REMS Program Live Training
This educational module contains information on selected YESCARTA™-associated adverse reactions, including cytokine release syndrome and neurologic toxicities. These are not all of the adverse reactions associated with YESCARTA™.
**Indication**

YESCARTA™ is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of 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, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

**Limitation of Use:** YESCARTA™ is not indicated for the treatment of patients with primary central nervous system lymphoma.

The full Prescribing Information includes **BOXED WARNING** for YESCARTA™.

Please see full Prescribing Information, including **BOXED WARNING** and Medication Guide.
YESCARTA™ REMS Program Overview
What Is the YESCARTA™ REMS (Risk Evaluation and Mitigation Strategy) Program?

A REMS Program is a strategy to manage known or potential risks associated with a drug and is required by the United States (US) Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. YESCARTA™ is available only under a program called the YESCARTA™ REMS Program because of the serious risks of cytokine release syndrome (CRS) and neurologic toxicities.

The goals of the YESCARTA™ REMS Program are to mitigate the risks of CRS and neurologic toxicities by:

- Ensuring that hospitals and their associated clinics that dispense YESCARTA™ are specially certified and have on-site, immediate access to a minimum of 2 doses of tocilizumab
- Ensuring that those who prescribe, dispense, or administer YESCARTA™ are aware of how to manage the risks of CRS and neurologic toxicities
Hospital Certification

To become certified to dispense YESCARTA™, hospitals and their associated clinics must:

1. Designate an authorized representative to complete the training program by completing and submitting the YESCARTA™ REMS Program Hospital Enrollment Form on behalf of the hospital and its associated clinics

2. Ensure that the authorized representative oversees implementation and compliance with the YESCARTA™ REMS Program requirements

3. Dispense YESCARTA™ only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and ready for administration within 2 hours

4. Recertify in the YESCARTA™ REMS Program if a new authorized representative is designated
5. Maintain documentation that all processes and procedures are in place and are being followed for the YESCARTA™ REMS Program; provide this documentation upon request to Kite, FDA, or a third party acting on behalf of Kite or FDA

6. Comply with audits by Kite, FDA, or a third party acting on behalf of Kite or FDA, to ensure that all training, processes, and procedures are in place and are being followed for the YESCARTA™ REMS Program

7. Report any adverse events suggestive of CRS or neurologic toxicities
Who Can Be an Authorized Representative?

An authorized representative at the hospital and its associated clinics can be a:

- Physician
- Nurse
- Any responsible individual assigned by the hospital and its associated clinics

One representative (the “authorized representative”) must enroll for each hospital and its associated clinics and attest to the enrollment requirements as stated on the Yescarta™ REMS Program Hospital Enrollment Form.
YESCARTA™ Authorized Representative Attestations

- Complete the YESCARTA™ REMS Program Live Training and successfully complete the YESCARTA™ REMS Program Knowledge Assessment
- Submit the completed YESCARTA™ REMS Program Hospital Enrollment Form to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com
- Submit the YESCARTA™ REMS Program Knowledge Assessment to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com
- Oversee implementation and compliance with the YESCARTA™ REMS Program
Ensure that the hospital and its associated clinics will establish processes and procedures that are subject to monitoring by Kite or a third party acting on behalf of Kite to help ensure compliance with the requirements of the YESCARTA™ REMS Program, including the following, before administering YESCARTA™:

- Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA™ are trained on the REMS Program requirements as described in the training materials, successfully complete the YESCARTA™ REMS Program Knowledge Assessment, and maintain training records for all staff.
- Put processes and procedures in place to ensure that staff involved in the prescribing, dispensing, or administering of YESCARTA™ are retrained if YESCARTA™ has not been dispensed at least once annually from the date of certification in the YESCARTA™ REMS Program.
- Prior to dispensing YESCARTA™, 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).
- Prior to dispensing YESCARTA™, provide patients/caregivers with the Patient Wallet Card.
Serious Risks of YESCARTA™
Serious Risks Associated With YESCARTA™

BOXED WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA™. Do not administer YESCARTA™ to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA™, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA™. Provide supportive care and/or corticosteroids as needed.
Cytokine Release Syndrome

• CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA™

• In a Kite clinical trial, CRS occurred in 94% (101/108) of patients receiving YESCARTA™, including Grade 3 or higher CRS in 13% (14/108) of patients

• The median time to onset was 2 days (range, 1-12 days)

• The median duration of CRS was 7 days (range, 2-58 days)

• 45% (49/108) of patients received tocilizumab after infusion of YESCARTA™

• Among patients who died after receiving YESCARTA™, 4 had ongoing CRS events at the time of death
Neurologic Toxicities

- Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA™
- Neurologic toxicities occurred in 87% of patients, including Grade 3 or higher neurologic toxicities in 31% of patients
- 98% of all neurologic toxicities occurred within the first 8 weeks of YESCARTA™ infusion
- The median time to onset was 4 days (range, 1-43 days) following YESCARTA™ infusion
- The median duration was 17 days
- Prolonged encephalopathy lasting up to 173 days was noted
- Serious events including leukoencephalopathy and seizures occurred with YESCARTA™
- Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA™
Management of CRS and Neurologic Toxicities
Patient Assessment of CRS Associated With YESCARTA™

Symptoms of CRS

<table>
<thead>
<tr>
<th>CRS</th>
<th>The following are signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary leak syndrome</td>
<td>Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Chills</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
</tbody>
</table>
Guidance on Managing CRS

• Identify CRS based on clinical presentation
• Evaluate for and treat other causes of fever, hypoxia, and hypotension
• If CRS is suspected, manage according to the recommendations on slide 18
• Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry
• For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function
• For severe or life-threatening CRS, consider intensive care supportive therapy
• Monitor patients at least daily for 7 days at the certified hospitals and their associated clinics following infusion for signs and symptoms of CRS
• Monitor patients for signs or symptoms of CRS for 4 weeks after infusion
## Guidance on Management of CRS

### Grading and Management of YESCARTA™-Related CRS

<table>
<thead>
<tr>
<th>CRS Grade*</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong>&lt;br&gt;Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Grade 2</strong>&lt;br&gt;Symptoms require and respond to moderate intervention&lt;br&gt;Oxygen requirement less than 40% FiO₂ or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity†</td>
<td>Administer tocilizumab‡ 8 mg/kg intravenously over 1 hour (not to exceed 800 mg)&lt;br&gt;Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen&lt;br&gt;Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses</td>
<td>Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab</td>
</tr>
<tr>
<td><strong>Grade 3</strong>&lt;br&gt;Symptoms require and respond to aggressive intervention&lt;br&gt;Oxygen requirement greater than or equal to 40% FiO₂ or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis</td>
<td>Per Grade 2</td>
<td>Administer methylprednisolone, 1 mg/kg intravenously twice daily or equivalent dexamethasone (eg, 10 mg intravenously every 6 hours)&lt;br&gt;Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days</td>
</tr>
<tr>
<td><strong>Grade 4</strong>&lt;br&gt;Life-threatening symptoms&lt;br&gt;Requirements for ventilator support, CVHD, or Grade 4 organ toxicity (excluding transaminitis)</td>
<td>Per Grade 2</td>
<td>Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above</td>
</tr>
</tbody>
</table>

Abbreviation: CVHD, continuous veno-venous hemodialysis.

†Refer to the table on the back for management of neurologic toxicity.
‡Refer to tocilizumab Prescribing Information for details.
### Symptoms of Neurologic Toxicities

<table>
<thead>
<tr>
<th>Neurologic Toxicities</th>
<th>The following are common signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Aphasia</td>
<td>Headache</td>
</tr>
<tr>
<td>Delirium</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Tremor</td>
</tr>
</tbody>
</table>
Guidance on Managing Neurologic Toxicities

• Monitor patients for signs and symptoms of neurologic toxicities
• Rule out other causes of neurologic symptoms
• Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry
• Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities
• Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities
• Monitor patients at least daily for 7 days at the certified hospitals and their associated clinics following infusion for signs and symptoms of neurologic toxicities
• Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly
# Guidance on Managing Neurologic Toxicities

## Grading and Management of YESCARTA™-Related Neurologic Toxicities

<table>
<thead>
<tr>
<th>Neurologic Event (Grading Assessment CTCAE 4.03)*</th>
<th>Concurrent CRS</th>
<th>No Concurrent CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 2</strong> Examples include: <strong>Somnolence</strong>—moderate, limiting instrumental ADLs</td>
<td><strong>Administer tocilizumab</strong> per the earlier table for management of Grade 2 CRS</td>
<td><strong>Administer dexamethasone 10 mg intravenously every 6 hours</strong></td>
</tr>
<tr>
<td><strong>Confusion</strong>—moderate disorientation</td>
<td><strong>If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids</strong></td>
<td><strong>Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days</strong></td>
</tr>
<tr>
<td><strong>Encephalopathy</strong>—limiting instrumental ADLs</td>
<td><strong>Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days</strong></td>
<td><strong>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</strong></td>
</tr>
<tr>
<td><strong>Dysphasia</strong>—moderate impairing ability to communicate spontaneously</td>
<td><strong>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Seizure(s)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ADLs, activities of daily living.

