of two doses of tocilizumab are available on-site for each patient for administration within 2 hours.
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
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)
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
- 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
- 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 KYMRIA AH 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

Myalgia, arthralgia
Nausea, vomiting, anorexia, diarrhea
Rash
Fatigue
Diaphoresis
Headache
Hypotension
Dyspnea, tachypnea, hypoxia
High fever
Rigors

Diagnosis based on clinical symptoms and events
CRS: associating events and organ dysfunction

- Hepatic dysfunction: elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
- Renal insufficiency: may require dialysis
- Respiratory failure, pulmonary edema
- Transient arrhythmia
- Transient cardiac insufficiency
- Cytopenias

Avoid myeloid growth factors, particularly GM-CSF, during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.

Liver lasts > 28 days

Cardiac

Respiratory

Renal
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
<table>
<thead>
<tr>
<th>CRS Grade*</th>
<th>Symptomatic treatment</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild symptoms requiring symptomatic treatment only (e.g., low grade fever, fatigue, anorexia, etc.)</td>
<td>Exclude other causes (e.g., infection) and treat specific symptoms (e.g., with antipyretics, antiemetics, analgesics, etc.)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| Grade 2   | Symptoms require and respond to moderate intervention                                    | Antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed | Administer tocilizumab intravenously over 1 hour:  
- 8 mg/kg (max. 800 mg) if body weight ≥30 kg  
- 12 mg/kg if body weight < 30 kg if no improvement 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  
If not improving, manage as appropriate grade below |
| Grade 3   | Symptoms require and respond to aggressive intervention                                  | High-flow oxygen  
Intravenous fluids, and high-dose or multiple vasopressors  
Treat other organ toxicities as per local guidelines | Per Grade 2  
If not improving, consider alternative therapy | Per Grade 2  
If not improving, manage as Grade 4 |
| Grade 4   | Life-threatening symptoms  
Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis) | Mechanical ventilation  
Intravenous fluids and high-dose vasopressor(s)  
Treat other organ toxicities as per local guidelines | Per Grade 2  
If not improving, consider alternative therapy | Administer methylprednisolone 1,000 mg intravenously one to two times per day for 3 days.  
If not improving, consider methylprednisolone 1,000 mg intravenously two to three times a day or alternate therapy.  
Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate |

*Lee et al. 2014  
Santomasso et al. 2021  
Refer to tocilizumab Prescribing Information for details.  
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.
## CRS grading scales for CAR-T cell therapy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Penn Grading Scale$^{1,2}$</th>
<th>2014 NCI Consensus (Lee) Grading Scale$^{3}$</th>
<th>ASTCT Grading Scale$^{4}$</th>
</tr>
</thead>
</table>
| 1     | • Mild reaction treated with supportive care only | • Symptoms are not life-threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgias, malaise) | • Fever (temperature ≥ 38°C)  
|       | • Moderate reaction requiring IV therapies or parenteral nutrition  
|       | • Mild signs of organ dysfunction (creatinine ≤ grade 2 or LFTs ≤ grade 3)  
|       | • Hospitalization for CRS or febrile neutropenia | • Symptoms require and respond to moderate intervention  
|       | • Oxygen requirement < 40% or hypotension responsive to fluids or low-dose pressors or grade 2 organ toxicity | • Fever (temperature ≥ 38°C)  
|       | • Hypotension not requiring vasopressors  
|       | • Hypoxia requiring low-flow (≤ 6 L/min) nasal cannula or blow-by | • Hypotension requiring vasopressors with or without vasopressin  
| 2     | • More severe reaction requiring hospitalization  
|       | • Moderate signs of organ dysfunction (grade 3 creatinine or grade 4 LFTs) related to CRS  
|       | • Hypotension treated with IV fluids$^a$ or low-dose pressors  
|       | • Hypoxemia requiring oxygenation, BiPAP, or CPAP | • Hypoxia requiring high-flow (> 6 L/min) nasal cannula, facemask, nonrebreather mask, or Venturi mask  
|       | • Hypotension requiring vasopressors with or without vasopressin  
|       | • Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation) | |  
| 3     | • Life-threatening complications, including hypotension requiring high-dose vasoactives or hypoxemia requiring mechanical ventilation | • Life-threatening symptoms  
|       | • Requirement for ventilator support or grade 4 organ toxicity (excluding transaminitis) | • Death related to AE  
| 4     | • 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.


Definition of high-dose vasopressors 1-3

<table>
<thead>
<tr>
<th>Vasopressor</th>
<th>Weight-based dosing (^a)</th>
<th>Flat dosing (if this is institutional practice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine monotherapy</td>
<td>≥ 0.2 µg/kg/min</td>
<td>≥ 20 µg/min</td>
</tr>
<tr>
<td>Dopamine monotherapy</td>
<td>≥ 10 µg/kg/min</td>
<td>≥ 1000 µg/min</td>
</tr>
<tr>
<td>Phenylephrine monotherapy</td>
<td>≥ 2 µg/kg/min</td>
<td>≥ 200 µg/min</td>
</tr>
<tr>
<td>Epinephrine monotherapy</td>
<td>≥ 0.1 µg/kg/min</td>
<td>≥ 10 µg/min</td>
</tr>
<tr>
<td>If no vasopressin</td>
<td>High dose if vasopressin + norepinephrine equivalent of ≥ 0.1 µg/kg/min (using VASST formula) (^b)</td>
<td>Vasopressin + norepinephrine equivalent of ≥ 10 µg/min (^c)</td>
</tr>
<tr>
<td>If no combination vasopressors (not vasopressin)</td>
<td>Norepinephrine equivalent of ≥ 0.2 µg/kg/min (^b)</td>
<td>Norepinephrine equivalent of ≥ 20 µg/min (using VASST formula) (^c)</td>
</tr>
</tbody>
</table>

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

neurological toxicities

KYMRIAH-associated
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.

### Types of neurological toxicities
- Early: concurrent with CRS and high fevers during the development and at the time of maximal grade of CRS
- Delayed onset: as CRS is resolving or following the resolution of CRS
- In the absence of CRS

### Onset and duration
- The majority of neurological toxicities occurred within 8 weeks following KYMRIAHM infusion
- The majority of events were transient

### Clinical presentation
- Major manifestations of neurological toxicities observed with KYMRIAHM include encephalopathy, delirium or related events
- Anxiety, dizziness, headache, peripheral neuropathy, and sleep disorders were the other most common neurological toxicities
- Other related manifestations: seizures, and aphasia
- The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS

### Monitoring
- Monitor patients for neurological events
### Neurological toxicities, cont.

<table>
<thead>
<tr>
<th>Diagnostic work-up</th>
<th>• Neurological work-up should be considered, as appropriate, to exclude other causes for neurological symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management</td>
<td>• Supportive care should be given for KYMRIAH-associated neurological toxicities</td>
</tr>
</tbody>
</table>
| Patients / guardians education | • Patients/guardians:  
  • Should be advised about the risk and symptoms of neurological toxicities that they may experience  
  • Should carry the KYMRIAH patient wallet card to remind them of the signs and symptoms of neurological toxicities that require immediate attention  
  • Should contact their healthcare professional if experiencing signs and symptoms of neurological toxicities  
  • 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

<table>
<thead>
<tr>
<th>ICANS Grade*</th>
<th>No concurrent CRS</th>
<th>Concurrent CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>ICE score:(b): 7-9 with no depressed level of consciousness</td>
<td>Offer supportive care with intravenous hydration and aspiration precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>ICE score:(b): 3-6 and/or Mild somnolence awaking to voice</td>
<td>Supportive care as above</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>ICE score:(b): 0-2* and/or Depressed level of consciousness awakening only to tactile stimulus and/or Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention and/or Focal or local edema on neuroimaging</td>
<td>Administer dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg intravenously every 12 hours).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>ICE score:(b): 0* (patient is unarousable and unable to perform ICE) and/or Stupor or coma and/or Life-threatening prolonged seizure (&gt;5 minutes) or repetitive clinical or electrical seizures without return to baseline in between and/or Diffuse cerebral edema on neuroimaging, decerebrate or decorticative posturing or papilledema, cranial nerve VI palsy, or Cushing’s triad</td>
<td>Consider mechanical ventilation for airway protection Administer high-dose methylprednisolone intravenously 1,000 mg one to two times per day for 3 days. If not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy. Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate. Treat seizures, status epilepticus, and cerebral edema as per institutional guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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. If not improving, consider methylprednisolone 1,000 mg intravenously two to three times per day or alternate therapy. Continue corticosteroids until improvement to Grade 1, and then taper as clinically appropriate. Treat seizures, status epilepticus, and cerebral edema as per institutional guidelines</td>
</tr>
</tbody>
</table>

---

* 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.

