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.

Please see full Prescribing Information, including BOXED WARNING and Medication Guide.
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
Hospital Certification (continued)

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 serious adverse events* suggestive of CRS or neurologic toxicities

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* Serious adverse events are defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
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
  - The Authorized Representative will determine relevant staff who require training
- Put processes and procedures in place to ensure that relevant 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 patient discharge, 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.
Management of CRS
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
Patient Assessment of CRS Associated With YESCARTA®

<table>
<thead>
<tr>
<th>The following are signs and symptoms of CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary leak syndrome</td>
</tr>
<tr>
<td>Heart attack</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Fever</td>
</tr>
</tbody>
</table>

(Capillary leak syndrome, Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), Cardiac arrhythmias, Hypoxia, Cardiac failure, Renal insufficiency, Chills, Tachycardia, Fever)
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 17
- Tocilizumab, an interleukin-6 receptor antagonist, is recommended for the management of Grade 2 or higher CRS associated with YESCARTA®
- Patients who experience Grade 2 or higher CRS (eg, 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></td>
<td>Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Symptoms require and respond to moderate intervention</td>
<td>Administer tocilizumab(^\text{b}) 8 mg/kg intravenously over 1 hour (not to exceed 800 mg)</td>
</tr>
<tr>
<td></td>
<td>Oxygen requirement less than 40% FiO(_2) or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity(^\text{c})</td>
<td>If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Symptoms require and respond to aggressive intervention</td>
<td>Per Grade 2</td>
</tr>
<tr>
<td></td>
<td>Oxygen requirement greater than or equal to 40% FiO(_2) or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis</td>
<td>Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Life-threatening symptoms</td>
<td>Per Grade 2</td>
</tr>
<tr>
<td></td>
<td>Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CVVHD, continuous veno-venous hemodialysis.


\(^{b}\)Refer to tocilizumab Prescribing Information for details.

\(^{c}\)Refer to the table on slides 22-23 for management of neurologic toxicity.
Management of Neurologic Toxicities
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®
### Patient Assessment of Neurologic Toxicities Associated With YESCARTA®

The following are common signs and symptoms of neurologic toxicities:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Aphasia</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
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<tr>
<td>Delirium</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td></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>
</table>
| **Grade 1** Examples include:  
Somnolence—mild drowsiness or sleepiness  
Confusion—mild disorientation  
Encephalopathy—mild limiting of ADLs  
Dysphasia—not impairing ability to communicate | Supportive care | Supportive care |

| **Grade 2** Examples include:  
Somnolence—moderate, limiting instrumental ADLs  
Confusion—moderate disorientation  
Encephalopathy—limiting instrumental ADLs  
Dysphasia—moderate, impairing ability to communicate spontaneously Seizure(s) |  
Administer tocilizumab per the table on slide 17 for management of Grade 2 CRS  
If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids  
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 intravenously 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 |

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>
<tbody>
<tr>
<td><strong>Grade 3</strong></td>
<td>Administer tocilizumab per the table on slide 17 for management of Grade 2 CRS</td>
<td>Administer dexamethasone 10 mg intravenous every 6 hours</td>
</tr>
<tr>
<td>Examples include:</td>
<td>In addition, administer dexamethasone 10 mg intravenous with the first dose of tocilizumab and repeat dose every 6 hours</td>
<td>Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days</td>
</tr>
<tr>
<td>Somnolence—obtundation or stupor</td>
<td>Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days</td>
<td>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</td>
</tr>
<tr>
<td>Confusion—severe disorientation</td>
<td>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy—limiting self-care ADLs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Grade 4** | Administer tocilizumab per the table on slide 17 for management of Grade 2 CRS | Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above |
| Life-threatening consequences | 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 |
| Urgent intervention indicated | Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis | |
| Requirement for mechanical ventilation | | |
| Consider cerebral edema | | |

Abbreviation: ADLs, activities of daily living.

Adverse Event Reporting

Reporting suspected adverse events after administration of therapy is important. It allows continued monitoring of the risk/benefit balance of therapy.

Healthcare providers are encouraged to report any suspected serious adverse events associated with YESCARTA® by contacting 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
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. The REMS Program website contains the most current version of REMS-related materials.