## Guidance on Managing Neurologic Toxicities

Grading and Management of YESCARTA™-Related Neurologic Toxicities (continued)

<table>
<thead>
<tr>
<th>Neurologic Event (Grading Assessment CTCAE 4.03)*</th>
<th>Concurrent CRS</th>
<th>No Concurrent CRS</th>
</tr>
</thead>
</table>
| **Grade 3**  
Examples include:  
Somnolence—obtundation or stupor  
Confusion—severe disorientation  
Encephalopathy—limiting self-care ADLs  
Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly | Administer tocilizumab per the earlier table for management of Grade 2 CRS  
In addition, administer dexamethasone 10 mg intravenous with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days  
Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis | Administer dexamethasone 10 mg intravenous every 6 hours  
Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days  
Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis |
| **Grade 4**  
Life-threatening consequences  
Urgent intervention indicated  
Requirement for mechanical ventilation  
Consider cerebral edema | Administer tocilizumab per the earlier table for management of Grade 2 CRS  
Administer methylprednisolone 1000 mg intravenous per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenous per day for 2 more days; if improves, then manage as above  
Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis | Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above  
Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis |

Abbreviation: ADLs, activities of daily living.

Adverse Reaction Reporting

Reporting suspected adverse reactions after administration of therapy is important. It allows continued monitoring of the risk/benefit balance of therapy. Healthcare providers are asked to report any suspected adverse reactions associated with YESCARTA™.

Please contact Kite at 1-844-454-KITE or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Patient Counseling
Patient Counseling

Talk to the patient about the risk of CRS and neurologic toxicities. Tell them to contact their healthcare provider and/or seek immediate care if experiencing the signs and symptoms associated with CRS and neurologic toxicities:

- Fever (100.4°F/38°C or higher)
- Difficulty breathing
- Chills or shaking chills
- Confusion
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhea
- Fast or irregular heartbeat
- Severe fatigue or weakness

Provide the YESCARTA™ Patient Wallet Card to the patient or the patient’s caregiver. Tell the patient to carry the Patient Wallet Card at all times and to share the Patient Wallet Card with any healthcare provider involved in the patient’s treatment.

Instruct patient to remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following YESCARTA™ infusion.
YESCARTA™ REMS
Program Resources
YESCARTA™ REMS Program Kit

Includes:
- YESCARTA™ full Prescribing Information and Medication Guide
- YESCARTA™ REMS Program Live Training
- YESCARTA™ REMS Program Knowledge Assessment
- YESCARTA™ REMS Program Hospital Enrollment Form
- YESCARTA™ Adverse Reaction Management Guide
- YESCARTA™ Patient Wallet Card
YESCARTA™ REMS Program Knowledge Assessment

• An authorized representative must enroll on behalf of the hospital and its associated clinics by answering all questions correctly

• Paper responses to the YESCARTA™ REMS Program Knowledge Assessment questions must be faxed to 1-310-496-0397 or emailed to YESCARTAREMS@kitepharma.com
YESCARTA™ REMS Program
Hospital Enrollment Form

• To finalize registration in the YESCARTA™ REMS Program, complete the form in its entirety.

• Fax this completed form to the YESCARTA™ REMS Program at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com.
YESCARTA™ Adverse Reaction Management Guide

This guide will help to:

• Identify patients with CRS or neurologic toxicities; rule out concurrent infection

• Grade the severity of CRS or neurologic toxicities

• Provide treatment of CRS or neurologic toxicities according to the severity grade, as shown in this guide
YESCARTA™ Patient Wallet Card

• Provide to all patients who receive YESCARTA™ and complete the treating oncologist contact information

• Patients should carry their wallet card to remind them
  - About the signs and symptoms of CRS and neurologic toxicities that require immediate attention
  - To remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following infusion

• Patients should show this card to all healthcare providers they see

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**Patient Wallet Card**

*Carry this card with you at all times. SHOW THIS CARD if you go to the emergency room or see any physician.*

Tell any healthcare provider that sees you that you are being treated with YESCARTA™

Stay within close proximity (within 2 hours) of the location where you received your treatment for at least 4 weeks after getting YESCARTA™️.*
Additional YESCARTA™ REMS Program Information and Resources

To enroll in the YESCARTA™ REMS Program or obtain information regarding enrollment in the program, call 1-844-454-KITE or visit the YESCARTA™ REMS Program website at www.YESCARTAREMS.com.