YESCARTA® (axicabtagene ciloleucel) suspension for intravenous infusion

PACKAGE INSERT

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, or active graft-versus-host disease (GVHD). 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 Controlled Distribution 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 (LBCL) 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.

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/m^2 intravenously and fludarabine 30 mg/m^2 intravenously on the fifth, fourth, and third day before infusion of YESCARTA.

Premedication

- Administer acetaminophen/paracetamol and diphenhydramine approximately 1 hour before YESCARTA

infusion.
- Consider the use of prophylactic corticosteroid in patients after weighing the potential benefits and risks *[see Warnings and Precautions (5.1 and 5.2)]*.

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 contact 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 cytokine release syndrome (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 (CRS)

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**
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If symptoms (e.g., fever) not improving after 24 hours, consider managing as Grade 2.	If not improving after 3 days, administer one dose of dexamethasone 10 mg intravenously.
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity.[b]	Administer tocilizumab [c] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). 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. If improving, discontinue tocilizumab.	Administer dexamethasone 10 mg intravenously once daily. If improving, manage as Grade 1 above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.
Grade 3 Symptoms require and respond to aggressive intervention. 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.	Per Grade 2. If improving, manage as appropriate grade above.	Dexamethasone 10 mg intravenously 3 times a day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2. If improving, manage as appropriate grade above.	Administer methylprednisolone 1000 mg intravenously once per day for 3 days. 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 methylprednisolone 1000 mg 2-3 times a day or alternate therapy.[d]

a. Lee et al. 2014.
b. Refer to Table 2 for management of neurologic toxicity.
c. Refer to tocilizumab package insert for details.
d. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, Intravenous Immune Globulin (IVIG) and Anti-Thymocyte Globulin (ATG).

Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicity/immune effector cell-associated neurotoxicity syndrome (ICANS) (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities/ICANS 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/ICANS 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 4 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 4 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 (13)]*.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients *[see Hypersensitivity Reactions (5.4)]*. Contraindications of the lymphodepleting chemotherapy must be considered.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. CRS occurred in 93% (100/108) of patients with LBCL receiving YESCARTA, including ≥ Grade 3 (Lee grading system[1]) CRS in 11%. *[see Adverse Reactions (6)]*. Among patients who died after receiving YESCARTA, two 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 29 days, except for one outlying observation of 58 days).

Key manifestations of CRS (>10%) included fever (83%), hypotension (44%), tachycardia (24%), hypoxia (23%) and chills (20%). 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 and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) *[see Adverse Reactions (6)]*.

The impact of tocilizumab and/or corticosteroids on the incidence and severity of CRS was assessed in two subsequent cohorts of LBCL patients. Among patients who received tocilizumab and/or corticosteroids for ongoing Grade 1 events (see Table 1) *[see Clinical Trials Experience (6.1)]*. CRS occurred in 93% (38/41), including 2% (1/41) with Grade 3 CRS; no patients experienced 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).

Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA *[see Clinical Trials Experience (6.1)]*. Thirty-one of the 39 patients (79%) developed CRS at which point the patients were managed with tocilizumab and/or therapeutic doses of corticosteroids with no patients

developing Grade 3 or higher CRS. The median time to onset of CRS was 5 days (range: 1 to 15 days) and the median duration of CRS was 4 days (range: 1 to 10 days). 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 *[See Neurologic Toxicities (5.2)]*.

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 (14)]*. 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 (including ICANS) that were fatal or life-threatening occurred following treatment with YESCARTA.

In ZUMA-1 Phase 1 and 2, neurologic toxicities occurred in 67% (72/108) of patients with LBCL, including ≥ Grade 3 cases in 32%. Ninety-three percent of all neurologic toxicities occurred within 7 days after YESCARTA infusion, with a median time to onset of 5 days (range: 1 to 17 days). The median duration of neurologic toxicities was 13 days. Neurologic events resolved in all but 4 subjects who had ongoing neurologic events at the time of death.

The most common neurologic toxicities (>10%) included encephalopathy (37%), tremor (31%), confusional state (27%), aphasia (18%), and somnolence (17%). 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 and one fatal case of late onset toxic/metabolic encephalopathy have occurred in patients treated with YESCARTA.

