Product Monograph

Including Patient Medication Information

PRYESCARTA®

Axicabtagene ciloleucel

Cell suspension in patient-specific single infusion bag, target of 2 × 10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg body weight with a maximum of 2 × 10^8 CAR-positive viable T cells, for intravenous infusion

Professed Standard

Other antineoplastic agent (Anatomical Therapeutic Chemical index code: L01XL03)

YESCARTA, indicated for:

- the treatment of adult patients with relapsed or refractory grade 1, 2 or 3a follicular lymphoma (FL) after two or more lines of systemic therapy.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for YESCARTA please refer to Health Canada's Notice of Compliance with conditions - drug products web site.

YESCARTA, indicated for:

- the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
- the treatment of adult patients with relapsed or refractory large B cell lymphoma (LBCL) after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), HGBL, and DLBCL arising from follicular lymphoma.

has been issued market authorization without conditions.

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Recent Major Label Changes

Warnings and Precautions, Secondary Malignancies (7)	12/2024
Warnings and Precautions, Immune (7)	01/2026
Warnings and Precautions, Neurologic (7)	01/2026

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Part 1: Healthcare Professional Information

1 Indications

YESCARTA (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for:

- the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
- the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), HGBL, and DLBCL arising from follicular lymphoma.
- the treatment of adult patients with relapsed or refractory grade 1, 2 or 3a follicular lymphoma (FL) after two or more lines of systemic therapy.

1.1. Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

No clinically important differences in safety or effectiveness were observed between patients aged 65 years and older compared to patients overall.

2 Contraindications

YESCARTA is contraindicated in patients who are hypersensitive to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 Dosage Forms, Strengths, Composition, and Packaging**.

3 Serious Warnings and Precautions Box

Serious Warnings and Precautions

- **Cytokine Release Syndrome (CRS),** including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Delay YESCARTA treatment if a patient has active uncontrolled infection or inflammatory disorders, active graft-versus-host disease (GVHD) or unresolved serious adverse reactions from prior therapies. Monitor for CRS after treatment with YESCARTA. Provide supportive care, tocilizumab, or tocilizumab and corticosteroids, as needed (see **7 Warnings and Precautions**).
- **Neurologic adverse reactions**, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or independently of CRS. Monitor for neurologic adverse reactions after treatment with YESCARTA. Provide supportive care, tocilizumab (if with concurrent CRS), or corticosteroids, as needed (see **7 Warnings and Precautions**).
- YESCARTA should be administered by experienced health professionals at specialized treatment centres (see **7 Warnings and Precautions**).

4 Dosage and Administration

YESCARTA should be administered by experienced health professionals at specialized treatment centres (see **7 Warnings and Precautions**).

4.1. Dosing Considerations

- For autologous use only; do NOT infuse YESCARTA if the information on the patient-specific label on the infusion bag does not match the intended patient.
- For intravenous (IV) use only; do NOT use a leukodepleting filter.
- Single infusion product.
- Do NOT irradiate YESCARTA.
- Consider delaying lymphodepleting chemotherapy and YESCARTA treatment if the patient has one or more of the following conditions: clinically significant cardiac dysfunction, pulmonary dysfunction, renal insufficiency, acute neurologic toxicity, active uncontrolled infection or inflammation, and active graft-versus host disease (see **14 Clinical trials**).

4.2. Recommended Dose and Dosage Adjustment

Adults

YESCARTA is provided as a single-dose, one-time treatment in a patient-specific infusion bag.

Each single infusion bag of YESCARTA contains a suspension of anti-CD19 chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. The target dose is 2 x 10^6 CAR-positive

viable T cells per kg body weight (range: 1 x 10^6 – 2.4 x 10^6 cells/kg), with a maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above.

Pediatrics (< 18 years of age)

Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years of age)

No dose adjustments are required for patients 65 years of age or older.

4.3. Reconstitution

Not applicable.

4.4. 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.

Confirm that 4 doses of tocilizumab and access to emergency equipment are available prior to infusion and during the recovery period (see **7 Warnings and Precautions**).

Preparing Patient for YESCARTA Infusion

Confirm availability of YESCARTA prior to starting the lymphodepleting regimen.

Pre-treatment *(lymphodepleting chemotherapy)*

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 intravenously on the 5th, 4th, and 3rd day before infusion of YESCARTA.

Premedication

- Administer acetaminophen 650 mg orally and diphenhydramine 12.5 to 25 mg intravenously or 25 mg orally 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 that the patient's identity matches 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. Instead, immediately contact Kite Konnect at 1-833-236-5483.

