

# 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<sup>®</sup> (tisagenlecleucel).

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### 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.**

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### Goals of the REMS

The goals of the Kymriah<sup>®</sup> (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 1-844-4KYMRIAH (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 1-844-4KYMRIAH (1-844-459-6742).

You are encouraged to report suspected adverse events with Kymriah to Novartis at <https://psi.novartis.com> or 1-888-669-6682 or the FDA at [www.fda.gov/medwatch](http://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.

 [Kymriah Prescribing Information](#)

 [Kymriah Medication Guide](#)

 [Kymriah REMS Live Training Program Slides](#)

 [Kymriah REMS Program Knowledge Assessment](#)

 [Kymriah REMS Program Patient Wallet Card](#)

 [Kymriah REMS Program Patient Wallet Card \(Español\)](#)

### INDICATION:

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 and 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.

[Click here to complete the Knowledge Assessment online](#)

Contact Us | Non-US Residents



## KYMRIAH REMS Program Knowledge Assessment / Enrollment

### KYMRIAH REMS Program Knowledge Assessment / Enrollment

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

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Hospital ID



## KYMRIAH REMS Program Knowledge Assessment / Enrollment

### KYMRIAH REMS Program Knowledge Assessment / Enrollment

Please use the Training Assessment link below to navigate to the online training and assessment. 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. If you are not sure if you have previously completed the Training Assessment or your Hospital Enrollment Form, please contact the Kymriah REMS Program at 1-844-4KYMRIAH for clarification.

XXXXXXXXXXXX - HOSPITAL NAME

Continue to  
**Training Assessment**

Continue to  
**Hospital Enrollment**



# 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).

This is where any error message will display

REMS ID

Email Address

Submit

The image shows a screenshot of a web form for hospital enrollment. At the top, there is a red banner with the text "This is where any error message will display". Below this are two input fields: "REMS ID" and "Email Address". A green "Submit" button is located at the bottom right of the form area.

# KYMRIAH™ REMS Program Hospital Enrollment

## 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 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 the 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](mailto:KymriahREMS@ubc.com) or complete it online at [www.Kymriah-REMS.com](http://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](http://www.Kymriah-REMS.com), or call the Kymriah REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742).

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

### Hospital Information

*Hospital Name <input type="text"/>		*Hospital National Provider Information (NPI)# <input type="text"/>	
*Address <input type="text"/>		*City <input type="text"/>	*State - Please Select - <input type="text"/>
*Phone: <input type="text"/>	*Fax: <input type="text"/>	*Zip Code: <input type="text"/>	

### Authorized Representative Information

*First Name <input type="text"/>	*Last Name <input type="text"/>	
*Credentials: <input type="radio"/> DO <input type="radio"/> MD <input type="radio"/> R.Ph <input type="radio"/> NP/PA <input type="radio"/> Other		
Other <input type="text"/>		
*Phone: <input type="text"/>	*Fax: <input type="text"/>	*Email: <input type="text"/>

### 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 or E-mail at [KymriahREMS@ubc.com](mailto:KymriahREMS@ubc.com).
- \* I must submit the completed *Kymriah REMS Program Knowledge Assessment* form to the REMS Call Center via fax to 1-844-590-0840 or E-mail at [KymriahREMS@ubc.com](mailto:KymriahREMS@ubc.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), FDA, or a third party acting on behalf of NPC or FDA 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 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. Prior to dispensing Kymriah, provide patients/caregivers the *Patient/Caregiver 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 or E-mail at [KymriahREMS@ubc.com](mailto:KymriahREMS@ubc.com).
- \* Report any adverse events suggestive of cytokine release syndrome or neurological toxicities of Kymriah to FDA at [www.fda.gov/medwatch](http://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, FDA, or a third party acting on behalf of Novartis or FDA.
- \* Comply with audits by Novartis, FDA, or a third party acting on behalf of Novartis or FDA.

*First Name <input type="text"/>	*Last Name <input type="text"/>	*Email: <input type="text"/>
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- \* By entering my name and selecting this box, I am authorizing these elements as my signature representing that I have completed all required fields on this form.

Submit



# KYMRIAH™ REMS Program Hospital Enrollment

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

Create New Authorized Representative



# KYMRIAH™ REMS Program Hospital Enrollment

## 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](#)



# KYMRIAH REMS Program Knowledge Assessment

## KYMRIAH REMS Program Knowledge Assessment Registration

To submit this form, please complete all fields below

### HOSPITAL 1 NAME

#### Representative Information

First name:

Last name:

Authorized Representative:

No  Yes

Credentials:

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

Phone:

Fax:

E-mail:

SUBMIT



## 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.





This educational module contains information on selected KYMRIAH-associated adverse events, including cytokine release syndrome and neurological toxicities, observed in clinical trials 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, and 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.



