

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YESCARTA safely and effectively. See full prescribing information for YESCARTA.

YESCARTA® (axicabtagene ciloleucel) suspension for intravenous infusion

Initial U.S. Approval: October 2017

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

See full prescribing information for complete boxed warning.

- 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 (2.2, 2.3, 5.1).
- 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 (2.2, 2.3, 5.2).
- YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program (5.3).

RECENT MAJOR CHANGES

Indications and Usage, Follicular Lymphoma (1.2)	03/2021
Dosage and Administration (2.3)	04/2021
Warnings and Precautions (5.1, 5.2)	04/2021

INDICATIONS AND USAGE

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.
Limitations of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma. (1.1)
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (1.2). 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). (1.2)

DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

- Do NOT use a leukodepleting filter.

- Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of YESCARTA. (2.2)
- Verify the patient's identity prior to infusion. (2.2)
- Premedicate with acetaminophen and an H1-antihistamine. (2.2)
- Confirm availability of tocilizumab prior to infusion. (2.1, 5.1)
- Dosing of YESCARTA is based on the number of chimeric antigen receptor (CAR)-positive viable T cells. (2.1)
- The target YESCARTA dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells. (2.1)
- Administer YESCARTA in a certified healthcare facility. (2.2, 5.1, 5.2, 5.3)

DOSAGE FORMS AND STRENGTHS

- YESCARTA is available as a cell suspension for infusion.
- YESCARTA comprises a suspension of 2×10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Monitor for hypersensitivity reactions during infusion. (5.4)
- Serious Infections: Monitor patients for signs and symptoms of infection; treat appropriately. (5.5)
- Prolonged Cytopenias: Patients may exhibit Grade 3 or higher cytopenias for several weeks following YESCARTA infusion. Monitor complete blood counts. (5.6)
- Hypogammaglobulinemia: Monitor and provide replacement therapy. (5.7)
- Secondary Malignancies: In the event that a secondary malignancy occurs after treatment with YESCARTA, contact Kite at 1-844-454-KITE (5483). (5.8)
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving YESCARTA. (5.9)

ADVERSE REACTIONS

The most common non-laboratory adverse reactions (incidence $\geq 20\%$) in patients with non-Hodgkin lymphoma are CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, febrile neutropenia, nausea, infections with pathogen unspecified, decreased appetite, chills, diarrhea, tremor, musculoskeletal pain, cough, hypoxia, constipation, vomiting, arrhythmias, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kite at 1-844-454-KITE (5483) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2021

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FULL PRESCRIBING INFORMATION

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 [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].**
- **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 [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)].**
- **YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program [see Warnings and Precautions (5.3)].**

1 INDICATIONS AND USAGE

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

1.1 Large B-cell Lymphoma

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.

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

1.2 Follicular 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 [see *Clinical Studies (14.2)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

2.1 Dose

Each single infusion bag of YESCARTA contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. The target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells.

2.2 Administration

YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient.

Preparing Patient for YESCARTA Infusion

Confirm availability of YESCARTA prior to starting the lymphodepleting regimen.

Pre-treatment

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of YESCARTA.

Premedication

- Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion.
- Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion

Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready.

- Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette.
- Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label.
- Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE).
- Place the infusion bag inside a second sterile bag per local guidelines.
- Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new medium prior to infusion.
- Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration

- For autologous use only.
- Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Do NOT use a leukodepleting filter.
- Central venous access is recommended for the infusion of YESCARTA.
- Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag.
- Prime the tubing with normal saline prior to infusion.
- Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw.
- Gently agitate the product bag during YESCARTA infusion to prevent cell clumping.
- After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered.

YESCARTA contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring

- Administer YESCARTA at a certified healthcare facility.
- Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation [*see Warnings and Precautions (5.1)*]. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. 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.

Table 1. CRS Grading and Management Guidance

CRS Grade ^a	Tocilizumab	Corticosteroids
<p>Grade 1</p> <p>Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).</p>	<p>If symptoms (e.g., fever) not improving after 24 hours, consider managing as Grade 2.</p>	<p>If not improving after 3 days, administer one dose of dexamethasone 10 mg intravenously.</p>
<p>Grade 2</p> <p>Symptoms require and respond to moderate intervention.</p> <p>Oxygen requirement less than 40% FiO₂ or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity.^b</p>	<p>Administer tocilizumab ^c 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).</p> <p>If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed.</p> <p>Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.</p> <p>If improving, discontinue tocilizumab.</p>	<p>Administer dexamethasone 10 mg intravenously once daily.</p> <p>If improving, manage as Grade 1 above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate.</p> <p>If not improving, manage as appropriate grade below.</p>
<p>Grade 3</p> <p>Symptoms require and respond to aggressive intervention.</p> <p>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.</p>	<p>Per Grade 2.</p> <p>If improving, manage as appropriate grade above.</p>	<p>Dexamethasone 10 mg intravenously three times a day.</p> <p>If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate.</p> <p>If not improving, manage as Grade 4.</p>
<p>Grade 4</p> <p>Life-threatening symptoms.</p> <p>Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).</p>	<p>Per Grade 2.</p> <p>If improving, manage as appropriate grade above.</p>	<p>Administer methylprednisolone 1000 mg intravenously once per day for 3 days.</p> <p>If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate.</p> <p>If not improving, consider methylprednisolone 1000 mg 2-3 times a day or alternate therapy.^d</p>

a. Lee et al. 2014.

b. Refer to Table 2 for management of neurologic toxicity.