*Santomasso et. al. 2021

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

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)
References

- Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric. The University of Texas MD Anderson Cancer Center website
  Published January 30, 2018. Accessed March 4, 2019. The pediatric guideline was approved by the Executive Committee of the Medical Staff on 1/30/2018.


REMS PROGRAM KNOWLEDGE ASSESSMENT

Hospital Information (All Fields Required)

Hospital Name:

Address:

City: State: Zip Code:

Phone: Fax:

First Name: Last Name:

Credentials: DO MD R.Ph NP/PA Other (please specify)

Phone: Fax: E-mail:

Authorized Representative: Yes No

Signature: Date (MM/DD/YYYY):

If you are the Authorized Representative for your hospital, please complete and submit the knowledge assessment to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com, or complete online at www.Kymriah-REMS.com. All others please complete online or send the form to your hospital’s Authorized Representative. Completion of this knowledge assessment does not guarantee your hospital will be certified to administer Kymriah®.

1- Kymriah® (tisagenlecleucel) is indicated for the treatment of:
   - A- Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
   - B- Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 2nd or later relapse
   - C- Adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)
   - D- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
   - E- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy
   - F- All except A and C

2- Delay Kymriah infusion if the patient has any of the following, except:
   - A- Active uncontrolled infection
   - B- Worsening of leukemia burden following lymphodepleting chemotherapy
   - C- Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
   - D- Active graft versus host disease
   - E- Unresolved serious adverse reactions from preceding chemotherapies

3- Clinically, patients with CRS can manifest with the following signs and symptom except:
   - A- High grade fever
   - B- Hypotension
   - C- Hair loss
   - D- Respiratory distress
   - E- Hypofibrinogenemia

4- Which one of the following is true regarding the time to onset of CRS? It typically occurs:
   - A- 7-14 days following Kymriah infusion, with a median time to onset of 10 days
   - B- 7-21 days following Kymriah infusion, with a median time to onset of 10 days
   - C- Median time to onset is 3-4 days following Kymriah infusion
   - D- Rarely starts during the first week following Kymriah infusion
5- As a part of planning for Kymriah infusion, it is required to have on-site, immediate access (within 2 hours) to a minimum of two doses of tocilizumab on site for each patient prior to dispensing and administering Kymriah to patients:
- A- True
- B- False

6- As a part of the patient and caregiver education for Kymriah, advise the patient to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving Kymriah:
- A- True
- B- False

7- A 5-year-old male with relapsed ALL following an allogeneic transplantation was treated with Kymriah. One day following infusion, he developed high grade fever (40-41°C) with neutropenia and was hospitalized. On day 2, he developed hypotension, which improved with fluid resuscitation. He was transferred to the PICU for close observation, and later developed recurrent hypotension, mild tachypnea and hypoxia (O₂ saturation 91%). He was started on norepinephrine at a low dose and O₂ supplement via nasal cannula. All of the following are correct, except:
- A- The patient has symptoms consistent with cytokine release syndrome and should be managed according to the CRS management algorithm
- B- Sepsis should be considered and treated adequately with broad spectrum antibiotics
- C- Avoid antipyretics as they may affect CAR-T cell efficacy
- D- Continue supportive care and close monitoring of hemodynamic, respiratory and neurological status

8- Neurological toxicities were observed with Kymriah, and the patient and the caregiver should be informed about this risk. All of the following are correct, except:
- A- May occur in the context of CRS, following the resolution of CRS or without CRS
- B- Symptoms range from headache and confusion to encephalopathy and seizures
- C- The majority of events were transient and self-limiting
- D- Can be prevented with the administration of tocilizumab

9- Which one of the following about neurological toxicities as a result of Kymriah is correct:
- A- Perform neurological work-up as appropriate to exclude other etiologies of neurological symptoms
- B- Management includes supportive care
- C- Majority occurred within 8 weeks following Kymriah infusion
- D- All of the above

10- A 30-year-old female with multiply relapsed DLBCL treated with Kymriah as an outpatient 2 days after completion of lymphodepleting chemotherapy. The patient and her caregiver should be advised about the following:
- A- The risk of CRS and neurological toxicities and to contact the healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
- B- The patient should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving Kymriah
- C- The patient should carry the Kymriah patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention
- D- All of the above

11. A 22-year-old male with relapsed/refractory Philadelphia chromosome negative B cell Acute Lymphoblastic Leukemia (ALL) developed grade 1 cytokine release syndrome (CRS) 6 hours after treatment with KYMRIAH, progressing to Grade 2 CRS on day 2. The patient was treated with two doses of tocilizumab, following which rapid clinical improvement was noted. On day 11, he presented with new fever and need for high oxygen therapy. His labs showed impaired renal and hepatic functions, along with coagulopathy and elevated ferritin.
Given the current clinical signs and symptoms, an evaluation for Hemophagocytic Lymphohistiocytosis/Macrophage activation syndrome (HLH/MAS) should be performed.
- A- True
- B- False
Risk Evaluation and Mitigation Strategy (REMS)

REMS Safety Information

A Risk Evaluation and Mitigation Strategy (REMS) is a program to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. The FDA has required a REMS for Kymriah® (tisagenlecleucel).

BOXED 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.

Goals of the REMS

The goals of the Kymriah® (tisagenlecleucel) 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 cytokine release syndrome and neurological toxicities.

Kymriah is only available at select treatment centers. For more information, please call the REMS Call Center at 1-844-459-6742.

To learn more about Kymriah and its serious risks and clinical manifestations, read the Prescribing Information and the Medication Guide.

The Kymriah REMS Program Patient Wallet Card (English and Spanish), the Kymriah REMS Live Training Program Slides, and Kymriah REMS Program Knowledge Assessment can be ordered through the REMS Call Center at 1-844-459-6742.

You are encouraged to report suspected adverse events with Kymriah to Novartis at www.report.novartis.com or 1-888-669-6682 or the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

Continue to check back on this website; it will be updated to include additional or new information intended to assist in the proper communication of the serious risks associated with Kymriah.

Click here to complete the Knowledge Assessment, Hospital Enrollment, or Audit Questionnaire online.
Please enter your Hospital ID and click on "Continue". If you have not been assigned a Hospital ID, please contact the KYMRIAH REMS Program at 1-844-4KYMRIAH (1-844-459-6742).

Hospital Information

Hospital ID:

Continue
Please proceed as follows:

- **Knowledge Assessment**: Please use the Training Assessment link below to navigate to the online training and Knowledge Assessment.
- **Hospital Enrollment**: If you are the Authorized Representative for your Hospital and you have not yet completed an Enrollment Form, please use the Hospital Enrollment link below to navigate to the online hospital enrollment form.
- **Audit**: If you received a notification to complete your first order or annual audit, please select the Audit link below.

If you are not sure if you have previously completed the training assessment or your Hospital Enrollment form, or if you have questions regarding the audit request, please contact the Kymria REMS Program at 1-844-4KYMRIAH.
KYMRIAH® REMS Program Audit

Please enter the required information and select "Submit".

If you have not been assigned a REMS ID, please contact the KYMRIAH REMS Program at 1-844-4KYMRIAH (1-844-459-6742).

This is where any error message will display

REMS ID

Email Address

Submit
KYMRIAH® REMS Audit

Novartis Kyrmiah Risk Evaluation & Mitigation Strategy (REMS) Audit Questionnaire
Questionnaire Type: First Order

The Authorized Representative of the Kyrmiah REMS Program must complete this audit questionnaire within 45 days of receipt.

Completion of the audit questionnaire is a requirement of the Kyrmiah REMS Program in order to ensure all processes and procedures are in place and functioning to support the requirements of the Kyrmiah REMS Program.

Failure to complete this questionnaire could result in the de-certification of your hospital. If you have any questions about the questionnaire or the Kyrmiah REMS Program, please call 1-844-4KYMRIA (1-844-459-6742).

NOTE: The Authorized Representative/Hospital Information section of this form has been pre-populated. If any information listed is incorrect, please call 1-844-4KYMRIA (1-844-459-6742).

To submit this form, please complete the fields below. Required fields are denoted by ***.