## KYMRIAH REMS Program Knowledge Assessment



### 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.





## KYMRIAH REMS Program Knowledge Assessment



### KYMRIAH REMS Goal

- 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 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





## KYMRIAH REMS Program Knowledge Assessment



### 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

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## KYMRIAH REMS Program Knowledge Assessment



### 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**





## KYMRIAH REMS Program Knowledge Assessment



### 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.





## KYMRIAH REMS Program Knowledge Assessment



### Conditions of Certification

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





### KYMRIAH Boxed Warning

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

**- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH.**

**Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**

**- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS.**

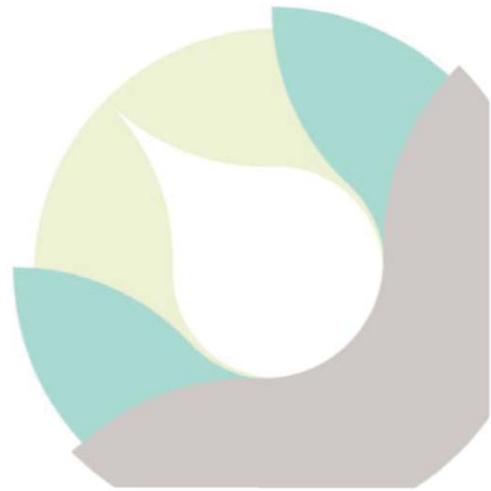
**Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed.**

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 **KYMRIAH**<sup>®</sup>  
(tisaqenlecleucel) Suspension for Intravenous Use



## 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 and adult patients with r/r DLBCL
- 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



## KYMRIAH REMS Program Knowledge Assessment



### 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)
  - 79% of patients developed CRS of any grade (Penn grading system); 49% developed CRS  $\geq$  grade 3
- The median time to onset of CRS was 3 days (range: 1-51 days), and in only two patients was onset after day 10\*
- The median time to resolution of CRS was 8 days (range: 1-36 days)\*
- Of the patients who developed CRS, 50% received tocilizumab:
  - 13% received two doses, 6% received three doses of tocilizumab
  - 26% received addition of corticosteroids (e.g. methylprednisolone).

\*Data for both ALL and DLBCL

 **KYMRIAH**<sup>®</sup>  
(tisaqenelecleucel) Suspension for IV infusion



## 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% of patients developed CRS of any grade (Penn grading system); 23% developed CRS  $\geq$  grade 3
- The median time to onset of CRS was 3 days (range: 1-51 days) following KYMRIAH infusion, and in only two patients was onset after day 10.\* The median duration of CRS was 8 days (range: 1-36 days)\*
- Of the patients who developed CRS, 21% received tocilizumab or corticosteroids:
  - 8% received one dose of tocilizumab and 13% received two doses of tocilizumab
  - 13% of patients received corticosteroids in addition to tocilizumab
  - Two patients received corticosteroids for CRS, without concomitant tocilizumab.
- Risk factors for developing severe CRS in adult with r/r DLBCL are not yet known

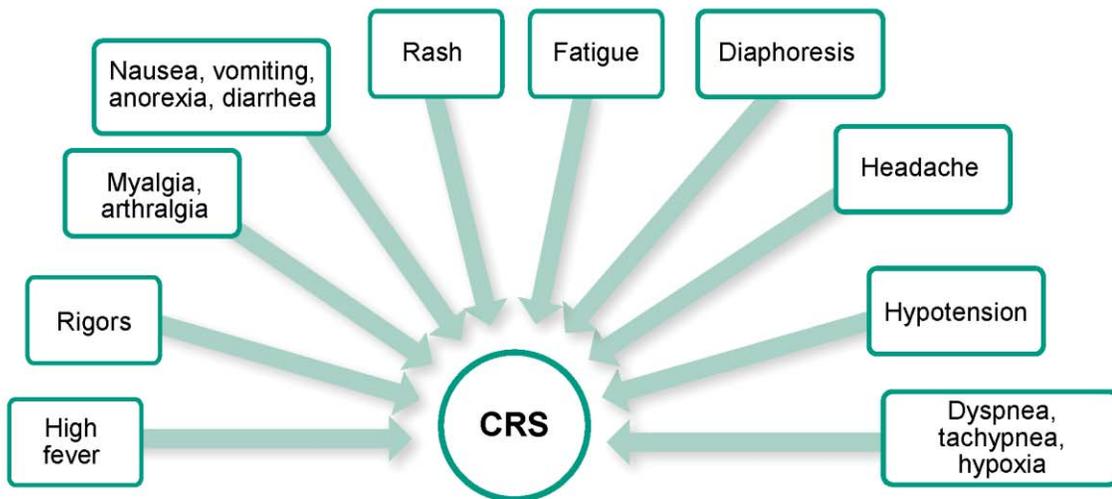
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\*Data for both ALL and DLBCL