c. Refer to tocilizumab Prescribing Information for details.

d. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities (Table 2). 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 levetiracetam for seizure prophylaxis for any grade of neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment ^a	Concurrent CRS	No Concurrent CRS
Grade 1	Administer tocilizumab per Table 1 for management of Grade 1 CRS. In addition, administer one dose of dexamethasone 10 mg intravenously. If not improving after 2 days, repeat dexamethasone 10 mg intravenously.	Administer one dose of dexamethasone 10 mg intravenously. If not improving after 2 days, repeat dexamethasone 10 mg intravenously.
	Consider levetiracetam for seizure prophylaxis.	
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously four times a day. If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.	Administer dexamethasone 10 mg intravenously four times a day. If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.
	Consider levetiracetam for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer methylprednisolone 1000 mg intravenously once daily. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.	Administer methylprednisolone 1000 mg intravenously once daily. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.
	Consider levetiracetam for seizure prophylaxis.	

Grading Assessment ^a	Concurrent CRS	No Concurrent CRS
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy. ^b	Administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy. ^b
	Consider levetiracetam for seizure prophylaxis.	

a. Severity based on Common Terminology Criteria for Adverse Events.

b. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

3 DOSAGE FORMS AND STRENGTHS

YESCARTA is available as a cell suspension for infusion.

A single dose of YESCARTA contains 2×10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL suspension in an infusion bag [see *How Supplied/Storage and Handling (16)*].

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. CRS occurred in 88% (224/254) of all patients with non-Hodgkin lymphoma (NHL) receiving YESCARTA, including \geq Grade 3 (Lee grading system¹) CRS in 10%. CRS occurred in 94% (101/108) of patients with large B-cell lymphoma (LBCL) in ZUMA-1, including \geq Grade 3 CRS in 13% [see *Adverse Reactions (6)*]. Among patients with LBCL who died after receiving YESCARTA, four had ongoing CRS events at the time of death. The median time to onset of CRS was 2 days (range: 1 to 12 days) and the median duration was 7 days (range: 2 to 58 days) for patients with LBCL.

CRS occurred in 84% (123/146) of patients with indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5, including \geq Grade 3 CRS in 8% (11/146) of patients with iNHL [see *Adverse Reactions (6)*]. Among patients with iNHL who died after receiving YESCARTA, one patient had an ongoing CRS event at the time of death. The median time to onset of CRS was 4 days (range: 1 to 20 days) and the median duration was 6 days (range: 1 to 27 days) for patients with iNHL.

Key manifestations of CRS ($\geq 10\%$) in all patients combined included fever (80%), hypotension (38%), tachycardia (29%), hypoxia (21%), chills (21%), and headache (13%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, multi-organ failure and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) [see *Adverse Reactions (6)*].

In a subsequent cohort of LBCL patients, tocilizumab and/or corticosteroids were administered for ongoing Grade 1 events (see Table 1) [see *Clinical Trials Experience (6.1)*]. CRS occurred in 93% (38/41) of these patients and 2% (1/41) had Grade 3 CRS, with no patients experiencing a Grade 4 or 5 event. The median time to onset of CRS was 2

days (range: 1 to 8 days) and the median duration of CRS was 7 days (range: 2 to 16 days). Key manifestations of CRS (> 5%) included pyrexia, hypotension, chills, headache, nausea, tachycardia, C-reactive protein increased, fatigue, hypoxia, and vomiting.

Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time [see *Patient Counseling Information (17)*]. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated [see *Dosage and Administration (2.3)*].

5.2 Neurologic Toxicities

Neurologic toxicities that were fatal or life-threatening occurred following treatment with YESCARTA. Neurologic toxicities occurred in 81% (206/254) of all patients with NHL receiving YESCARTA, including \geq Grade 3 cases in 26%.

Neurologic toxicities occurred in 87% (94/108) of patients with LBCL, including \geq Grade 3 cases in 31%. The median time to onset was 4 days (range: 1 to 43 days) and the median duration was 17 days. Neurologic toxicities occurred in 77% (112/146) of patients with iNHL, including \geq Grade 3 in 21%. The median time to onset was 6 days (range: 1 to 79 days) and the median duration was 16 days. Ninety-eight percent of all neurologic toxicities in patients with LBCL and 99% of all neurologic toxicities in patients with iNHL occurred within the first 8 weeks of YESCARTA infusion. Neurologic toxicities occurred within the first 7 days of YESCARTA infusion in 89% of affected patients with LBCL and 74% of affected patients with iNHL.

The most common neurologic toxicities (\geq 10%) in all patients combined included encephalopathy (53%), headache (45%), tremor (31%), dizziness (20%), delirium (16%), aphasia (15%), and insomnia (11%). 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.

In a subsequent cohort of LBCL patients who received corticosteroids at the onset of Grade 1 toxicities (Table 2), neurologic toxicities occurred in 78% (32/41) of these patients and 20% (8/41) had Grade 3 neurologic toxicities with no patients experiencing a Grade 4 or 5 event. The median time to onset of neurologic toxicities was 6 days (range: 1 to 93 days) with a median duration of 8 days (range: 1 to 144 days). The most common neurologic toxicities were consistent with the overall LBCL population treated with YESCARTA [see *Clinical Trials Experience (6.1)*].

Monitor patients at least daily for 7 days at the certified healthcare facility 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 [see *Dosage and Administration (2.3)*].

