



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 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 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 Materials

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



KYMRIAH REMS Materials, cont.

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



Site Certification

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

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



Authorized Representative

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



Conditions of Certification

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



KYMRIAH Boxed Warning

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

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

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

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

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

KYMRIAH-associated Cytokine Release Syndrome





Cytokine Release Syndrome (CRS)

- CRS, including fatal or life-threatening reactions, was the most common adverse event in the KYMRIA^H 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



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

- In the KYMRIA[®]H 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



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 KYMRIA administration

Infection

- Infections occur concurrently with CRS, may increase the risk of fatal events
- Prior to administration of KYMRIA, 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



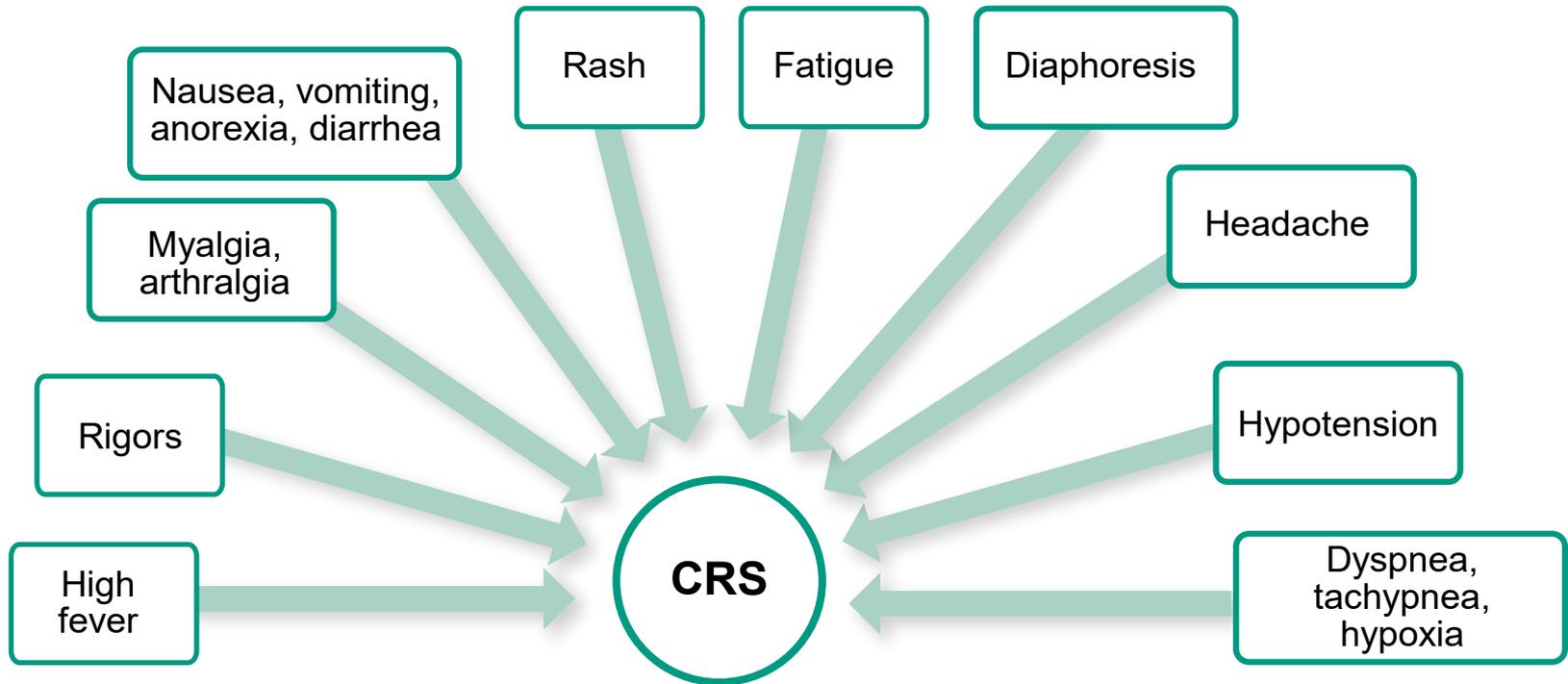
CRS in adult patients with r/r DLBCL

- In the KYMRIA^H 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 KYMRIA^H 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

*Data for both ALL and DLBCL



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 KYMRIA^H 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">– High fever– Hypoxia– Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.



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

CRS Severity

CRS requiring moderate to aggressive intervention (one or more of the following):

- Hemodynamic instability despite intravenous fluids and vasopressor support
- Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation
- Rapid clinical deterioration

Management

- Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed.
- Administer tocilizumab
 - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour
 - Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg)
- Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement.
- If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS
- Limit to a maximum total of 4 doses of tocilizumab doses
- 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.



