What Is the YESCARTA and TECARTUS REMS Program?

A REMS is a program required by the United States (US) Food and Drug Administration (FDA). The FDA has determined that a REMS is necessary to ensure that the benefits of YESCARTA and TECARTUS outweigh the risks of cytokine release syndrome and neurologic toxicities. YESCARTA and TECARTUS are available only through the YESCARTA and TECARTUS REMS Program.

Boxed Warning for YESCARTA

Cytokine Release Syndrome

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with YESCARTA
- CRS occurred in 90% (379/422) of patients with non-Hodgkin lymphoma (NHL) receiving YESCARTA, including ≥ Grade 3 CRS in 9%
- CRS occurred in 93% (256/276) of patients with large B-cell lymphoma (LBCL), including ≥ Grade 3 CRS in 9%
- CRS occurred in 84% (123/146) of patients with indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5, including ≥ Grade 3 CRS in 8%
- For patients with LBCL, the median time to onset of CRS in:
  - ZUMA-1 was 2 days following infusion (range: 1-12 days)
  - ZUMA-7 was 3 days following infusion (range: 1-10 days)
- For patients with iNHL, the median time to onset of CRS was 4 days (range: 1-20 days)
- For patients with LBCL, the median duration of CRS in:
  - ZUMA-1 was 7 days (range: 2-58 days)
  - ZUMA-7 was 7 days (range: 2-43 days)
For patients with iNHL the median duration of CRS was 6 days (range: 1-27 days)
• 45% (49/108) of patients with LBCL in ZUMA-1, and 67% (112/168) of patients with LBCL in ZUMA-7 received tocilizumab after infusion of YESCARTA
• 51% (75/146) of patients with iNHL received tocilizumab after infusion of YESCARTA
• Among patients who died after receiving YESCARTA, 4 patients with LBCL and 1 patient with iNHL had ongoing CRS events at the time of death
• Key manifestations of CRS (≥10%) in all patients combined include fever (85%), hypotension (40%), tachycardia (32%), chills (22%), hypoxia (20%), headache (15%), and fatigue (12%)
• Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), renal insufficiency, cardiac failure, respiratory failure, cardiac arrest, capillary leak syndrome, multi-organ failure, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
• The impact of earlier treatment with tocilizumab and/or corticosteroids on the incidence and severity of CRS was assessed in two subsequent cohorts of LBCL patients (ZUMA-1). Among patients who received tocilizumab and/or corticosteroids for ongoing Grade 1 events:
  o CRS occurred in 93% (38/41) including 2% (1/41) with Grade 3 CRS; no patients experienced a Grade 4 or 5 event
  o The median time to onset of CRS was 2 days (range: 1-8 days)
  o The median duration of CRS was 7 days (range: 2-16 days)
Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA:
  o Thirty-one out of 39 patients (79%) developed CRS with no patients developing Grade 3 or higher CRS
  o The median time to onset of CRS was 5 days (range: 1-15 days)
  o The median duration of CRS was 4 days (range: 1-10 days)
  o Although there is no known mechanistic explanation, consider the risk and benefits of prophylactic corticosteroids in the context of pre-existing comorbidities for the individual patient and the potential for the risk of Grade 4 and prolonged neurologic toxicities