Authorized Representative Information:

Authorized Representative Name: John Smith
Authorized Representative Credentials: MD
Authorized Representative Phone Number: 555 555-1212
Authorized Representative Email Address: 555 555-3434

Hospital Information:

Hospital Name: ABC Hospital
Hospital Address Line 1: 123 Main Street
Hospital Address Line 2:
City: Philadelphia
State: PA
Zip Code: 99999

Hospital Certification Date in the REMS: 5/5/2020
Hospital REMS ID: 12345
Date of first order placed for Kyrmiah**: 1/1/2020
**Date based on order shipped date

Authorized Representative Responsibilities:

* 1) Have there been any changes to the Authorized Representative since the hospital was initially certified?
   - Yes
   - No

* 2) Is there a training log available that tracks training for all relevant staff involved in the prescribing (for purposes of this REMS, "prescribing" includes medication orders), dispensing, or administering of Kyrmiah?
   - Yes
   - No

Verification of processes, procedures, or other measures for the dispensing and administration of Kyrmiah within the Kyrmiah REMS Program:

DO YOU HAVE DOCUMENTATION FOR THE FOLLOWING?

* 3) Processes and procedures to ensure new staff involved in prescribing, dispensing, or administering of Kyrmiah are trained:
   - Yes
   - No

* 4) Processes in place for routine re-education of all staff involved in the prescribing, dispensing, or administering of Kyrmiah if Kyrmiah has not been dispensed at least once annually from the date of certification in the Kyrmiah REMS Program:
   - N/A
   - Yes
   - No

* 5) Documentation that a minimum of two doses of tocilizumab are being available on-site, prior to dispensing Kyrmiah for each patient and ready for immediate administration (within 2 hours):
   - Yes
   - No

* 6) Processes in place to ensure patients and their guardians are being provided with the Kyrmiah REMS Program Patient Wallet Card before discharge?
   - Yes
   - No

* 7) Processes in place to ensure any adverse events suggestive of cytokine release syndrome or neurological toxicities are reported?
   - Yes
   - No

Delays in obtaining tocilizumab:

* Were there any delays in obtaining tocilizumab?
   - Yes
   - No

I certify, as the Authorized Representative on the Kyrmiah REMS Program for my hospital, that I have completed this audit questionnaire to the best of my knowledge:

☐ * Signature of Authorized Representative

Submit
KYMRIAH® REMS Audit

Novartis Kymriah Risk Evaluation & Mitigation Strategy (REMS) Audit Questionnaire
Questionnaire Type: First Order

The Authorized Representative of the Kymriah REMS Program must complete this audit questionnaire within 45 days of receipt.

Compliance with the audit procedures as a requirement of the Kymriah REMS Program is in order to ensure all processes and procedures are in place and functioning to support the requirements of the Kymriah REMS Program.

Failure to complete this questionnaire could result in the de-registration of your facility. If you have any questions about this postmarket or the Kymriah REMS Program, please call 1-844-4KYMRIAH (1-844-459-6742).

NOTES: (The Authorized Representative/Hospital Information section of this form has been pre-populated. If any information listed is incorrect, please call 1-844-4KYMRIAH (1-844-459-6742).

To submit this form, please complete the fields below. Required fields are denoted by "**".

Authorized Representative Information:

Authorized Representative Name: John Smith
Authorized Representative Credentials: MD
Authorized Representative Phone Number: 555-555-2323
Authorized Representative Email Address: 555-555-3343

Hospital Information:

Hospital Name: ABC Hospital
Hospital Address Line 1: 123 Main Street
City/County: XYZ
State/Province: IL
Zip Code: 60606
Hospital Certification Date in the REMS: 1/1/2020
Hospital REMS ID: 12345
Contact Information:
Hospital REMS ID: 12345
Date of first order placed for Kymriah**: 1/1/2020

Authorized Representative Responsibilities:

** Did the facility ever change the Authorized Representative since the hospital was initially certified?**

* No
* Yes

** Previously Authorized Representative First Name:**

** Previously Authorized Representative Last Name:**

Add Another Previous Authorized Representative:

** Is there a training log available that tracks training for all relevant staff involved in the prescribing of this product?**

* Yes
* No

** Is there a training log available that tracks training for all relevant staff involved in the prescribing of this product?**

* Yes
* No

If no training log is available, include: training schedule, training calendar, or training notes.

Verification of processes, procedures, or other measures for the dispensing and administration of Kymriah within the Kymriah REMS Program:

DO YOU HAVE DOCUMENTATION FOR THE FOLLOWING?

** Processes and procedures to ensure no staff involved in prescribing, dispensing, or administering of Kymriah are trained?**

* Yes
* No

** Please provide documentation with this completed form.**

** Processes in place for review in education of all staff involved in the prescribing, dispensing, or administering of Kymriah? If Kymriah has not been dispensed at least once annually from the date of certification in the Kymriah REMS Program?**

* Yes
* No

** Documentation that exists of at least one of the following: training calendars, training notes, training records.**

* Yes
* No

** Processes in place for patients and their guardians are being provided with the Kymriah REMS Program Patient Information Card before discharge?**

* Yes
* No

** Processes in place to ensure any adverse events suggestive of cytokine release syndrome or neurological side effects are reported?**

* Yes
* No

** Please provide further information here.**

Delays in obtaining tocilizumab:

** Were there any delays in obtaining tocilizumab?**

* Yes
* No

** Please provide further information here.**

PLEASE UPLOAD THE REQUIRED DOCUMENTATION FOR DOCUMENTATION-RELATED QUESTIONS ANSWERED "YES" ABOVE.

Ensure, as the Authorized Representative on the Kymriah REMS Program for my hospital, that I have completed this audit questionnaire to the best of my knowledge:

* Signature of Authorized Representative

Submit
KYMRIAH® REMS Audit

Novartis Kyriah Risk Evaluation & Mitigation Strategy (REMS) Audit Questionnaire

Questionnaire Type: First Order

The Authorized Representative of the Kyriah REMS Program must complete this audit questionnaire on the 45th day of receipt. Completion of the audit questionnaire is a requirement of the Kyriah REMS Program. In order for processes and procedures to be in place and functioning, the support of the Kyriah REMS Program may be required. Follow the instructions on the reverse side of the questionnaire. If you have any questions about the questionnaire or the Kyriah REMS Program, please call 1-844-999-5069 (MON-FRI 8:30-5:00).

NOTE: The Authorized Representative’s Hospital Certification is complete for 30 days. If any information listed is incorrect, please call 1-844-999-5069 (MON-FRI 8:30-5:00).

To submit this form, please complete the fields below. Required fields are denoted by ***.

Authorized Representative Information:

Authorized Representative Name: John Smith
Authorized Representative Credential: MD
Authorized Representative Phone Number: 123-456-7890
Authorized Representative Email Address: j.smith@hospitalabc.com

Hospital Information:

Hospital Name: ABC Hospital
Address Line 1: 123 Main Street
City: Philadelphia
State: PA
Zip Code: 19101

Hospital Certification Date in the REMS: 5/3/2020 Hospital REMS ID: 12345
Date of first order placed for Kyriah™: 1/2/2020
**Date based on order shipped date

Authorized Representative Responsibilities:

**Verify Hospital level and confirm if the Authorized Representative overseeing the hospital was initially certified?
Yes ** No
**Previous Authorized Representative First Name
**Previous Authorized Representative Last Name

Remove Previous Authorized Representative

**Do you have a tracking log available that tracks training for all relevant staff involved in the prescribing (for purposes of this REMS, “prescribing” includes medication inquiry, dispensing, or administering of Kyriah™)?
Yes ** No

**Please provide a copy of the training log with this completed document. Please note, this log should detail relevant staff attending 25 hours on the Kyriah™ Knowledge Assessment. The latest tracking report and from the REMS is acceptable. All prescribing physicians should be trained.

Verification of processes, procedures, or other measures for the dispensing and administration of Kyriah within the Kyriah REMS Program:

DO YOU MANAGE THE FOLLOWING?

**Do you have procedures in place to ensure accurate and complete recording of all dispensed medication?
Yes ** No

**Do you have a process in place to ensure accurate and complete recording of all medications administered to patients?
Yes ** No

**Do you have documentation that demonstrates two doses of tocilizumab are being available at a time, prior to dispensing Kyriah for each patient and ready for immediate administration (within 1 hour)?
Yes ** No

**Do you have procedures in place to ensure patients and their parents are informed of the use of tocilizumab and any associated risks or side effects?
Yes ** No

**Do you have procedures in place to ensure any adverse events suggestive of cytokine release syndrome or neurological sequelae are reported?
Yes ** No

Additional comments:

[Signature of Authorized Representative]

PLEASE UPLOAD THE REQUIRED DOCUMENTATION FOR DOCUMENTATION-RELATED QUESTIONS ANSWERED "YES" ABOVE:

File

Drag & Drop files here

Please provide your documentation in .pdf format only.

Submit
Thank you for submitting your audit questionnaire and supporting documentation.