5.3 YESCARTA and TECARTUS REMS Program

Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program [see *Boxed Warning and Warnings and Precautions (5.1 and 5.2)*]. The required components of the YESCARTA and TECARTUS REMS Program are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaTecartusREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions

Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

5.5 Serious Infections

Severe or life-threatening infections occurred in patients after YESCARTA infusion. Infections (all grades) occurred in 47% (119/254) of all patients with NHL. Grade 3 or higher infections occurred in 19% of patients, Grade 3 or higher infections with an unspecified pathogen in 15%, bacterial infections in 5%, viral infections in 2%, and fungal infections in 1%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic antimicrobials according to local guidelines.

Febrile neutropenia was observed in 40% of all patients with NHL after YESCARTA infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

In immunosuppressed patients, including those who have received YESCARTA, life-threatening and fatal opportunistic infections including disseminated fungal infections (e.g., candida sepsis and aspergillus infections) and viral reactivation (e.g., human herpes virus-6 [HHV-6] encephalitis and JC virus progressive multifocal leukoencephalopathy [PML]) have been reported. The possibility of HHV-6 encephalitis and PML should be considered in immunosuppressed patients with neurologic events and appropriate diagnostic evaluations should be performed.

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 30% of all patients with NHL and included neutropenia (22%), thrombocytopenia (13%), and anemia (5%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. Hypogammaglobulinemia occurred in 17% of all patients with NHL. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies

Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome [see Warnings and Precautions (5.1, 5.3)]
- Neurologic Toxicities [see Warnings and Precautions (5.2, 5.3)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.4)]
- Serious Infections [see Warnings and Precautions (5.5)]
- Prolonged Cytopenias [see Warnings and Precautions (5.6)]
- Hypogammaglobulinemia [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in the WARNINGS AND PRECAUTIONS and in this section reflect exposure to YESCARTA in two open-label, single-arm studies in which 108 patients with relapsed or refractory LBCL (ZUMA-1 study) and 146 patients with relapsed or refractory iNHL (including 124 with FL; ZUMA-5 study) received a single dose of CD19-positive CAR T cells.

Relapsed or Refractory Large B-cell Lymphoma

The safety of YESCARTA was evaluated in ZUMA-1, a study in which 108 patients with relapsed/refractory large B-cell lymphoma received CD19-positive CAR T cells based on a recommended dose which was weight-based [see *Clinical Studies (14)*]. Patients with a history of central nervous system (CNS) disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median age of the study population was 58 years (range: 23 to 76 years); 68% were male. The baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 43% of patients and 1 in 57% of patients.

The most common adverse reactions (incidence $\geq 20\%$) included CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections with pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions ($> 2\%$) included encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia.

The most common ($\geq 10\%$) Grade 3 or higher reactions included febrile neutropenia, fever, CRS, encephalopathy, infections with pathogen unspecified, hypotension, hypoxia, and lung infections.

Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.

Table 3 summarizes the adverse reactions that occurred in at least 10% of patients treated with YESCARTA and Table 4 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients.

Table 3. Summary of Adverse Reactions Observed in at Least 10% of Patients Treated with YESCARTA in ZUMA-1 (N = 108)

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
<i>Blood and Lymphatic System Disorders</i>		
Febrile neutropenia	34	31
<i>Cardiac Disorders</i>		
Tachycardia ^a	57	2
Arrhythmia ^b	23	7

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
<i>Gastrointestinal Disorders</i>		
Diarrhea	38	4
Nausea	34	0
Vomiting	26	1
Constipation	23	0
Abdominal pain ^c	14	1
Dry mouth	11	0
<i>General Disorders and Administration Site Conditions</i>		
Fever ^d	86	16
Fatigue ^e	46	3
Chills	40	0
Edema ^f	19	1
<i>Immune System Disorders</i>		
Cytokine release syndrome	94	13
Hypogammaglobulinemia ^g	15	0
<i>Infections and Infestations</i>		
Infections with pathogen unspecified	26	16
Viral infections	16	4
Bacterial infections	13	9
<i>Investigations</i>		
Decreased appetite	44	2
Weight decreased	16	0
Dehydration	11	3
<i>Musculoskeletal and Connective Tissue Disorders</i>		
Motor dysfunction ^h	19	1
Pain in extremity ⁱ	17	2
Back pain	15	1
Muscle pain	14	1
Arthralgia	10	0
<i>Nervous System Disorders</i>		
Encephalopathy ^j	57	29
Headache ^k	45	1
Tremor	31	2
Dizziness ^l	21	1
Aphasia ^m	18	6
<i>Psychiatric Disorders</i>		
Delirium ⁿ	17	6
<i>Respiratory, Thoracic and Mediastinal Disorders</i>		
Hypoxia ^o	32	11
Cough ^p	30	0
Dyspnea ^q	19	3
Pleural effusion	13	2
<i>Renal and Urinary Disorders</i>		
Renal insufficiency	12	5
<i>Vascular Disorders</i>		
Hypotension ^r	57	15
Hypertension	15	6
Thrombosis ^s	10	1

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
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The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxia, renal insufficiency, and hypotension.