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) ^a	vasopressin + norepinephrine equivalent of ≥ 10 µg/min ^b
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 0.2 µg/kg/min ^a	Norepinephrine equivalent of ≥ 20 µg/min (using VASST formula) ^b

VASST* Vasopressor Equivalent Equation

^a 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]¹

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

*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 KYMRIA^H infusion
- The majority of events were transient

Clinical presentation

- Major manifestations of neurological toxicities observed with KYMRIA^H 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

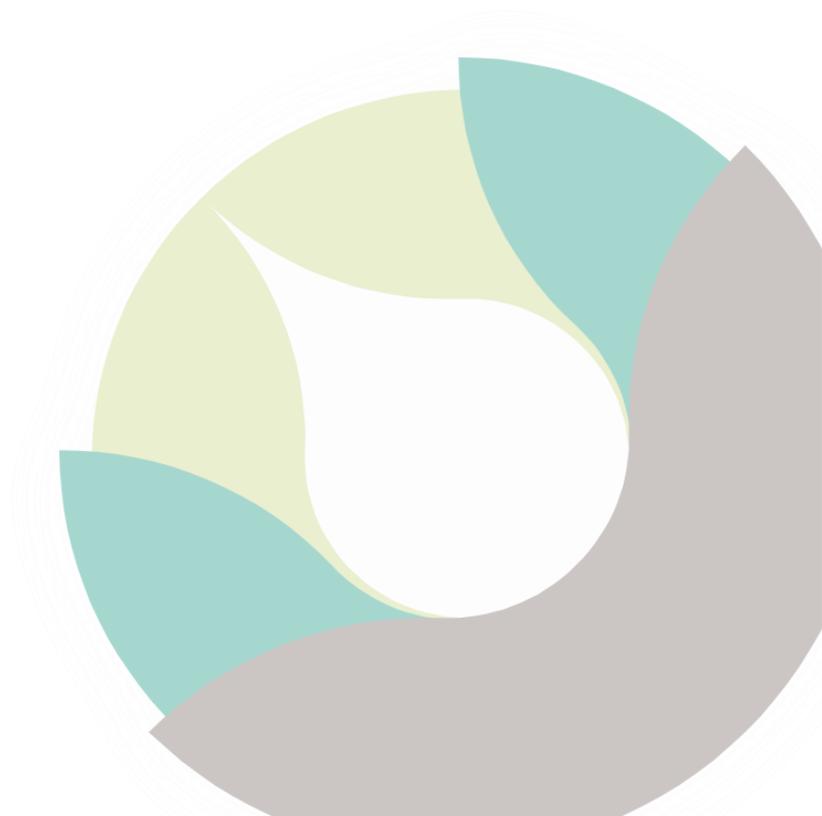
Management

- Supportive care should be given for KYMRIA[®]H-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 KYMRIA[®]H 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 KYMRIA[®]H.

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

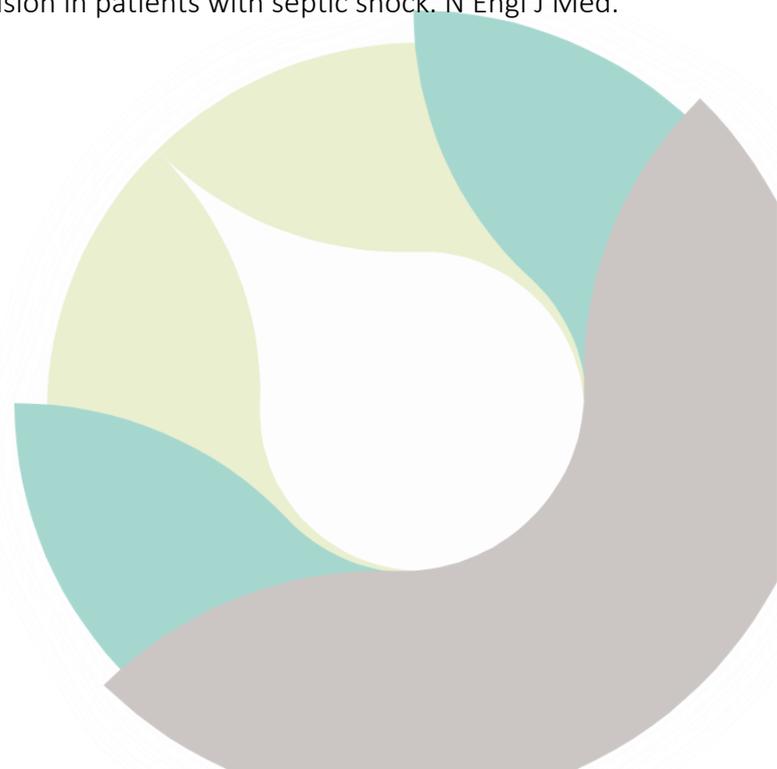
Healthcare providers are encouraged to report suspected adverse events of Kymriah[®] to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at <https://psi.novartis.com> or by calling 1-888-669-6682.

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



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