This documentation will be reviewed and you will be alerted if clarifications are needed.
Novartis Kymriah Risk Evaluation & Mitigation Strategy (REMS)
Audit Questionnaire
Questionnaire Type: Annual

The Authorized Representative of the Kymriah REMS Program must complete this audit questionnaire within 45 days of receipt.

Completion of the audit questionnaire is a requirement of the Kymriah REMS Program in order to ensure all processes and procedures are in place and functioning to support the requirements of the Kymriah REMS Program.

Failure to complete this questionnaire could result in the deactivation of your hospital. If you have any questions about the questionnaire or the Kymriah REMS Program, please call 1-844-4KYMRIAH (1-844-456-9873).

NOTE: The Authorized Representative/Hospital Information section of this form has been pre-populated. If any information listed is incorrect, please call 1-844-4KYMRIAH (1-844-456-9873).

To submit this form, please complete the fields below. Required fields are denoted by **.

Authorized Representative Information:
Authorized Representative Name: John Smith
Authorized Representative Credentials: MD
Authorized Representative Phone Number: 555 555-1212
Authorized Representative Email Address: 555 555-3434

Hospital Information:
Hospital Name: ABC Hospital
Hospital Address Line 1: 123 Main Street
Hospital Address Line 2:
City: Philadelphia
State: PA
Zip Code: 99999
Hospital Certification Date in the REMS: 5/3/2020
Hospital REMS ID: 12345
Date of first order placed for Kymriah**: 1/1/2020
**Date based on order shipped date

Authorized Representative Responsibilities:
*1) Have there been any changes to the Authorized Representative since your last audit?
  ○ Yes  ○ No

*2) Is there a training log available that tracks training for all relevant staff involved in the prescribing (for purposes of this REMS, “prescribing” includes medication orders), dispensing, or administering of Kymriah?
  ○ Yes  ○ No

Verification of processes, procedures, or other measures for the dispensing and administration of Kymriah within the Kymriah REMS Program:

DO YOU HAVE DOCUMENTATION FOR THE FOLLOWING?
* 3) Processes and procedures to ensure new staff involved in prescribing, dispensing, or administering of Kymriah are trained:
  ○ Yes  ○ No

* 4) Documentation that a minimum of two doses of tocilizumab being available on-site, prior to dispensing Kymriah for each patient and ready for immediate administration (within 2 hours):
  ○ Yes  ○ No

* 5) Processes in place to ensure patients and their guardians are being provided with the Kymriah REMS Program Patient Wallet Card before discharge?
  ○ Yes  ○ No

* 6) Processes in place to ensure any adverse events suggestive of cytokine release syndrome or neurological toxicities are reported?
  ○ Yes  ○ No

Delays in obtaining tocilizumab:

* Were there any delays in obtaining tocilizumab?
  ○ Yes  ○ No

I certify, as the Authorized Representative on the Kymriah REMS Program for my hospital, that I have completed this audit questionnaire to the best of my knowledge:

☐ * Signature of Authorized Representative

Submit
Novartis Kymlria Risk Evaluation & Mitigation Strategy (REMS) Audit Questionnaire
Questionnaire Type: Annual

The Authorized Representative of the Kymlria REMS Program must complete this audit questionnaire within 45 days of receipt.

Completion of the audit questionnaire is a requirement of the Kymlria REMS Program in order to ensure all processes and procedures are in place and functioning to support the requirements of the Kymlria REMS Program.

Failure to complete this questionnaire could result in the deactivation of your hospital. If you have any questions about the questionnaire or the Kymlria REMS Program, please call 1-844-485-5981 (in U.S.) 540-439-6742.

NOTE: The Authorized Representative/Independent Information section of this form has been pre-populated. If any information listed is incorrect, please call 1-844-485-5981 (in U.S.) 540-439-6742.

To submit this form, please complete the fields below. Required fields are denoted by ***.

**Authorized Representative Information:**
Authorized Representative Name: [Name]
Authorized Representative Credentials: [MD]
Authorized Representative Phone Number: [Number]
Authorized Representative Email Address: [Email]

**Hospital Information:**
Hospital Name: [Name]
Hospital Address: [Address]
Hospital City/State/Zip: [City/State/Zip]
Hospital Certification Date in the REMS: [Date]

**Authorized Representative Responsibilities:**
1. Have there been any changes to the Authorized Representative since your last audit?
   - No
   - Yes

2. Previous Authorized Representative First Name: [Name]
   Previous Authorized Representative Last Name: [Name]

3. Is there a training log available that tracks training for all relevant staff involved in the prescribing purposes of this REMS, ‘prescribing’ includes prescription ordering, dispensing, or administering of Kymlria?
   - No
   - Yes

4. Please provide a copy of the training log with this completed document. Please note, this log should reflect relevant staff actively working on the REMS Knowledge Assessment. The latest training AF Report sent from the REMS is acceptable. All prescribing physicians should be present.

**Verification of processes, procedures, or other measures for the dispensing and administration of Kymlria within the Kymlria REMS Program:**

**DO YOU HAVE DOCUMENTATION FOR THE FOLLOWING?**

- [ ] Processes and procedures to ensure new staff involved in prescribing, dispensing, or administering of Kymlria are trained:
  - [ ] No
  - [ ] Yes

- [ ] Please provide documentation with this completed form.

**Delays in obtaining tocilizumab:**

- [ ] Are there any delays in obtaining tocilizumab?
  - [ ] No
  - [ ] Yes

- [ ] Please provide further information here.

**PLEASE UPLOAD THE REQUIRED DOCUMENTATION FOR DOCUMENTATION-RELATED QUESTIONS ANSWERED “YES” ABOVE.**

Please provide your documentation in pdf format only.

**Additional Comments:**

- [ ] Additional comments on the Kymlria REMS Program for your hospital.
- [ ] Signature of Authorized Representative

Submit
Novartis Kymriah Risk Evaluation & Mitigation Strategy (REMS) Audit Questionnaire
Questionnaire Type: Annual

The Authorized Representative of the Kymriah REMS Program must complete this audit questionnaire within 45 days of receipt.

A completed audit questionnaire is a requirement for the Kymriah REMS Program in order to assess all processes and procedures and to place and fund the support of the Kymriah REMS Program.

Failed to complete this questionnaire could result in non-compliance with your hospital. If you have any questions about the questionnaire or the Kymriah REMS Program, please call 1-844-RMSEMS (1-844-767-3627).

NOTE: The Authorized Representative of the Hospital Information section of this form has been pre-populated. If any information listed is incorrect, please call 1-844-RMSEMS (1-844-767-3627).

To submit this form, please complete the fields below. Required fields are denoted by ***

Authorized Representative Information:
Authorized Representative Name: John Smith
Authorized Representative Phone Number: 555-555-1232
Authorized Representative Email Address: john.smith@company.com

Hospital Information:
Hospital Name: ABC Hospital
Hospital Address: 123 Main Street
City: Philadelphia
State: PA
Zip Code: 19123

Hospital REMS ID: 12345
Date of last order placed for Kymriah***: 1/1/2020

Authorized Representative Responsibilities:
1. Have there been any changes to the Authorized Representative since your last audit?  
   Yes  No
2. Previous Authorized Representative First Name  
   John
3. Previous Authorized Representative Last Name  
   Smith

Add Another Previous Authorized Representative

4. Is there a training log available that tracks training for all relevant staff involved in the prescribing of Kymriah?  
   Yes  No

Verification of processes, procedures, or other measures for the dispensing and administration of Kymriah within the Kymriah REMS Program:

1. Is there written documentation for the following?  
   Yes  No  
   a. Processes and procedures to ensure new staff involved in prescribing, dispensing, or administering of Kymriah are trained.
   b. Documentation that a minimum of one dose of Kymriah is available on-site, prior to dispensing Kymriah for each patient and ready for immediate administration within 2 hours.
   c. Processes in place to ensure patients and their guardians are being provided with the Kymriah REMS Program Patient Wallet Card before discharge.
   d. Processes in place to ensure any adverse events suggestive of cytokine release syndrome or neurotoxicologic features are reported.

Delays in obtaining tocilizumab:

A. Are there any delays in obtaining tocilizumab?  
   Yes  No  

Additional Comments:

- OR -

Please upload the required documentation for documentation-related questions answered "Yes" above.

Please provide your documentation in .pdf format only.

Additional Comments:

- OR -

Please provide your documentation in .pdf format only.

Drag & Drop files here
Thank you for submitting your audit questionnaire and supporting documentation.

This documentation will be reviewed and you will be alerted if clarifications are needed.
KYMRIAH® REMS Program Hospital Enrollment

Please enter the required information and select "Submit".