- a. Tachycardia includes tachycardia, sinus tachycardia.
- b. Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, bundle branch block right, electrocardiogram QT prolonged, extra-systoles, heart rate irregular, supraventricular extra systoles, supraventricular tachycardia, ventricular arrhythmia, ventricular tachycardia.
- c. Abdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper.
- d. Fever includes fever, febrile neutropenia.
- e. Fatigue includes fatigue, malaise.
- f. Edema includes face edema, generalized edema, local swelling, localized edema, edema, edema genital, edema peripheral, periorbital edema, peripheral swelling, scrotal edema.
- g. Hypogammaglobulinemia includes hypogammaglobulinemia, blood immunoglobulin D decreased, blood immunoglobulin G decreased.
- h. Motor dysfunction includes muscle spasms, muscular weakness.
- i. Pain in extremity includes pain not otherwise specified, pain in extremity.
- j. Encephalopathy includes cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor.
- k. Headache includes headache, head discomfort, sinus headache, procedural headache.
- l. Dizziness includes dizziness, presyncope, syncope.
- m. Aphasia includes aphasia, dysphasia.
- n. Delirium includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness.
- o. Hypoxia includes hypoxia, oxygen saturation decreased.
- p. Cough includes cough, productive cough, upper-airway cough syndrome.
- q. Dyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress.
- r. Hypotension includes diastolic hypotension, hypotension, orthostatic hypotension.
- s. Thrombosis includes deep vein thrombosis, embolism, embolism venous, pulmonary embolism, splenic infarction, splenic vein thrombosis, subclavian vein thrombosis, thrombosis, thrombosis in device.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following:

- *Blood and lymphatic system disorders:* Coagulopathy (2%)
- *Cardiac disorders:* Cardiac failure (6%), cardiac arrest (4%)
- *Immune system disorders:* Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%)
- *Infections and infestations disorders:* Fungal infections (5%)
- *Nervous system disorders:* Ataxia (6%), seizure (4%), dyscalculia (2%), myoclonus (2%)
- *Respiratory, thoracic and mediastinal disorders:* Pulmonary edema (9%)
- *Skin and subcutaneous tissue disorders:* Rash (9%)
- *Vascular disorders:* Capillary leak syndrome (3%)

Laboratory Abnormalities:

Table 4. Grade 3 or 4 Laboratory Abnormalities Occurring in $\geq 10\%$ of Patients in ZUMA-1 Following Treatment with YESCARTA (N = 108)

	Grades 3 or 4 (%)
Lymphopenia	100
Leukopenia	96
Neutropenia	93
Anemia	66
Thrombocytopenia	58
Hypophosphatemia	50
Hyponatremia	19
Uric acid increased	13
Direct bilirubin increased	13
Hypokalemia	10
Alanine aminotransferase increased	10

In a subsequent, open label, safety management cohort in ZUMA-1 that evaluated the safety and efficacy of YESCARTA with the use of corticosteroid and/or tocilizumab for Grade 1 CRS or neurologic events (see Tables 1 and 2), a total of 46 patients with relapsed or refractory LBCL were enrolled and 41 patients were treated with YESCARTA. Of the remaining five patients who were not treated, 2 patients died prior to receiving YESCARTA and three patients were ineligible due to disease progression. Twenty-eight patients (68%) treated with YESCARTA received bridging therapy between leukapheresis and lymphodepleting chemotherapy. Thirty-two patients (78%) treated with YESCARTA received tocilizumab and /or corticosteroid for CRS and/or neurologic events. Fifteen out of thirty-six with Grade 1 CRS and twenty one of twenty-four subjects with Grade 2 CRS received both tocilizumab and/or corticosteroids. Among subjects who received treatment for Grade 1 or Grade 2 CRS, most subjects (13 of 15 and 19 of 21 subjects, respectively) received both tocilizumab and corticosteroids. The most common dosing frequency was QD, and most subjects received 1 or 2 doses of each drug. Ten of twenty-seven subjects with Grade 1 and seven of fifteen subjects with Grade 2 neurologic events were treated with tocilizumab and/or corticosteroids. Similar number of subjects received corticosteroids only or in combination with tocilizumab (Grade 1: 4 and 5 subjects, respectively; Grade 2: 3 subject each). The most common dosing frequency was QD, the number of doses received by each subject varies more than the observed for Grade 1 or Grade 2 CRS.

Relapsed or Refractory Follicular Lymphoma

The safety of YESCARTA was evaluated in ZUMA-5, a study that included 146 patients with relapsed or refractory iNHL (124 patients with FL and 22 with marginal zone lymphoma) who received CD19-positive CAR T cells [see *Clinical Studies (14)*]. Patients with a history of CNS disorders or autoimmune disease requiring systemic immunosuppression were ineligible. The median age was 61 years (range: 34 to 79 years), 43% were female, 93% were white, 3% were black, and 1% were Asian.

The most common non-laboratory adverse reactions (incidence $\geq 20\%$) included fever, CRS, hypotension, encephalopathy, fatigue, headache, infections with pathogen unspecified, tachycardia, febrile neutropenia, musculoskeletal pain, nausea, tremor, chills, diarrhea, constipation, decreased appetite, cough, vomiting, hypoxia, arrhythmia, and dizziness. Serious adverse reactions occurred in 48% of patients. Serious adverse reactions in $> 2\%$ of patients included febrile neutropenia, encephalopathy, fever, CRS, infections with pathogen unspecified, pneumonia, hypoxia, and hypotension.

The most common ($\geq 10\%$) Grade 3 or higher reactions included febrile neutropenia, encephalopathy, and infections with pathogen unspecified. Fatal adverse reactions occurred in 1% of patients and included CRS and fungal infection.

Fifty-one percent (75/146) of patients received tocilizumab after infusion of YESCARTA.

Table 5 summarizes the adverse reactions, excluding laboratory terms, that occurred in at least 10% of patients treated

with YESCARTA and Table 6 describes Grade 3 or 4 laboratory abnormalities that developed or worsened in at least 10% of patients.