Neurologic Toxicities
• Neurologic toxicities (including immune effector cell-associated neurotoxicity syndrome (ICANS)) that were fatal or life-threatening occurred following treatment with YESCARTA
• Neurologic toxicities occurred in 78% (330/422) of patients with NHL receiving YESCARTA, including ≥ Grade 3 cases in 25%
• Neurologic toxicities occurred in 87% (94/108) of patients with LBCL in ZUMA-1, including ≥ Grade 3 cases in 31% and in 74% (124/168) of patients in ZUMA-7 including ≥ Grade 3 cases in 25%
• Neurologic toxicities occurred in 77% (112/146) of patients with iNHL, including ≥ Grade 3 in 21%
• Neurologic toxicities occurred within the first 7 days of YESCARTA infusion for 87% of affected patients with LBCL and 74% of affected patients with iNHL
• For patients with LBCL, the median time to onset of neurologic toxicities in:
  o ZUMA-1 was 4 days (range: 1-43 days)
  o ZUMA-7 was 5 days (range: 1-133 days)
For patients with iNHL, the median time to onset of neurologic toxicities was 6 days (range: 1-79 days)
• For patient with LBCL, the median duration of neurologic toxicities in:
  o ZUMA-1 was 17 days
  o ZUMA-7 was 15 days
For patients with iNHL, the median duration was 16 days
• The most common neurologic toxicities (≥10%) in all patients combined included encephalopathy (50%), headache (43%), tremor (29%), dizziness (21%), aphasia (17%), delirium (15%), and insomnia (10%)
• Prolonged encephalopathy lasting up to 173 days was noted
• Serious events including aphasia, leukoencephalopathy, dysarthria, lethargy, and seizures occurred in patients treated with YESCARTA
• Fatal and serious cases of cerebral edema and encephalopathy, including late-onset encephalopathy, have occurred in patients treated with YESCARTA
• The impact of earlier treatment with tocilizumab and/or corticosteroids on the incidence and severity of neurologic toxicities was assessed in two subsequent cohorts of LBCL patients (ZUMA-1)
  Among patients who received corticosteroids at the onset of Grade 1 toxicities:
  o Neurologic toxicities occurred in 78% (32/41) and 20% (8/41) had Grade 3 neurologic toxicities; no patients experienced a Grade 4 or Grade 5 event
  o The median time to onset of neurologic toxicities was 6 days (range: 1-93 days)
  o The median duration was 8 days (range: 1-144 days)
Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA:
  o Thirty-three out of the 39 patients (85%) developed neurologic toxicities and 8% (3/39) developed Grade 3 and 5% (2/39) developed Grade 4 neurologic toxicities
The median time to onset of neurologic toxicities was 6 days (range: 1-274 days)
- The median duration of 12 days (range: 1-107 days)
- Prophylactic corticosteroids for management of CRS and neurologic toxicities may result in higher grade of neurologic toxicities or prolongation of neurologic toxicities, delay the onset and decrease the duration of CRS

Boxed Warning for TECARTUS

Cytokine Release Syndrome

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with TECARTUS
- CRS occurred in 91% (75/82) of patients with MCL, including ≥ Grade 3 (Lee grading system\(^1\)) CRS in 18% of patients. CRS occurred in 92% (72/78) of patients with ALL, including ≥ Grade 3 (Lee grading system\(^1\)) CRS in 26% of patients
- Among the patients with MCL who died after receiving TECARTUS, one had a fatal CRS event. Three patients with ALL had ongoing CRS events at the time of death
- The median time to onset of CRS was 3 days (range: 1-13 days), and the median duration of CRS was 10 days (range: 1-50 days) for patients with MCL. The median time to onset of CRS was 5 days (range: 1-12 days) and the median duration of CRS was 8 days (range: 2-63 days) for patients with ALL
- Key manifestations of CRS (>10%) were similar in MCL and ALL and included fever (93%), hypotension (62%), tachycardia (59%), chills (32%), hypoxia (31%), headache (21%), fatigue (20%), and nausea (13%)
- Serious events associated with CRS in MCL and ALL combined (≥2%) included hypotension, fever, hypoxia, tachycardia, and dyspnea


Neurologic Toxicities

- Neurologic events, including those that were fatal or life-threatening, occurred following treatment with TECARTUS
- The median time to onset for neurologic events was 6 days (range: 1-32 days) with a median duration of 21 days (range: 2-454 days) in patients with MCL. The median time to onset for neurologic events was 7 days (range: 1-51 days) with a median duration of 15 days (range: 1-397 days) in patients with ALL
Neurologic events occurred in 81% (66/82) of patients with MCL, including ≥ Grade 3 in 37% of patients. Neurologic events occurred in 87% (68/78) of patients with ALL, including ≥ Grade 3 in 35% of patients.

Nine patients (3 patients with MCL and 6 patients with ALL) had ongoing neurologic events at the time of death.

Neurologic events resolved for 119 out of 134 (89%) of all patients treated with TECARTUS.

Ninety-one percent of all treated patients experienced the first CRS or neurological event within the first 7 days after TECARTUS infusion.