If you have not been assigned a REMS ID, please contact the KYMRIAH REMS Program at 1-844-4KYMRIAH (1-844-459-6742).
KYMRIAH® REMS Program Hospital Enrollment Form

Kymriah is only available through the Kymriah Risk Evaluation and Mitigation Strategy (REMS) Program. Hospitals and their associated clinics that dispense Kymriah must be certified to the Kymriah REMS Program. In order to become specially certified to dispense Kymriah, hospitals and associated clinics must designate an Authorized Representative to:

- Complete the certification process by completing this Kymriah REMS Program Hospital Enrollment Form on behalf of the hospital and their associated clinics.
- Oversee implementation and compliance with the Kymriah REMS Program requirements as outlined below.

Please complete all required fields below and submit this enrollment form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com. You will receive a confirmation via E-mail. If you have any questions, require additional information, or need further copies of any of the Kymriah REMS Program documents, please visit the REMS program website at www.Kymriah-REMS.com, or call the Kymriah REMS Call Center at 1-844-KYMRIAH (1-844-545-9742).

To submit this form, please complete the fields below. Required fields are denoted by an asterisk (*).

**Hospital Information**

- **Hospital Name:**
- **Address:**
- **City:** [Please Select]
- **State:**
- **Zip Code:**
- **Phone:**
- **Fax:**

**Authorized Representative Information**

- **First Name:**
- **Last Name:**
- **Credentials:**
  - MD
  - DO
  - RN
  - NP/PA
  - Other (please specify):
- **Phone:**
- **Fax:**
- **Email:**

**Authorized Representative Responsibilities**

On behalf of my hospital/associated clinics, I understand and agree to comply with the following Kymriah REMS Program requirements:

- I must complete the Kymriah REMS Live Training Program and successfully complete the Kymriah REMS Program Knowledge Assessment.
- Those participating in Kymriah clinical trials and/or the pre-approval safety training will be exempt from the live training but will be required to review the REMS materials on the REMS website.
- I must submit this completed Kymriah REMS Program Hospital Enrollment Form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
- I must submit the completed Kymriah REMS Program Hospital Enrollment Form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
- I will oversee implementation and compliance with the Kymriah REMS Program.
- I will ensure that my hospital and associated clinics will establish processes and procedures that are subject to monitoring by Novartis Pharmaceuticals Corporation (NPC), a third party acting on behalf of NPC to help ensure compliance with the requirements of the Kymriah REMS Program, including the following, before administering Kymriah:
  - Ensuring all relevant staff involved in the prescribing, dispensing or administering of Kymriah are trained on the REMS Program requirements and successfully complete the Kymriah REMS Program Knowledge Assessment; and maintain records of staff training.
  - Performing periodic re-educations of all staff involved in the prescribing, dispensing or administering of Kymriah and maintaining records of re-training if Kymriah has not been dispensed at least once annually from the date of certification in the Kymriah REMS Program.
  - Prior to dispensing Kymriah, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on site for each patient and are ready for immediate administration (within 2 hours).
  - Before discharge, provide patients and their legal guardians the Patient Medication Card.

As a condition of certification, the certified hospital must:

- Ensure that if the hospital designates a new authorized representative, the new authorized representative must review the Kymriah REMS Live Training Program, complete the Kymriah REMS Program Knowledge Assessment, complete a new Kymriah REMS Program Hospital Enrollment Form and submit the forms via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
- Report any adverse events suggestive of cytokine release syndrome or neurological toxicities of Kymriah to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at 1-855-Novartis or 1-888-959-5562.
- Dispose Kymriah to patients only after verifying that a minimum of 2 doses of tocilizumab is available on-site for each patient and are ready for immediate administration (within 2 hours).
- Maintain documentation of all processes and procedures for the Kymriah REMS Program and provide 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.

* By entering my name and selecting this box, I am authorizing those elements as my signature representing that I have completed all required fields on this form.

Submit
Kymriah® REMS Program Hospital Enrollment

An authorized representative for this hospital already exists. Please view the account representative information below. If this person is no longer the authorized representative for your hospital on the Kymriah REMS program, you may create a new authorized representative by clicking the button below.

First Name: Smith
Last Name: John
Credentials: MD
Phone: 555-555-1212
Fax: 555-555-3434
Email: e@a.com

Create New Authorized Representative
KYMRIAH® REMS Program Hospital Enrollment

There is no record of a completed training and knowledge assessment associated to the email address entered. You may begin the training or return to complete the knowledge assessment by clicking the button below.

REMS ID: 123456789
Email Address: a@a.com

Continue to Training
**KYMRIA-H REMS Program Knowledge Assessment Registration**

To submit this form, please complete all fields below.

**HOSPITAL 1 NAME**

**Representative Information**

<table>
<thead>
<tr>
<th>First name:</th>
<th>Last name:</th>
<th>Authorized Representative:</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEST1</td>
<td>Test</td>
<td>☐ No ☐ Yes</td>
</tr>
</tbody>
</table>

**Credentials:**

- ☐ DO
- ☐ MD
- ☐ LPnC
- ☐ NP/PA
- ☐ Other (please specify)

<table>
<thead>
<tr>
<th>Phone:</th>
<th>Fax:</th>
<th>E-mail:</th>
</tr>
</thead>
<tbody>
<tr>
<td>456-545-4545</td>
<td>456-545-4545</td>
<td><a href="mailto:Test89@Test.com">Test89@Test.com</a></td>
</tr>
</tbody>
</table>

[Submit]
KYMRIAH REIMS Program Knowledge Assessment

KYMRIAH
(tisagenlecucel) Suspension for IV infusion

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.

NOVARTIS
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).
KYMRIAHG REMS Goals

- The goals of the KYMRIAHG 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 KYMRIAHG are specially certified and have on-site, immediate access to tocilizumab.
  - Ensuring those who prescribe, dispense, or administer KYMRIAHG are aware of how to manage the risks of CRS and neurological toxicities.
KYMRIAH REMS Program Knowledge Assessment

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
KYMRIA H REMS Program Knowledge Assessment

KYMRIA H REMS Materials, cont.

• KYMRIA H 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

• KYMRIA H REMS Program Hospital Enrollment Form
  ▪ Must be completed by the authorized representative (via email, fax, or online) to certify the hospital

• KYMRIA H 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.
WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAHI. Do not administer KYMRIAHI 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 KYMRIAHI, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAHI. Provide supportive care as needed.
- KYMRIAHI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAHI REMS.
KYMRIAH-associated Cytokine Release Syndrome
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)
KYMRIAH REMS Program Knowledge Assessment

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
- 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
- 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

- Nausea, vomiting, anorexia, diarrhea
- Myalgia, arthralgia
- Rigors
- High fever
- Rash
- Fatigue
- Diaphoresis
- Headache
- Hypotension
- Dyspnea, tachypnea, hypoxia

**Diagnosis based on clinical symptoms and events**
## CRS: associating events and organ dysfunction

<table>
<thead>
<tr>
<th>Organ</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>- Hepatic dysfunction: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinemia</td>
</tr>
<tr>
<td>Renal</td>
<td>- Renal insufficiency, may require dialysis</td>
</tr>
<tr>
<td>Respiratory</td>
<td>- Respiratory failure, pulmonary edema</td>
</tr>
<tr>
<td>Cardiac</td>
<td>- Transient cardiac insufficiency</td>
</tr>
<tr>
<td></td>
<td>- Transient arrhythmia</td>
</tr>
<tr>
<td>Cytopenias lasting &gt; 28 days</td>
<td>- Avoid myeloid growth factors, particularly GM-CSF, during the first 3 weeks after KYMRIAHH infusion or until CRS has resolved</td>
</tr>
</tbody>
</table>
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 and/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

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Symptomatic Treatment</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild symptoms requiring symptomatic treatment only (e.g., low-grade fever, fatigue, anorexia, etc.)</td>
<td>Exclude other causes (e.g., infection) and treat specific symptoms (e.g., with antipyretics, antiemetics, analgesics, etc.)</td>
<td>In patients with persistent (&gt;3 days) or refractory fever, consider managing as Grade 2 CRS.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Symptoms require and respond to moderate intervention</td>
<td>Antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed</td>
<td>Administer tocilizumab* intravenously over 1 hour:</td>
</tr>
<tr>
<td></td>
<td>Oxygen requirement &lt;40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity</td>
<td></td>
<td>- 8 mg/kg (max, 800 mg) if body weight &lt; 30 kg &lt;br&gt;- 12 mg/kg if body weight ≥ 30 kg</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Symptoms require and respond to aggressive intervention</td>
<td>High-flow oxygen Intravenous fluids, and high-dose or multiple vasopressors Treat other organ toxicities as per local guidelines</td>
<td>Per Grade 2 if not improving, consider alternative therapy&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Oxygen requirement ≥40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 organ toxicity (excluding transaminases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening symptoms &lt;br&gt;Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminases)</td>
<td>Mechanical ventilation Intravenous fluids and high-dose vasopressor(s) Treat other organ toxicities as per local guidelines</td>
<td>Per Grade 2 if not improving, consider alternative therapy&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Mueh et al. 2018<br><sup>2</sup> Santomasso et al. 2021<br><sup>3</sup> Refer to tocilizumab Prescribing Information for details.<br><sup>4</sup> 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, naxitamab, tocilizumab, ransumab, WPS, and ATS.
## CRS grading scales for CAR-T cell therapy

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

<sup>1</sup>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.