Table 5. Summary of Adverse Reactions Observed in at Least 10% of Patients Treated with YESCARTA in ZUMA-5 (N = 146)

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
<i>Blood and lymphatic system disorders</i>		
Febrile neutropenia ^a	41	41
<i>Cardiac Disorders</i>		
Tachycardia ^b	44	1
Arrhythmia ^c	21	2
<i>Gastrointestinal Disorders</i>		
Nausea	40	0
Diarrhea ^d	29	1
Constipation	28	0
Vomiting	24	1
Abdominal pain ^e	16	0
<i>General Disorders and Administration Site Conditions</i>		
Fever	85	8
Fatigue ^f	49	1
Chills	29	0
Edema ^g	13	1
<i>Immune System Disorders</i>		
Cytokine release syndrome	84	8
Immunoglobulins decreased ^h	18	1
<i>Infections and Infestations</i>		
Infections with pathogen unspecified	45	14
Pneumonia ⁱ	13	8
Fungal infections	12	2
Viral Infections	13	2
<i>Metabolism and Nutrition Disorders</i>		
Decreased appetite ^j	26	1
<i>Musculoskeletal and Connective Tissue Disorders</i>		
Musculoskeletal pain ^k	40	1
Motor dysfunction ^l	18	2
<i>Nervous System Disorders</i>		
Encephalopathy ^m	49	16
Headache	45	1
Tremor	31	1
Dizziness ⁿ	20	0
Aphasia	14	4
Neuropathy peripheral ^o	12	0
Ataxia ^p	10	0
<i>Psychiatric Disorders</i>		
Delirium ^q	16	5
Insomnia	16	0
Affective disorder ^r	10	1

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
<i>Respiratory, Thoracic and Mediastinal Disorders</i>		
Cough ^s	25	0
Hypoxia	23	8
Dyspnea ^t	12	1
Nasal congestion	10	0
<i>Skin and Subcutaneous Tissue Disorders</i>		
Rash ^u	19	3
<i>Vascular Disorders</i>		
Hypotension ^v	51	4
Hypertension	13	6
Thrombosis ^w	12	4

- a. Febrile neutropenia includes febrile neutropenia, fever overlapping with neutropenia.
- b. Tachycardia includes tachycardia, sinus tachycardia.
- c. Arrhythmia includes atrial fibrillation, atrioventricular block first degree, bradycardia, sinus bradycardia, supraventricular tachycardia, ventricular arrhythmia, ventricular extra systoles, ventricular tachycardia, electrocardiogram QT prolonged, electrocardiogram T wave inversion.
- d. Diarrhea includes diarrhea, colitis, enteritis.
- e. Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, dyspepsia, epigastric discomfort.
- f. Fatigue includes asthenia, fatigue, decreased activity, malaise.
- g. Edema includes edema, face edema, generalized edema, localized edema, edema peripheral, peripheral swelling, pulmonary edema, swelling face.
- h. Immunoglobulins decreased includes hypogammaglobulinemia, blood immunoglobulin G decreased.
- i. Pneumonia includes pneumonia streptococcal, pneumonia, lung infiltration. Pneumonia is also summarized under infections with pathogen unspecified.
- j. Decreased appetite includes decreased appetite, hypophagia.
- k. Musculoskeletal pain includes musculoskeletal pain, arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, myalgia, neck pain, osteoarthritis, pain in extremity.
- l. Motor dysfunction includes motor dysfunction, muscle rigidity, muscle spasms, muscle strain, muscular weakness.
- m. Encephalopathy includes agraphia, amnesia, aphonia, apraxia, CAR T-cell-related encephalopathy syndrome, cognitive disorder, disturbance in attention, dysarthria, dysgraphia, dyskinesia, encephalopathy, lethargy, loss of consciousness, memory impairment, somnolence, speech disorder, confusional state, mental status changes, immune effector cell-associated neurotoxicity, neurotoxicity, toxic encephalopathy.
- n. Dizziness includes dizziness, presyncope, syncope, vertigo.
- o. Neuropathy peripheral includes allodynia, cervical radiculopathy, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy.
- p. Ataxia includes ataxia, balance disorder, gait disturbance, vestibular disorder.
- q. Delirium includes agitation, delirium, hallucination, restlessness.
- r. Affective disorder includes anxiety, depression, impulsive behavior, mania, panic attack.
- s. Cough includes cough, productive cough, upper-airway cough syndrome.
- t. Dyspnea includes dyspnea, dyspnea exertional.
- u. Rash includes dermatitis bullous, erythema, pruritus, rash, rash macular, rash maculo-papular, Stevens-Johnson syndrome, urticaria.
- v. Hypotension includes capillary leak syndrome, hypotension, hypoperfusion, orthostatic hypotension.
- w. Thrombosis includes deep vein thrombosis, embolism, peripheral ischemia, pulmonary embolism, thrombosis in device, vascular occlusion, jugular vein thrombosis.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following:

- *Blood and lymphatic system disorders:* Coagulopathy (6%)
- *Cardiac disorders:* Cardiac failure (2%)
- *Eye disorders:* Visual impairment (5%), blindness (1%)
- *Gastrointestinal disorders:* Dysphagia (6%)
- *General disorders and administration site conditions:* Multiple organ dysfunction syndrome (1%)
- *Infections and infestations:* Bacterial infections (8%), sepsis (2%), herpesvirus infection (4%)
- *Musculoskeletal and connective tissue disorders:* Muscle injury (1%)