The impact of tocilizumab and/or corticosteroids on the incidence and severity of neurologic toxicities was assessed in two subsequent cohorts of LBCL patients in ZUMA-1. Among patients who received corticosteroids at the onset of Grade 1 toxicities (see Table 2), neurologic toxicities occurred in 78% (32/41) and 20% (8/41) had Grade 3 neurologic toxicities; no patients experienced 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).

Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA *[see Clinical Trials Experience (6.1)]*. Of these 39 patients, 33 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 neurological toxicities was 6 days (range: 1-274 days) with a median duration of 12 days (range: 1 to 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 *[See Cytokine Release Syndrome (5.1)]*. 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 Controlled Distribution Program

Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a Controlled Distribution Program *[see Boxed Warning and Warnings and Precautions (5.1 and 5.2)]*. The required components of the YESCARTA Controlled Distribution Program are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the Controlled Distribution Program 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.

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 39% of LBCL patients treated. Grade 3 or higher infections occurred in 26% of patients, Grade 3 or higher infections with an unspecified pathogen in 19%, bacterial infections in 9% and viral infections in 6%. 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 36% of patients 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 38% of patients and included neutropenia (26%), thrombocytopenia (24%), and anemia (10%). 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 16% of patients. 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 asiamedinfo@gilead.com to obtain instructions on patient samples to collect for testing.

5.9 Tumour Lysis Syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to YESCARTA infusion. Signs and symptoms of TLS should be monitored, and events managed according to standard guidelines.

5.10 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 an open-label, single-arm study in which 108 patients with relapsed or refractory LBCL (ZUMA-1 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 (11)]*. 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 ≥ 20%) included CRS, encephalopathy, fatigue, decreased appetite, headache, fever, febrile neutropenia, diarrhea, nausea, tremor, tachycardia, cough, other pathogen infections, hypotension, vomiting, viral infections, dizziness, constipation, and edema. Serious adverse reactions occurred in 49% of patients. The most common serious adverse reactions (> 2%) included encephalopathy, other pathogen infections, CRS, bacterial infections, fever, viral infections, aphasia, delirium, cardiac arrest, and dyspnea.

The most common (≥ 10%) Grade 3 or higher reactions included febrile neutropenia, encephalopathy, other pathogen infections, and CRS.

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 (%)
Blood Disorders		
Febrile neutropenia	36	32
Cardiac Disorders		
Tachycardia [a]	29	1
Arrhythmia [b]	18	3

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Gastrointestinal Disorders		
Diarrhea	35	4
Nausea	31	0
Vomiting	24	1
Constipation	20	0
Abdominal pain [c]	15	2
Dry mouth	11	0
General Disorders and Administration Site Conditions		
Fatigue [d]	43	3
Fever	39	3
Edema [e]	20	1
Chills	19	0
Immune System Disorders		
Cytokine release syndrome	93	11
Hypogammaglobulinemia [f]	16	0
Infections and Infestations		
Other pathogen infections	28	19
Viral infections	21	6
Bacterial infections	15	9
Investigations		
Decreased appetite	41	2
Weight decreased	15	0
Dehydration	11	3
Musculoskeletal and Connective Tissue Disorders		
Motor dysfunction [g]	17	1
Pain in extremity [h]	17	1
Back pain	14	1
Muscle pain	10	1
Arthralgia	10	0
Nervous System Disorders		
Encephalopathy [i]	58	31
Headache [j]	40	1
Tremor	31	2
Dizziness [k]	21	0
Aphasia	18	7
Psychiatric Disorders		
Delirium [l]	17	6
Anxiety	11	1
Respiratory, Thoracic and Mediastinal Disorders		
Cough [m]	29	0
Dyspnea [n]	17	3
Hypoxia [o]	14	2
Pleural effusion	13	2
Vascular Disorders		
Hypotension [p]	27	6
Hypertension	15	6