<sup>2</sup>Defined as multiple fluid boluses for blood pressure support.


### Definition of high-dose vasopressors 1-3

<table>
<thead>
<tr>
<th>Vasopressor</th>
<th>Weight-based dosing (^a)</th>
<th>Flat dosing (if this is institutional practice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine monotherapy</td>
<td>≥ 0.2 μg/kg/min</td>
<td>≥ 20 μg/min</td>
</tr>
<tr>
<td>Dopamine monotherapy</td>
<td>≥ 10 μg/kg/min</td>
<td>≥ 1000 μg/min</td>
</tr>
<tr>
<td>Phenylephrine monotherapy</td>
<td>≥ 2 μg/kg/min</td>
<td>≥ 200 μg/min</td>
</tr>
<tr>
<td>Epinephrine monotherapy</td>
<td>≥ 0.1 μg/kg/min</td>
<td>≥ 10 μg/min</td>
</tr>
</tbody>
</table>

If no vasopressor

<table>
<thead>
<tr>
<th>Vasopressor equivalent of ≥ 0.2 μg/kg/min (^b)</th>
<th>Norepinephrine monotherapy equivalent of ≥ 0.1 μg/kg/min (using VASST formula) (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressin + norepinephrine equivalent of ≥ 10 μg/min (^c)</td>
<td>Norepinephrine equivalent of ≥ 20 μg/min (using VASST formula) (^c)</td>
</tr>
</tbody>
</table>

**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] \(^c\)

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

**References**

KYMRIAH-associated neurological toxicities
Neurological toxicities

- Neurological toxicities, which may be severe or life-threatening can occur following treatment with KYMRIA
- Major manifestations of neurological toxicities observed with KYMRIA include encephalopathy and delirium
- The majority of neurological toxicities occurred within 8 weeks following KYMRIA infusion and were transient
- In KYMRIA pivotal clinical trials, neurological toxicities, occurred after KYMRIA 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 KYMRIA 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
- Delayed onset: as CRS is resolving or following the resolution of CRS
- In the absence of CRS

**Onset and duration**
- The majority of neurological toxicities occurred within 8 weeks following Kymriah infusion
- The majority of events were transient

**Clinical presentation**
- Major manifestations of neurological toxicities observed with Kymriah include encephalopathy, delirium or related events
- Anxiety, dizziness, headache, peripheral neuropathy, and sleep disorders were the other most common neurological toxicities
- Other related manifestations: seizures, and aphasia
- The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS
## 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:
  - Should be advised about the risk and symptoms of neurological toxicities that they may experience
  - Should carry the KYMRIAH patient wallet card to remind them of the signs and symptoms of neurological toxicities that require immediate attention
  - Should contact their healthcare professional if experiencing signs and symptoms of neurological toxicities
  - 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

<table>
<thead>
<tr>
<th>ICANS Grade</th>
<th>Non-concurrent CRS</th>
<th>Concurrent CRS</th>
</tr>
</thead>
</table>
| **Grade 1** | ICE score \( \leq 7.9 \) with no depressed level of consciousness | Offer supportive care with intravenous hydration and aspiration precautions. Administrator 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 post the first dose.  

**Grade 2** | ICE score \( \leq 3.6 \) and/or | Supportive care as above. 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. Administrator tocilizumab at any grade CRS, as per dosage recommendation in Table 1. If satisfactory to tocilizumab post 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. |
| and/or | Add semicircle waking to voice. | |
| **Grade 3** | ICE score \( \leq 1.2 \) and/or | Drowsy level of consciousness, awakening only to tactile stimuli, and/or Any clinical seizure focal or generalized that requires rapid or nonconvulsive seizures on EEG that resolve with intervention, and/or | Administrator dexamethasone 10 mg intravenously every 6-12 hours or methylprednisolone equivalent (1 mg/kg) intravenously every 12 hours. Administrator tocilizumab at any grade CRS, as per dosage recommendation in Table 1. Administrator 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 |
| and/or | Depressed level of consciousness, awakening only to tactile stimuli, and/or | |
| and/or | Any clinical seizure focal or generalized that requires rapid or nonconvulsive seizures on EEG that resolve with intervention, and/or | |
| and/or | Flaccid focal or generalized seizures on neuroimaging. | |
| **Grade 4** | ICE score \( \leq 0.8 \) (patient is unarousable and unable to perform ICE) and/or | Consider mechanical ventilation for airway protection. Administrator high-dose methylprednisolone intravenously 1,000 mg once to two times per day for 3 days if not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy.  

**Contraindications until improvement to Grade 3, and then taper as clinically appropriate.** | Administrator tocilizumab at any grade CRS, as per dosage recommendation in Table 1. Administrator high-dose methylprednisolone 1,000 mg intravenously one to two times per day for 3 days. If not improving, consider methylprednisolone 1,000 mg intravenously two to three times per day or alternate therapy.  

**Contraindications until improvement to Grade 3, and then taper as clinically appropriate.** |
| and/or | Apnea or coma and/or | |
| and/or | Life-threatening prolonged seizure (30 minutes) or repetitive clinical or electrical seizures without return to baseline in between and/or | |
| and/or | Stiffness of cerebral edema on neuroimaging, demonstrate or decontaminate, paresis, paraesthesia, cerebral edema as per institutional guidelines. | |

*ICE criteria for grading Nishitani et al 2013: N3C criteria for grading N3 used in clinical trials.

**ICE Assessment Tool:** (1) Orientation: orientation to year, month, day, and hospital: 4 points. (2) Naming: ability to name three objects (e.g., point to clock, pen, and button): 5 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): 3 point. (5) Attention: ability to count backward from 100 by 10: 1 point. (Santamorese et al. 2013)

*Alternate therapy may include anakinra, sirolimus, nivolumab, cyclophosphamide, antithymocyte globulin, or intrathecal hydrocortisone (55 mg) plus methotrexate (12 mg).

*If a patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global apnea, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)
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
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.KYMRIAHEMS.com or call 1-844-4KYMRIAHE(1-844-459-6742)
References

- Chimeric Antigen Receptor (CAR) Cell Therapy
  Toxicity Assessment and Management – Pediatric.
  The University of Texas MD Anderson Cancer Center website
  Published January 30, 2018. Accessed March 4, 2019. The pediatric guideline was approved by the Executive Committee of the Medical Staff on 1/30/2018.


Question 1:
Kymriah® (tisagenlecleucel) is indicated for the treatment of:
- Patients up to 25 years of age with newly-diagnosed high-risk acute lymphoblastic leukemia (ALL)
- Patients up to 25 years of age with relapsed or refractory ALL
- Adult patients with newly-diagnosed diffuse large B-cell lymphoma (DLBCL)
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, not otherwise specified, high grade B-cell lymphomas and DLBCL arising from follicular lymphoma
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy
- All except A and C

Question 2:
Delay Kymriah infusion if the patient has any of the following, except:
- Active uncontrolled infection
- Worsening of leukemia burden following lymphodepleting chemotherapy
- Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
- Active graft versus host disease
- Unresolved serious adverse reactions from preceding chemotherapy

Question 3:
Clinically, patients with CRS can manifest with the following signs and symptoms, except:
- High fever
- Hypotension
- Fever
- Respiratory distress
- Hypovolemia

Question 4:
Which one of the following is true regarding the time to onset of CRS? It typically occurs:
- 7-14 days following Kymriah infusion, with a median time to onset of 10 days
- 1-7 days following Kymriah infusion, with a median time to onset of 10 days
- Median time to onset is 3-4 days following Kymriah infusion
- Rarely starts during the first week following Kymriah infusion

Question 5:
As a part of planning for Kymriah infusion, it is required to have an on-site, immediate access (within 2 hour) to a minimum of two doses of tocilizumab on site for each patient prior to dispensing and administering Kymriah to patients:
- True
- False

Question 6:
As a part of the patient and caregiver education for Kymriah, advise the patient to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machines) for at least 8 weeks after receiving Kymriah:
- True
- False