- *Nervous system disorders:* Seizure (2%), hemiparesis (2%), ischemic stroke (1%)
- *Renal and urinary disorders:* Renal insufficiency (8%)
- *Respiratory, thoracic and mediastinal disorders:* Respiratory failure (1%)
- *Vascular disorders:* Hemorrhage (8%)

Laboratory Abnormalities:

Table 6. Grade 3 or 4 Laboratory Abnormalities Occurring in $\geq 10\%$ of Patients in ZUMA-5 Following Treatment with YESCARTA (N = 146)

	Grades 3 or 4 (%)
Neutropenia	92
Leukopenia	92
Thrombocytopenia	35
Anemia	30
Hypophosphatemia	25
Lymphopenia	23
Hyponatremia	10
Hyperglycemia	10
Hyperuricemia	10
Hypocalcemia	10

6.2 Immunogenicity

YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in ZUMA-1. In ZUMA-5, 19 patients (13%) were antibody-positive at baseline, and 3 patients (2%) who had negative test results at baseline had positive test results after Day 0 in the screening ELISA. Results of a confirmatory cell-based assay, leveraging a properly folded and expressed extracellular portion of the CAR (ScFv, hinge and linker) demonstrated that all patients treated with YESCARTA that had a positive result in the screening ELISA were antibody negative at all time points tested. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of YESCARTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders

Spinal cord edema, myelitis, quadriplegia, and dysphagia

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA.

Infertility

There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use

The safety and efficacy of YESCARTA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 254 patients with NHL who received YESCARTA in clinical trials, 78 patients (31%) were 65 years of age and older. Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

11 DESCRIPTION

YESCARTA (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare YESCARTA, a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognize and eliminate CD19-expressing target cells.

YESCARTA is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and activated with anti-CD3 antibody in the presence of IL-2, then transduced with the replication incompetent retroviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed prior to infusion [*see Dosage and Administration (2.2), How Supplied/Storage and Handling (16)*].

In addition to T cells, YESCARTA may contain NK and NK-T cells. The formulation contains 5% dimethyl sulfoxide (DMSO) and 2.5% albumin (human).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

YESCARTA, a CD19-directed genetically modified autologous T cell immunotherapy, binds to CD19-expressing cancer cells and normal B cells. Studies demonstrated that following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

12.2 Pharmacodynamics

After YESCARTA infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF- α , IFN- γ , and sIL2R α were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days.

Due to the on-target effect of YESCARTA, a period of B-cell aplasia is expected.

Among patients with LBCL with an ongoing response at 24 months, 13 of 29 evaluable patients (45%) had no detectable B cells at baseline, and the majority of patients at Month 3 (28 of 35 evaluable patients [80%]) and Month 6 (25 of 32 evaluable patients [78%]) had no detectable B cells. At Month 24, 24 of 32 evaluable patients (75%) had detectable B cells.

12.3 Pharmacokinetics

Following infusion of YESCARTA, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7 - 14 days after YESCARTA infusion.

Age (range: 23 to 76 years) and gender had no significant impact on AUC Day 0 - 28 and C_{\max} of YESCARTA.

Among patients with LBCL (n=96 evaluable), the number of anti-CD19 CAR T cells in blood was positively associated with objective response [complete remission (CR) or partial remission (PR)]. The median anti-CD19 CAR T cell C_{\max} levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23) (43.6 cells/ μ L vs 21.2 cells/ μ L). Median AUC Day 0 - 28 in responding patients (n=73) was 251% of the corresponding level in nonresponders (n=23) (557.1 days \times cells/ μ L vs. 222.0 days \times cells/ μ L).

Among patients with FL (n=81 evaluable), the median anti-CD19 CAR T-cell C_{\max} levels in responders (n=74) were 40.1 cells/ μ L and 46.0 cells/ μ L in nonresponders (n=7). The median AUC Day 0 - 28 in responding FL patients (n=74) were 465.8 days \times cells/ μ L and 404.5 days \times cells/ μ L in nonresponders (n=7).

Some patients required tocilizumab and corticosteroids for management of CRS and neurologic toxicities. Patients treated with tocilizumab (n=44) had 262% and 232% higher anti-CD19 CAR T cells as measured by AUC Day 0 - 28 and C_{\max} respectively, as compared to patients who did not receive tocilizumab (n=57). Similarly, patients that received corticosteroids (n=26) had 217% and 155% higher AUC Day 0 - 28 and C_{\max} compared to patients who did not receive corticosteroids (n=75).

Hepatic and renal impairment studies of YESCARTA were not conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with YESCARTA. No studies have been conducted to evaluate the effects of YESCARTA on fertility.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory Large B-Cell Lymphoma

A single-arm, open-label, multicenter trial evaluated the efficacy of a single infusion of YESCARTA in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/ μ L, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection.

Following lymphodepleting chemotherapy, YESCARTA was administered as a single intravenous infusion at a target dose of 2×10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the fifth, fourth, and third day before YESCARTA. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for YESCARTA infusion and for a minimum of 7 days afterward.

Of 111 patients who underwent leukapheresis, 101 received YESCARTA. Of the patients treated, the median age was 58 years (range: 23 to 76 years), 67% were male, and 89% were white. Most (76%) had DLBCL, 16% had transformed follicular lymphoma, and 8% had primary mediastinal large B-cell lymphoma. The median number of prior therapies was 3 (range: 1 to 10), 77% of the patients had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT.

One out of 111 patients did not receive the product due to manufacturing failure. Nine other patients were not treated, primarily due to progressive disease or serious adverse reactions following leukapheresis. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was 2.0×10^6 CAR-positive viable T cells/kg (range: 1.1 to 2.2×10^6 cells/kg).