The most common neurologic events (>10%) were similar in MCL and ALL and included encephalopathy (57%), headache (37%), tremor (34%), confusional state (26%), aphasia (23%), delirium (17%), dizziness (15%), anxiety (14%), and agitation (12%).

Serious events (≥2%) including encephalopathy, aphasia, confusional state, and seizures occurred after treatment with TECARTUS.

**YESCARTA and TECARTUS REMS Program Requirements**

Hospitals and their associated clinics must be enrolled in the YESCARTA and TECARTUS REMS Program to be able to dispense YESCARTA and/or TECARTUS.

All relevant staff involved in the prescribing, dispensing, or administering of YESCARTA and/or TECARTUS are trained on the YESCARTA and TECARTUS REMS Program requirements, and must successfully complete a YESCARTA and TECARTUS REMS Program Knowledge Assessment.

**Hospital Enrollment Instructions**

An authorized representative must enroll in the YESCARTA and TECARTUS REMS Program on behalf of the hospital and its associated clinics. To be enrolled in the YESCARTA and TECARTUS REMS Program, the representative must:

1. Complete the training program, which includes review of:
   - YESCARTA and TECARTUS full Prescribing Information
   - YESCARTA and TECARTUS REMS Program Training
   - YESCARTA and TECARTUS Adverse Reaction Management Guide
   - Successfully complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment.
Complete the YESCARTA and TECARTUS REMS Program Hospital Enrollment Form.

Oversee implementation and compliance with the YESCARTA and TECARTUS REMS Program requirements:

- Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA and/or TECARTUS are trained on the REMS Program requirements and successfully complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment. The authorized representative will determine relevant staff who require training.
- Maintain training records of staff.
- Ensure that the hospital and its associated clinics have a minimum of 2 doses of tocilizumab 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 and 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 or TECARTUS infusion.
- Put processes and procedures in place to ensure that relevant new staff are trained, and relevant staff are retrained if YESCARTA or TECARTUS has not been dispensed at least once annually from the date of certification in the YESCARTA and TECARTUS REMS Program.

**Indication**

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.

- 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.
• Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

**Indication**

TECARTUS is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

• Adult patients with relapsed or refractory mantle cell lymphoma (MCL). This indication is approved under accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

• Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

**Where to Find YESCARTA and TECARTUS REMS Program Information and Resources**

For more information about the YESCARTA and TECARTUS REMS Program, see the Program Resources or call 1-844-454-KITE (5483).

**Reporting Adverse Reactions**

Hospitals and their associated clinics must report any serious adverse event* suggestive of CRS or neurologic toxicities to Kite at 1-844-454-KITE (5483) or medinfo@kitepharma.com or [www.Gilead.com](http://www.Gilead.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Healthcare providers are also encouraged to report any suspected serious adverse events* associated with YESCARTA or TECARTUS as outlined above.

*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
Need Help?
If you have questions about the YESCARTA and TECARTUS REMS Program or need help registering, call 1-844-454-KITE.

LEFT HAND CORNER:

Resources for Healthcare Professionals

Download All Resources

YESCARTA and TECARTUS REMS Program Knowledge Assessment
YESCARTA and TECARTUS REMS Program Training
YESCARTA and TECARTUS REMS Program Hospital Enrollment Form
YESCARTA and TECARTUS Adverse Reaction Management Guide

YESCARTA and TECARTUS REMS Training
Log in to the YESCARTA and TECARTUS REMS Learning Management System [When the end user clicks on this hyperlink, an intermediary page loads which states: Contact your institution’s Authorized Representative for REMS Training. You are now leaving YescartaTecartusREMS.com. Select CANCEL to return or OK to continue.]

Resources for Patients

All patients treated with YESCARTA or TECARTUS receive a Patient Wallet Card listing adverse reactions and other information. Patients should carry the card with them at all times and show it to any healthcare professional who treats them, including in the emergency room. Non-English-speaking patients are given Patient Wallet Cards in both English and their native language. They should carry both versions of the card with them at all times.

YESCARTA and TECARTUS REMS Patient Wallet Card

Chinese         English         Spanish

Adobe Reader is required to view PDFs. If you do not have it installed, download it here.

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