Question 7:
A 5-year-old male with relapsed ALL following an allogeneic transplantation was treated with Kymriah. One day following infusion, he developed high grade fever (40.5°C) with neutropenia and was hospitalized. On day 2, he developed hypoglycemia, which improved with fluid resuscitation. He was transferred to the PICU for close observation, and later developed recurrent hypotension, mild tachypnea and hypoxia (52% saturation 75%). He was started on neoprophylaxis at a low dose and CO2 supplementation via nasal cannula. All of the following are correct, except:
- The patient has symptoms consistent with cytokine release syndrome and should be managed according to the CRS management algorithm
- Lymphocytopenia should be considered and treated adequately with broad spectrum antibiotics
- Avoid antivirals as they may affect CAR T cell efficacy
- Continue supportive care and close monitoring of hemodynamic, respiratory and neurological status

Question 8:
Neurological toxicities were observed with Kymriah, and the patient and the caregiver should be informed about this risk. All of the following are correct, except:
- May occur in the context of CRS, following the resolution of CRS or without CRS
- Symptoms range from headache and confusion to encephalopathy and seizures
- The majority of events were transient and self-limiting
- Can be prevented with the administration of tocilizumab

Question 9:
Which one of the following about neurological toxicities as a result of Kymriah is correct:
- Perform neurological work-up as appropriate to exclude other etiologies of neurological symptoms
- Management includes supportive care
- Majority occurred within 8 weeks following Kymriah infusion
- All of the above

Question 10:
A 50-year-old female with multiply relapsed DLBCL treated with Kymriah as an outpatient 2 days after completion of lymphodepleting chemotherapy. The patient and her caregiver should be advised about the following:
- The risk of CRS and neurological toxicities and to contact the healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
- The patient should plan to stay within 2-hours of the treatment site for at least 4-weeks after receiving Kymriah
- The patient should carry the Kymriah patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention
- All of the above

Question 11:
A 22-year-old male with relapsed/refractory Philadelphia chromosome negative B cell Acute lymphoblastic Leukemia (ALL) developed grade 1 cytokine release syndrome (CRS) 6 hours after treatment with Kymriah, progressing to Grade 2 CRS on day 2. The patient was treated with two doses of tocilizumab, following which rapid clinical improvement was noted. On day 11, he presented with new fever and need for high oxygen therapy. His labs showed impaired renal and hepatic functions, along with coagulopathy and elevated liver. The current clinical signs and symptoms, an evaluation for Hemophagocytic lymphohistocytosis/Macrophage activation syndrome (HLH/MAS) should be performed.
- True
- False
Question 2: Kymriah™ (t Aside recombination) is indicated for the treatment of:

- Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
- Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 3rd or later relapse
- Adult patients with relapsed/refractory large B-cell lymphoma (LBCL)
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including (I.B.J), otherwise specified, high-grade B-cell lymphomas and (I.B.J), arising from follicular lymphoma
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

All except A and C

Question 3: Delay Kymriah infusion if the patient has any of the following, except:

- Active uncontrolled infection
- Worsening of leukemic burden following lymphodepleting chemotherapy
- Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
- Active gut versus host disease
- Unexplained severe adverse reactions from preceding chemotherapies

Question 4: What one of the following is true regarding the time to onset of CRS it typically occurs:

- 5-14 days following Kymriah infusion, with a median time to onset of 12 days
- 2-7 days following Kymriah infusion, with a median time to onset of 6 days
- Medium time to onset is 2-9 days following Kymriah infusion
- Randomly starts during the first week following Kymriah infusion

Question 5: CRS IV is part of planning for Kymriah infusion, it is required to have on site, immediate access (within 2 hours) to a minimum of two doses of glucocorticoids on site for each patient prior to dispensing and administering Kymriah to patients:

- True
- False

Question 6: As a part of the patient and caregiver education for Kymriah, advise the patient to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving Kymriah:

- True
- False

Question 7: A 65-year-old male with relapsed ALL following an allogeneic transplantation was treated with Kymriah. One day following infusion, he developed high-grade fever (40.4C) with neutropenia and was hospitalized. On day 3, he developed hypotension, which improved with fluid resuscitation. He was transferred to the ICU for close observation, and later developed recurrent hypotension, mild tachycardia and hypoxia (75% saturation). If he was started on ciprofloxacin at a low dose and O2 supplement via nasal cannula. All of the following are correct, except:

- The patient has symptoms consistent with cytokine release syndrome and should be managed according to the CRS management algorithm.
- Lipoic acid should be considered and treated adequately with a broad spectrum antibiotic.
- Nasal endotracheal tube may affect cough and cell/defensive reflexes.
- Continue supportive care and close monitoring of hemodynamic, respiratory and neurological status

Question 8: Neurological toxicities were observed with Kymriah, and the patient and the caregiver should be informed about this risk. All of the following are correct, except:

- May occur in the context of CRS, following the resolution of CRS or without CRS
- Symptoms range from headache and confusion to encephalopathy and seizures
- The majority of events were transient and self-limiting
- Can be presented with the administration of glucocorticoids

Question 9: Which one of the following about neurological toxicities as a result of Kymriah is correct:

- Perform neurological work-up to determine the risk of developing CRS or without CRS
- Management includes supportive care, monitoring and testing of neurological symptoms
- May occur within 8 weeks following Kymriah infusion
- All of the above

Question 10: A 60-year-old female with multiply relapsed DBCL treated with Kymriah as an outpatient 2 days after completion of lymphodepleting chemotherapy. The patient and her caregiver should be advised about the following:

- The risk of CRS and neurological toxicities and to contact the healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
- The patient should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving Kymriah
- The patient should carry the Kymriah patient wallet and to record the signs and symptoms of CRS and neurological toxicities that require immediate attention
- All of the above

Question 11: A 32-year-old male with relapsed refractory Philadelphia chromosome negative B cell Acute lymphoblastic leukemia (ALL) developed grade 1 cytokine release syndrome (CRS) 6 hours after treatment with Kymriah. Progressing to Grade 2 CRS on day 3, the patient was treated with two doses of tocilizumab, following which rapid clinical improvement was noted. On day 11, he presented with new fever and need for high oxygen therapy. His labs showed impaired renal and hepatic functions, along with coagulopathy and elevated ferritin. Given the current clinical signs and symptoms, an evaluation for Hepatitis B, Hepatitis C, HIV and Syphilis should be performed.

- True
- False
Please review the 2 questions answered incorrectly, marked in red and denoted with an "X".

You may click on "Retake Training" to review the training slides. At the end of the review, you will be able to retake the assessment. Do you may immediately retake the assessment by clicking on "Retake Assessment".

**Question 1:** X

Kymria® (lisocabtagene maraleucel) is indicated for the treatment of:

- Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
- Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 2nd or later relapse
- Adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicle lymphoma
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy
- (all except A and B)

**Question 2:**

Delay febrile infusion if the patient has any of the following, except:

- Active uncontrolled infection
- Worsening of leukemic burden following lymphodepleting chemotherapy
- Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
- Active graft-versus-host disease
- Uncontrolled serious adverse reactions from previous chemotherapies

**Question 3:**

Clinically, patients with CRS can manifest with the following signs and symptoms, except:

- High grade fever
- Hypotension
- Hair Loss
- Respiratory distress
- Hypoalbuminemia

**Question 4:** X

Which one of the following is true regarding the time to onset of CRS? It typically occurs:

- 3-4 days following Kymria infusion, with a median time to onset of 10 days
- 7-21 days following Kymria infusion, with a median time to onset of 10 days
- Median time to onset in 3-4 days following Kymria infusion
- Rarely starts during the first week following Kymria infusion

**Question 5:** X

As a part of planning for Kymria infusion, it is required to have on-site, immediate access (within 2 hours) to a minimum of two doses of tocilizumab on site for each patient prior to dispensing and administering Kymria to patients:

- True
- False

**Question 6:** X

As a part of the patient and caregiver education for Kymria, the patient is to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving Kymria:

- True
- False

**Question 7:**

A 5-year-old male with relapsed ALL following an allogeneic transplantation was treated with Kymria. One day following infusion, he developed high grade fever (38.5°C) with neutropenia and was hospitalized. On day 2, he developed hypotension, which improved with fluid resuscitation. He was transferred to the PICU for close observation, and later developed recurrent hypotension, mild tachypnea and hypoxia (O2 saturation 95%). If it was started on romiplostim at a low dose and O2 supplement ate nasal cannula. All of the following are correct, except:

- The patient has symptoms consistent with cytokine release syndrome and should be managed according to the CRS management algorithm
- Supportive care should be considered and treated adequately with broad spectrum antibiotics
- Avoid antipyretics as they may affect CAR T cell efficacy
- Continue supportive care and close monitoring of hemodynamic, respiratory and neurological status