Efficacy was established on the basis of complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee (Table 7 and Table 8). The median time to response was 0.9 months (range: 0.8 to 6.2 months). Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR) (Table 8). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).

Table 7. Response Rate in Patients with Relapsed or Refractory LBCL

	Recipients of YESCARTA (N = 101)
Objective Response Rate^a (95% CI)	73 (72%) (62, 81)
Complete Remission Rate (95% CI)	52 (51%) (41, 62)
Partial Remission Rate (95% CI)	21 (21%) (13, 30)

CI, confidence interval.

a. Per 2007 revised International Working Group criteria, as assessed by the independent review committee.

Table 8. Duration of Response in Patients with Relapsed or Refractory LBCL

	From N of 101
Number of Responders	73
DOR (Months)^a	
Median ^b	9.2
(95% CI)	(5.4, NE)
Range ^c	0.03+, 14.4+
DOR if Best Response is CR (Months)	
Median ^b	NE
(95% CI)	(8.1, NE)
Range ^c	0.4, 14.4+
DOR if Best Response is PR (Months)	
Median ^b	2.1
(95% CI)	(1.3, 5.3)
Range ^c	0.03+, 8.4+
Median Follow-up for DOR (Months)^{a, b}	7.9

CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission.

- Among all responders. DOR is measured from the date of first objective response to the date of progression or death from relapse or toxicity.
- Kaplan-Meier estimate.
- A “+” sign indicates a censored value.

14.2 Relapsed or Refractory Follicular Lymphoma

Efficacy in FL is based on a single-arm, open-label, multicenter trial (ZUMA-5; NCT03105336) that evaluated a single infusion of YESCARTA in adult patients with relapsed or refractory FL after two or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. The study excluded patients with active or serious infections, transformed lymphoma or other aggressive lymphomas, prior allogeneic HSCT, or any history of CNS lymphoma or CNS disorders. Following lymphodepleting chemotherapy, YESCARTA was administered as a single intravenous infusion with a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the fifth, fourth, and third day before YESCARTA.

Of 123 patients with FL who underwent leukapheresis, 120 received YESCARTA. Of the remaining three patients (2%) who were not treated, one was ineligible due to thrombocytopenia, one went into remission prior to initiating lymphodepletion, and one died of cardiac arrest. There were no manufacturing failures. Of the 120 patients with FL infused with YESCARTA, the 81 consecutive patients included in the primary efficacy analysis had at least 9 months of potential follow-up from date of first response.

Among the 81 patients with FL included in the primary efficacy analysis, the median age was 62 years (range: 34 to 79 years), 46% were female, 93% were white, 4% were black, and 3% were Asian. The median number of prior systemic therapies was 3 (range: 2 to 9), with 32% having 2 prior lines, 22% having 3 prior lines, and 46% having ≥ 4 prior lines. Thirty-one percent had received a PI3K inhibitor, 72% had progression within 6 months of the most recent regimen, and 56% had progression within 24 months of initiating their first anti-CD20 combination therapy. Between leukapheresis and administration of YESCARTA, one patient (1%) in the primary efficacy analysis received bridging therapy.

Among the 81 patients included in the primary efficacy analysis, the median time from leukapheresis to product delivery was 17 days (range: 13 to 33 days) and leukapheresis to product infusion was 27 days (range: 19 to 250 days). The median dose of YESCARTA was 2.0×10^6 CAR T cells/kg (range 1.3 to 2.1×10^6 CAR T cells/kg). All treated patients received YESCARTA infusion on day 0 and were hospitalized until at least day 7.

Efficacy was established on the basis of objective response rate and DOR as determined by an independent review committee (Table 9 and Table 10). The median time to response in the primary efficacy population was 1.0 month (range: 0.8 – 3.1 months).

Table 9 Response Rate in Patients with Relapsed or Refractory FL

	Primary Efficacy Analysis (N = 81)	All Leukapheresed Patients (N = 123)
Objective Response Rate^a, n (95% CI)	74 (91%) (83, 96)	110 (89%) (83, 94)
Complete Remission ^b , n (95% CI)	49 (60%) (49, 71)	76 (62%) (53, 70)
Partial Remission, n (95% CI)	25 (31%) (21, 42)	34 (28%) (20, 36)

CI, confidence interval.

- Per the International Working Group Lugano Classification (Cheson 2014), as assessed by the independent review committee.
- Complete remission required documentation of a negative bone marrow biopsy after treatment, in patients who did not have a negative bone marrow biopsy between their most recent disease progression prior to ZUMA-5 and initiation of lymphodepleting chemotherapy.

Table 10 Duration of Response in Patients with Relapsed or Refractory FL

	From N of 81
Number of Responders	74
DOR (Months)^a	
Median ^b	NE
(95% CI)	(20.8, NE)
Range ^c	0.0, 25.0+
Rate of Continued Remission^{a, b, d}	
At 12 months (95% CI), %	76.2 (63.9, 84.7)
At 18 months (95% CI), %	74.2 (61.5, 83.2)
Median Follow-up for DOR (Months)^{a, b}	14.5

CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission.

- Among all responders in the primary efficacy population. DOR is measured from the date of first objective response to the date of progression or death from any cause.
- Kaplan-Meier estimate.
- A “+” sign indicates a censored value.
- Measured from the date of first objective response to the date of progression or death.

15 REFERENCES

- Lee DW et al (2014). Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014 Jul 10; 124(2): 188-195.