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 discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness.
d. Fatigue includes fatigue, malaise.
e. Edema includes face edema, generalized edema, swelling, localized edema, edema, edema genital, edema peripheral, periorbital edema, peripheral swelling, scrotal edema.
f. Hypogammaglobulinemia includes hypogammaglobulinemia, blood immunoglobulin G decreased.
g. Motor dysfunction includes muscle spasms, muscular weakness.
h. Pain in extremity includes pain, pain in extremity.
i. Encephalopathy includes cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor, toxic encephalopathy.
j. Headache includes headache, head discomfort, procedural headache.
k. Dizziness includes dizziness, presyncope, syncope.
l. Delirium includes agitation, delirium, delusion, disorientation, hallucination, irritability, restlessness.
m. Cough includes cough, productive cough, upper-airway cough syndrome.
n. Dyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress.
o. Hypoxia includes hypoxia, oxygen saturation decreased.
p. Hypotension includes diastolic hypotension, hypotension, orthostatic hypotension.

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

- *Blood disorders:* Coagulopathy (2%)
- *Cardiac disorders:* Cardiac failure (2%), cardiac arrest (3%)
- *Immune system disorders:* Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (2%)
- *Infections and infestations disorders:* Fungal infections (6%)
- *Nervous system disorders:* Ataxia (6%), neuropathy (6%), seizure (4%), dyscalculia (2%), myoclonus (2%)
- *Respiratory, thoracic and mediastinal disorders:* Pulmonary edema (7%)
- *Renal and urinary disorders:* Renal insufficiency (8%)
- *Skin and subcutaneous tissue disorders:* Rash (6%)
- *Vascular disorders:* Thrombosis (6%), Capillary leak syndrome (1%)

Laboratory Abnormalities:

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

Laboratory Abnormalities	Grades 3 or 4 (%)
Lymphopenia	99
Leukopenia	96
Neutropenia	94
Anemia	65
Thrombocytopenia	56
Hypophosphatemia	52
Hyponatremia	23
Uric acid increased	15
Direct bilirubin increased	13
Hypokalemia	11
Alanine aminotransferase increased	12
Aspartate Aminotransferase increased	10

The safety and efficacy of YESCARTA was evaluated in two subsequent cohorts of LBCL patients. The first subsequent, open label, safety management cohort in ZUMA-1 evaluated the safety and efficacy of YESCARTA with the use of tocilizumab and/or corticosteroid and prophylactic levetiracetam (750mg PO or IV twice daily) 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 5 patients who were not treated, 2 patients died prior to receiving YESCARTA and 3 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 of 36 with Grade 1 CRS and 21 of 24 patients with Grade 2 CRS received both tocilizumab and/or corticosteroids. Among patients who received treatment for Grade 1 or Grade 2 CRS, most patients (13 of 15 and 19 of 21 patients, respectively) received both tocilizumab and corticosteroids. The most common dosing frequency was QD, and most patients received 1 or 2 doses of each drug. Ten of 27 patients with Grade 1 and 7 of 15 patients with Grade 2 neurologic events were treated with tocilizumab and/or corticosteroids. Similar number of patients received corticosteroids only or in combination with tocilizumab (Grade 1: 4 and 5 patients, respectively; Grade 2: 3 patients 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.

The second subsequent, open label, safety management cohort in ZUMA-1 evaluated the safety and efficacy of YESCARTA with the use of prophylactic corticosteroids (oral dexamethasone 10 mg once daily for 3 days, starting prior to YESCARTA infusion on Day 0) and prophylactic levetiracetam (750 mg PO or IV) *[see Warnings and Precautions (5.1 and 5.2)]*.

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. 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 post approval 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, dysphagia, ICANS, and status epilepticus.

7 USE IN SPECIFIC POPULATIONS

7.1 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.

7.2 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.

7.3 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 package insert 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.

7.4 Pediatric Use

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

7.5 Geriatric Use

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.

8 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 (13)]*.

In addition to T cells, YESCARTA may contain NK and NK-T cells. Cryostor CS10 (contains DMSO), sodium chloride and human albumin are present as excipients.

YESCARTA is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette.

9 CLINICAL PHARMACOLOGY

9.1 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.

9.2 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 sIL2Rα 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.

9.3 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.

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 non-responders (n=23) (43.6 cells/μL vs 21.2 cells/μL). Median AUC Day 0 - 28 in responding patients (n=73) was 251% of the corresponding level in non-responders (n=23) (557.1 days × cells/μL vs. 222.0 days × cells/μL).