 **KYMRIAH**<sup>®</sup>  
(tisaqenlecleucel) Suspension for IV infusion



## CRS signs and symptoms



**Diagnosis based on clinical symptoms and events**



## CRS: associating events and organ dysfunction

### Liver

- Hepatic dysfunction: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinemia

### Renal

- Renal insufficiency, may require dialysis

### Respiratory

- Respiratory failure, pulmonary edema

### Cardiac

- Transient cardiac insufficiency
- Transient arrhythmia

### Cytopenias lasting > 28 days

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



### 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 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
- 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
- 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



### CRS: Management, cont.

- Corticosteroids may be administered in cases of life-threatening emergencies
- Due to the known lympholytic effect of corticosteroids:
  - Do not use corticosteroids for premedication except in the case of a life-threatening emergency
  - Avoid the use of corticosteroids after infusion except in cases of life-threatening emergencies
  - Physiologic replacement doses are allowed for adrenal insufficiency



## KYMRIAH CRS management algorithm (1/2)

CRS Severity	Management
Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
CRS requiring mild intervention (one or more of the following): <ul style="list-style-type: none"><li>– High fever</li><li>– Hypoxia</li><li>– Mild hypotension</li></ul>	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.

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## KYMRIAH CRS management algorithm, cont. (2/2)

CRS Severity	Management
<p>CRS requiring moderate to aggressive intervention (one or more of the following):</p> <ul style="list-style-type: none"><li>- Hemodynamic instability despite intravenous fluids and vasopressor support</li><li>- Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation</li><li>- Rapid clinical deterioration</li></ul>	<ul style="list-style-type: none"><li>• Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed.</li><li>• Administer tocilizumab<ul style="list-style-type: none"><li>- Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour</li><li>- Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg)</li></ul></li><li>• Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement.</li><li>• If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS</li><li>• Limit to a maximum total of 4 doses of tocilizumab doses</li><li>• If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high flow oxygen are no longer needed, then taper</li></ul>



## Definition of high-dose vasopressors

Vasopressor	Dose for ≥ 3 Hours	
	Weight-based dosing	Flat dosing (if this is institutional practice)
Norepinephrine monotherapy	≥ 0.2 µg/kg/min	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min	≥ 1000 µg/min
Phenylephrine monotherapy	≥ 2 µg/kg/min	≥ 200 µg/min
Epinephrine monotherapy	≥ 0.1 µg/kg/min	≥ 10 µg/min
If on vasopressin	High dose if vasopressin + norepinephrine equivalent of ≥ 0.1 µg/kg/min (using VASST formula) <sup>a</sup>	vasopressin + norepinephrine equivalent of ≥ 10 µg/min <sup>b</sup>
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 0.2 µg/kg/min <sup>a</sup>	Norepinephrine equivalent of ≥ 20 µg/min (using VASST formula) <sup>b</sup>

### VASST\* Vasopressor Equivalent Equation

<sup>a</sup> 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]<sup>1</sup>

<sup>b</sup> Norepinephrine-equivalent dose [flat dosing (µg/min)] = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10]<sup>2,3,4</sup>

\*See references slide



## KYMRIAH-associated neurological toxicities





### 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 72% of patients, with  $\geq$  grade 3 in 21% of patients
  - In adult patients with r/r DLBCL (JULIET study): seen in 58% of patients, with  $\geq$  grade 3 in 18% of patients
- All patients with r/r ALL and the majority of patients with r/r DLBCL were treated with supportive care alone.
  - 2 patients with r/r DLBCL received corticosteroids for persistent neurotoxicity after resolution of CRS
- 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 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, mutism and aphasia
- Patients should be monitored for neurological toxicities during and after resolution 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 during or after resolution of CRS

### 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.

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## **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



## KYMRIAH REMS Program Knowledge Assessment



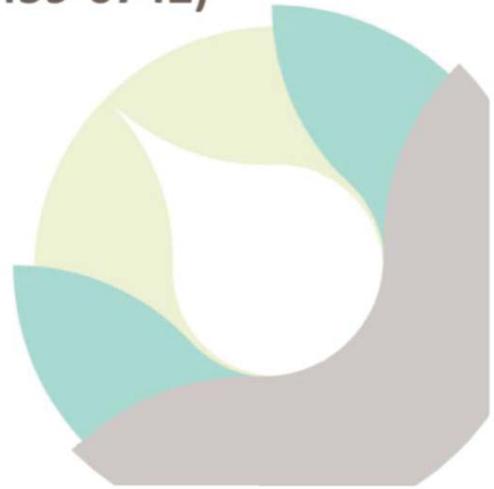
### Reporting Adverse Events

Healthcare providers are encouraged to report suspected adverse events of Kymriah® to FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or by calling 1-800-FDA-1088 or Novartis at <https://psi.novartis.com> or by calling 1-888-669-6682.