16 HOW SUPPLIED/STORAGE AND HANDLING

YESCARTA is supplied in an infusion bag (NDC 71287-119-01) containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% DMSO and 2.5% albumin (human).

Each YESCARTA infusion bag is individually packed in a metal cassette (NDC 71287-119-02). YESCARTA is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry shipper.

- Match the identity of the patient with the patient identifiers on the cassette and infusion bag upon receipt.
- Store YESCARTA frozen in the vapor phase of liquid nitrogen (less than or equal to minus 150°C).
- Thaw before using [*see Dosage and Administration (2)*].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ensure that patients understand the risk of manufacturing failure (< 1% in clinical trials). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period.

Advise patients to seek immediate attention for any of the following:

- Cytokine Release Syndrome (CRS) - Signs or symptoms associated with CRS, including fever, chills, fatigue, tachycardia, nausea, hypoxia, and hypotension [*see Warnings and Precautions (5.1) and Adverse Reactions (6)*].
- Neurologic Toxicities - Signs or symptoms associated with neurologic events, including encephalopathy, seizures, changes in level of consciousness, speech disorders, tremors, and confusion [*see Warnings and Precautions (5.2) and Adverse Reactions (6)*].
- Serious Infections - Signs or symptoms associated with infection [*see Warnings and Precautions (5.5) and Adverse Reactions (6)*].
- Prolonged Cytopenia - Signs or symptoms associated with bone marrow suppression, including neutropenia, anemia, thrombocytopenia, or febrile neutropenia [*see Warnings and Precautions (5.6) and Adverse Reactions (6)*].

Advise patients of the need to:

- Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion for at least 8 weeks after infusion [*see Warnings and Precautions (5.9)*].
- Have periodic monitoring of blood counts.
- Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy [*see Warnings and Precautions (5.8)*].

Manufactured by, Packed by, Distributed by:

Kite Pharma, Inc.
Santa Monica, CA 90404
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125643-GS-006

MEDICATION GUIDE

YESCARTA (pronounced yes-kar-ta) (axicabtagene ciloleucel)

Read this Medication Guide before you start your YESCARTA treatment. The more you know about your treatment, the more active you can be in your care. Talk with your healthcare provider if you have questions about your health condition or treatment. Reading this Medication Guide does not take the place of talking with your healthcare provider about your treatment.

What is the most important information I should know about YESCARTA?

YESCARTA may cause side effects that are life-threatening and can lead to death. Call or see your healthcare provider or get emergency help right away if you get any of the following:

- 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

It is important to tell your healthcare provider that you received YESCARTA and to show them your YESCARTA Patient Wallet Card. Your healthcare provider may give you other medicines to treat your side effects.

What is YESCARTA?

YESCARTA is a treatment for your large B-cell lymphoma or follicular lymphoma, two types of non-Hodgkin lymphoma. It is used when at least two other kinds of treatment have failed to control your cancer. YESCARTA is different than other cancer medicines because it is made from your own white blood cells, which have been modified to recognize and attack your lymphoma cells.

Before getting YESCARTA, tell your healthcare provider about all your medical problems, including if you have or have had:

- Neurologic problems (such as seizures, stroke, or memory loss)
- Lung or breathing problems
- Heart problems
- Liver problems
- Kidney problems
- A recent or active infection

Tell your healthcare provider about all the medications you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive YESCARTA?

- Since YESCARTA is made from your own white blood cells, your blood will be collected by a process called “leukapheresis” (loo-kah-fur-ee-sis), which will concentrate your white blood cells.
- Your blood cells will be sent to a manufacturing center to make your YESCARTA.
- Before you get YESCARTA, you will get 3 days of chemotherapy to prepare your body.

- When your YESCARTA is ready, your healthcare provider will give it to you through a catheter placed into your vein (intravenous infusion). The infusion usually takes less than 30 minutes.
- You will be monitored where you received your treatment daily for at least 7 days after the infusion.
- You should plan to stay close to the location where you received your treatment for at least 4 weeks after getting YESCARTA. Your healthcare provider will help you with any side effects that may occur.
- You may be hospitalized for side effects and your healthcare provider will discharge you if your side effects are under control, and it is safe for you to leave the hospital.
- Your healthcare provider will want to do blood tests to follow your progress. It is important that you do have your blood tested. If you miss an appointment, call your healthcare provider as soon as possible to reschedule.

What should I avoid after receiving YESCARTA?

- Do not drive, operate heavy machinery, or do other dangerous things for 8 weeks after you get YESCARTA because the treatment can cause sleepiness, confusion, weakness, and temporary memory and coordination problems.
- Do not donate blood, organs, tissues, or cells for transplantation.

What are the possible or reasonably likely side effects of YESCARTA?

The most common side effects of YESCARTA include:

- Fever (100.4°F/38°C or higher)
- Low white blood cells (can occur with a fever)
- Low red blood cells
- Low blood pressure (dizziness or lightheadedness, headache, feeling tired, short of breath)
- Fast heartbeat
- Confusion
- Difficulty speaking or slurred speech
- Nausea
- Diarrhea

These are not all the possible side effects of YESCARTA. Call your healthcare provider about any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

General information about the safe and effective use of YESCARTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about YESCARTA, talk with your healthcare provider. You can ask your healthcare provider for information about YESCARTA that is written for health professionals. You can get additional information by contacting Kite at 1-844-454-KITE (5483) or at www.Yescarta.com.

What are the ingredients in YESCARTA?

Active ingredients: axicabtagene ciloleucel.

Inactive ingredients: albumin (human); DMSO.

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