**Question 8:**

Neurological toxicities were observed with Kymria, and the patient and the caregiver should be informed about this risk. All of the following are correct, except:

- May occur in any context of CRS or without CRS
- Symptoms range from headache and confusion to encephalopathy and seizures
- The majority of events were transient and self-limiting
- Can be prevented with the administration of tocilizumab

**Question 9:**

Which one of the following about neurological toxicities as a result of Kymria is correct:

- Perform neurological work-up as appropriate to rule out etiologies of neurological symptoms
- Management includes supportive care
- Majority occurred within 8 weeks following Kymria infusion
- All of the above

**Question 10:**

A 30-year-old female with multiply relapsed DLBCL, treated with Kymria as an exception 2 days after completion of lymphodepleting chemotherapy, the patient and her caregivers should be advised about the following:

- The risk of CRS and neurological toxicities and to contact the healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
- The patient should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving Kymria
- The patient should carry an immunosuppressant card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention
- All of the above

**Question 11:**

A 22-year-old male with relapsed/refractory Philadelphia chromosome negative B cell Acute Lymphoblastic Leukemia (ALL) developed grade 1 cytokine release syndrome (CRS) 6 hours after treatment with Kymria, progressing to Grade 2 CRS in 3 days. The patient was treated with two doses of tocilizumab, following which rapid clinical improvement was noted. On day 11, he presented with new fever and need for high oxygen therapy. His labs showed improved renal and hepatic functions, along with coagulopathy and leukocytosis. Given the current clinical signs and symptoms, an evaluation for Hemophagocytic Lymphohistiocytosis/Macrophage activation syndrome (HIES/MAS) should be performed:

- True
- False
**KYMRIAH REMS Program Knowledge Assessment**

Please complete the following assessment. You are required to answer all questions correctly in order to pass the assessment. You have 2 attempt(s) to correctly answer all questions.

**Question 1:**
Kymriah® (tisagenlecleucel) is indicated for the treatment of:

- [ ] Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
- [ ] Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 2nd or later relapse
- [ ] Adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)
- [ ] Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
- [ ] Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy
- [ ] All except A and C

**Question 3:**
Clinically, patients with CRS can manifest with the following signs and symptoms, except:

- [ ] High grade fever
- [ ] Hypotension
- [ ] Hair Loss
- [ ] Respiratory distress
- [ ] Hypofibrinogenemia

Submit
CONGRATULATIONS!

You have successfully completed the KYMRIAH Knowledge Assessment.

Click [here](#) for a copy of your Certificate of Completion
Certificate of Completion
KYMRIA REMS Program

This is to certify that

Test test
IjNgEFA
661

has successfully completed the
KYMRIA REMS Program Knowledge Assessment on

October 13, 2017

Please print this certificate and provide it to your authorized representative.
If you are the authorized representative and you have not completed the KYMRIA REMS Program Hospital Enrollment Form, please complete and fax the form to 1-844-590-0840 or email the form to KYMRIA@ubc.com

KYMRIA
Risk Evaluation and Mitigation Strategy (REMS)
KYMRIAH REMS Program Knowledge Assessment

You have exceeded the number of attempts to pass this assessment. Please contact the KYMRIAH REMS Call Center at 1-844-KYMRIAH (1-844-596-7424) to unlock your account and retake the KYMRIAH REMS Live Training Program and Knowledge Assessment.

Question 1: X
Kymriah® (tisagenleucel) is indicated for the treatment of:
- Patients up to 25 years of age with newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
- Patients up to 25 years of age with relapsed or refractory acute lymphoblastic leukemia
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
- Adult patients with relapsed or refractory follicular lymphoma (FL), if they have two or more lines of systemic therapy
- All except a and c

Question 2: Delayed infusion infection if the patient has any of the following, except:
- Active systemic infection
- Worsening of immune function following lymphodepletion chemotherapy
- Severe neutropenia and thrombocytopenia following lymphodepletion chemotherapy
- Active granulocytic host disease
- Unresolved serious adverse reactions from previous chemotherapies

Question 3: Clinically, patients with CRS can manifest with the following signs and symptoms, except:
- High fever
- Hypersensitivity
- Slim cheeks
- Respiratory distress
- Encephalopathy

Which of the following is true regarding the time to onset of CRS typically occurs:
- 7-10 days following Kymriah infusion, with a median time to onset of 10 days
- 7-21 days following Kymriah infusion, with a median time to onset of 21 days
- Median time to onset is 3 days following Kymriah infusion
- Ready starts during the first week following Kymriah infusion

Question 4: As a part of planning for infusion, it is required to have two doses of tocilizumab on site for each patient prior to discharging and administering Kymriah to patients:
- True
- False

Question 5: A 5-year-old male with refractory ALL was treated with Kymriah. One day following infusion, he developed high fever (103°F) and was hospitalized. On day 3, he developed hypotension, which improved with fluid resuscitation. He was transferred to the PICU for close observation, and later developed recurrent hypotension, multiorgan dysfunction, and hypoxia (hypo 02 saturation of 85%). He was started on oncosteplase as a low dose and o2 supplementation via nasal cannula. The patient is now stable with normalization of blood pressure and O2 saturation. What is the next step in management?
- Administer one dose of tocilizumab at 0.4 mg/kg intravenously
- Start IV methotrexate at 2 mg/kg/day
- Administer one dose of tocilizumab (0.6 mg/kg intravenously)
- Continue close monitoring and supportive care

Question 6: Neurological toxicities were observed with Kymriah, and the patient and the caregiver should be informed about this risk. All of the following are correct, except:
- May occur in the context of CRS, following the resolution of CRS or without CRS
- Symptoms range from headache and confusion to encephalopathy and seizures
- The majority occurred within 6 weeks following Kymriah infusion
- Can be prevented with the administration of tocilizumab

Question 7: All of the following are Neurological events as a results of Kymriah in correct, except:
- Phenytoin labwork is appropriate as an appropriate to exclude other etiologies of neurological symptoms
- Management includes supportive care
- Management includes high dose systemic corticosteroids
- Multiorgan occurred within 6 weeks following Kymriah infusion

Question 8: A 12-year-old female with relapsed ALL following an allo-HCT transplantation was treated with Kymriah. One day post infusion, she developed high grade fever (103°F) and rigors, and started on broad spectrum antibiotics. Subsequently, she developed hypoxemia requiring multiple fluid boluses and high dose vasopressors (norepinephrine and epinephrine). Hypo 02 and O2 saturation requiring humidified Flow O2 (30%) administered oxygen therapy, sepsis criteria and multiorgan failure, and multiorgan failure and renal failure. She was treated with 2 doses of tocilizumab, IV methylprednisolone at 2 mg/kg/day, and broad spectrum antibiotics. The patient has transient short delayed improvement is hemodynamic stability, with inability to wean vasopressor or ventilator setting. What is the appropriate next step in management?
- Control level for the evaluation of arterial stiffness
- Start IV methylprednisolone at 2 mg/kg/day
- Second dose of tocilizumab (if improvement with steroids within 24 hours) (ability to wean vasopressors and persistent fever)

All of the above

Question 9: A 30-year-old female with multiple relapsed (4x) treated with Kymriah. On day 3 following infusion, the patient developed symptoms consistent with severe CRS including persistent high grade fever, hypotension requiring high dose vasopressors, progressive respiratory distress requiring intubation and mechanical ventilator, fever and renal function abnormalities. She was treated with 2 doses of tocilizumab, IV methylprednisolone at 2 mg/kg/day, and broad spectrum antibiotics. The patient had transient short delayed improvement is hemodynamic stability, with inability to wean vasopressors or ventilator settings. What is the appropriate next step in management?
- Evaluate the patient for seizures
- Administer one dose of IV phenytoin at 13 mg/kg
- Cefotaxime (2g IV) and dexamethasone and replace with amphotericin, fresh frozen plasma antiinflammatory agents
- All of the above

Question 10: A 22-year-old male with relapsed/refractory Philadelphia chromosome negative B-cell Acute Lymphoblastic Leukemia (ALL) developed grade 1 cytokine release syndrome (CRS) 6 hours after treatment with KYMRIAH, progressing to grade 2 CRS on day 2. The patient was treated with two doses of tocilizumab, following which rapid clinical improvement was noted. On day 15, he presented with new fever and improvement for high Oxygen therapy. His labs showed improved renal and hepatic functions, along with coagulopathy and encephalopathy. Given the current clinical signs and symptoms, an evaluation for Hemophagocytic Lymphohistiocytosis/Macrophage activation syndrome (HLH/MAS) should be performed.
- True
- False