## KYMRIAH REMS Program Knowledge Assessment

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



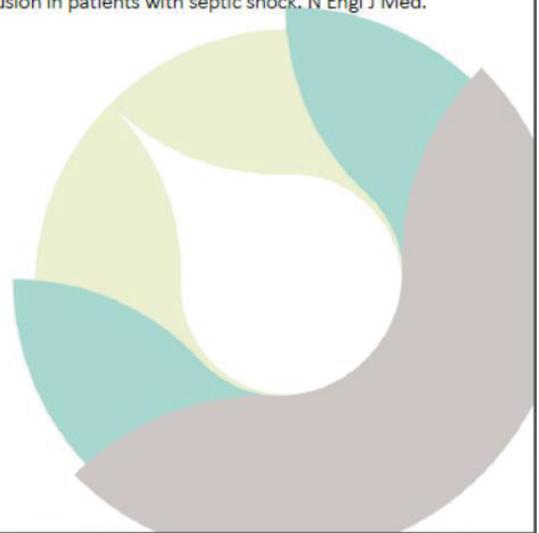
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## KYMRIAH REMS Program Knowledge Assessment

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4. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-87. doi:10.1056/NEJMoa067373





# KYMRIAH REMS Program Knowledge Assessment



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East Hanover, New Jersey 07936-1080

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KYD-1207304

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## 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 **3** 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
- Both B and D

### 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 chemotherapies

Submit

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**Question 3**

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

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

**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
  - 7-21 days following Kymriah infusion, with a median time to onset of 10 days
  - Median time to onset is 3 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 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 machinery) for at least 8 weeks after receiving Kymriah:

Submit

#### 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 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 (O<sub>2</sub> saturation 91%). He was started on norepinephrine at a low dose and O<sub>2</sub> 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
- Sepsis should be considered and treated adequately with broad spectrum antibiotics
- Start myeloid growth factor to expedite neutrophil recovery
- 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

Submit

**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 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:

- 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

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## KYMRIAH REMS Program Knowledge Assessment

Please complete the following assessment. You are required to answer all questions correctly in order to pass the assessment.

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All questions are required to be answered prior to submitting Knowledge Assessment.

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- Both B and D

### Question 2

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

- Active uncontrolled infection
- Worsening of leukemia burden following lymphodepleting chemotherapy
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- Active graft versus host disease

Submit

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Submit

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- All of the above**



## KYMRIAH REMS Program Knowledge Assessment

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. Or, you may immediately retake the assessment by clicking on "Retake Assessment".

### Question 1 ✘

**Kymriah™ (tisagenlecleucel) is indicated for the treatment of:**

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- Both B and D

### Question 2 ✔

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- C Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy**
- Active graft versus host disease
- Unresolved serious adverse reactions from preceding chemotherapies

Retake Training

Retake Assessment

- Active uncontrolled infection
- Worsening of leukemia burden following lymphodepleting chemotherapy
- Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
- Active graft versus host disease
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**Question 3** ✖

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- Hypofibrinogenemia

**Question 4** ✔

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Retake Training

Retake Assessment



## 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

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## KYMRIAH REMS Program Knowledge Assessment

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### **CONGRATULATIONS!**

You have successfully completed the KYMRIAH Knowledge Assessment.

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

# Certificate of Completion

## KYMRIAH REMS Program



This is to certify that

**Test test**

**ljNgEFA  
661**

has successfully completed the  
KYMRIAH 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 KYMRIAH REMS Program Hospital Enrollment Form,  
please complete and fax the form to 1-844-590-0840 or email the form to [KymriahREMS@ubc.com](mailto:KymriahREMS@ubc.com)

KYMRIAH  
Risk Evaluation and Mitigation Strategy (REMS)

 **KYMRIAH™**  
(tsisagenlecleucel) Suspension for intravenous use



## KYMRIAH REMS Program Knowledge Assessment

You have exceeded the number of attempts to pass this assessment.

Please contact the KYMRIAH REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742) to unlock your account and retake the KYMRIAH REMS Live Training Program and Knowledge Assessment.

### Question 1: ✘

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