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.

10 NONCLINICAL TOXICOLOGY

10.1 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.

11 CLINICAL STUDIES

11.1 Relapsed or Refractory Large B-Cell Lymphoma

DLBCL, PMBCL and DLBCL arising from follicular lymphoma (ZUMA-1)

A single-arm, open-label, multicenter trial evaluated the efficacy of a single infusion of YESCARTA in adult patients with relapsed or refractory LBCL. 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/μL, 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/m^2 intravenously and fludarabine 30 mg/m^2 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 during Phase 2, 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).

DLBCL in ZUMA-1 included patients with DLBCL not otherwise specified, other DLBCL subtypes, and HGBL based on the 2016 WHO-classification. Forty-seven patients were evaluable for MYC, BCL-2, and BCL-6 status. Thirty were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 5 were found to have HGBL with MYC, BCL-2 or BCL-6 gene rearrangement (double- and triple-hit); and 2 were found to have HGBL not otherwise specified. Sixty-six patients were evaluable for cell-of-origin classifications (germinal center B-cell type [GCB] or activated B-cell type [ABC]). Of these, 49 patients had GCB-type and 17 patients had ABC-type.

The response rate in patients with relapsed or refractory LBCL is presented in Table 5. The median time to response was 1.0 months (range: 0.8 to 12.2 months). Response durations were longer in patients who achieved complete remission (CR), as compared to patients with a best response of partial remission (PR) (Table 6). Of the 55 patients who achieved CR, 17 initially had stable disease (7 patients) or PR (10 patients), with a median time to improvement of 2.1 months (range: 1.8 to 14.4 months).

Table 5. Response Rate in Patients with Relapsed or Refractory LBCL by Central Assessment

	Recipients of YESCARTA (N = 101)
Objective Response Rate (ORR)[a] (95% CI)	75 (74%) (65%, 82%)
Complete Remission Rate (95% CI)	55 (54%) (44%, 64%)
Partial Remission Rate (95% CI)	20 (20%) (13%, 29%)

CI, confidence interval.

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

Table 6. Duration of Response (DOR) in Patients with Relapsed or Refractory LBCL by Central Assessment

	From N of 101
Number of Responders	75
DOR (Months)[a]	
Median[b]	NE
(95% CI)	(10.9, NE)
Range[c]	0.0, 29.5+
DOR if Best Response is CR (Months)	
Median[b]	NE
(95% CI)	(NE, NE)
Range[c]	0.4, 29.5+
DOR if Best Response is PR (Months)	
Median[b]	2.1

(95% CI)	(1.3, 11.1)
Range[c]	0.0, 20.3+
Median Follow-up for DOR (Months)[a, b]	22.9

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

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

SCHOLAR-1

A retrospective, patient-level, pooled analysis of outcomes in refractory aggressive NHL (N = 636) was conducted (Crump et al., 2017) to provide confirmation of the prespecified control response rate of 20% and historical context for interpreting the ZUMA-1 results. The analysis included patients who had not responded (SD or PD) to their last line of therapy, or had relapsed within 12 months after ASCT. Response and survival after treatment with available standard-of-care therapy was evaluated. The ORR was 26% [95% CI (21, 31)] and the CR rate was 7% [95% CI (3, 15)], with a median OS of 6.3 months.

12 REFERENCES

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

13 HOW SUPPLIED/STORAGE AND HANDLING

YESCARTA is supplied in an infusion bag 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. 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 150ºC).
- Thaw before using *[see Dosage and Administration (2)]*.

14 SHELF LIFE

Refer to patient labels.

The stability of YESCARTA upon completion of thawing is up to 3 hours at room temperature (20˚C to 25°C). However, YESCARTA infusion must begin within 30 minutes of thaw completion and the total YESCARTA infusion time must not exceed 30 minutes.

15 PATIENT COUNSELING INFORMATION

Advise the patient to read the HSA approved Patient Information Leaflet.

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 asiamedinfo@gilead.com if they are diagnosed with a secondary malignancy *[see Warnings and Precautions (5.8)]*.

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