- Once the patient's identity 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 Konnect at 1-833-236-5483).
- Place the infusion bag inside a second sterile bag or 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. Thawing should take approximately 3-5 minutes.
- Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours. Do NOT refreeze.

Administration

- For autologous use only.
- Confirm that 4 doses of tocilizumab and access to 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 0.9% sodium chloride solution prior to infusion.
- Infuse the entire content of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature (20°C to 25°C) for up to 3 hours after thaw. Do NOT refreeze.
- 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 0.9% sodium chloride solution at the same infusion rate to ensure all YESCARTA is delivered.

4.5. Missed Dose

Not Applicable.

5 Overdose

No data are available regarding overdose of YESCARTA.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous Infusion	Each patient-specific, single infusion bag of YESCARTA contains a suspension of anti-CD19 CAR-positive viable T cells in approximately 68 mL for a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: $1 \times 10^6 – 2.4 \times 10^6$ cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T cells.	Cryostor® CS10, sodium chloride; human serum albumin

7 Warnings and Precautions

Please see the **Serious Warnings and Precautions** Box at the beginning of Part I: Health Professional Information.

General

YESCARTA should be administered in a qualified treatment facility with personnel trained in handling and administering YESCARTA. The management of patients treated with YESCARTA should occur at a healthcare facility with personnel trained in monitoring and managing CRS and neurotoxicity. The facility should have immediate access to appropriate emergency equipment and intensive care unit, and must have on-site, immediate access to tocilizumab
.

YESCARTA is intended solely for autologous use and must under no circumstances be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the YESCARTA infusion bag and cassette. Do NOT infuse YESCARTA if the information on the patient-specific label does not match the intended patient (see **4 Dosage and Administration**).

Patients with central nervous system (CNS) lymphoma were excluded from the pivotal studies. Therefore, the safety and efficacy of YESCARTA have not been established in this population. For other patient selection criteria, see **14 Clinical trials**.

Patients treated with YESCARTA should not donate blood, organs, tissues and cells for transplantation.

Carcinogenesis and Mutagenesis

Secondary Malignancies

Patients treated with YESCARTA may develop secondary hematological malignancies. T-cell malignancies have occurred following treatment with genetically modified autologous T-cell immunotherapies and may present as soon as weeks following infusion. There have been fatal outcomes.

Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company for reporting and to obtain instructions on collection of patient samples for testing of secondary malignancies of T-cell origin.

Driving and Operating Machinery

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.

Endocrine and Metabolism

Tumour lysis syndrome (TLS)

TLS may occur in patients treated with conditioning chemotherapy and YESCARTA. To minimize the risk of TLS, patients with elevated uric acid or high tumour burden should receive prophylactic treatment (allopurinol, or an alternative prophylaxis) prior to YESCARTA treatment.

Immune

Cytokine release syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. CRS occurred in 92% of patients with LBCL and 78% of patients with FL (82% of patients with indolent non-Hodgkin lymphoma [iNHL] overall), including ≥ Grade 3 (Lee grading system[1]) CRS in 8% of patients with LBCL and 6% of patients with FL (7% of patients with iNHL overall). The median time to onset of CRS was 3 days (range: 1 to 12 days) for patients with LBCL and 4 days (range: 1 to 15 days) for patients with FL/iNHL overall and the median duration of CRS was 7 days (range: 2 to 58 days) for patients with LBCL and 6 days (range: 1 to 27 days) for patients with FL/iNHL overall. The most common manifestations of CRS (>10%) include fever (94%), hypotension (43%), tachycardia (37%), chills (24%), hypoxia (22%), and headache (15%). CRS can cause end organ dysfunctions. Serious events that may be associated with CRS include: fever; hypotension; hypoxia; tachycardia; tachypnea; cardiac arrhythmias (including atrial fibrillation/flutter and ventricular tachycardia); renal insufficiency; headache; ejection fraction decreased; cardiac failure; dyspnea; cardiac arrest; metabolic acidosis; aspartate aminotransferase increased; alanine aminotransferase increased; blood bilirubin increased; coagulopathy; capillary leak syndrome; and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (see **8 Adverse Reactions**).

In a subsequent cohort of LBCL patients (ZUMA-1, Cohort 4), tocilizumab and/or corticosteroids were administered for ongoing Grade 1 events (see Table 2). CRS occurred in 93% of patients and 2% 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 6.5 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.

Confirm that 4 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor

patients at least daily for 7 days at the specialized healthcare facility following infusion for signs and symptoms of CRS.Healthcare professionals can consider hospitalization for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to remain within proximity of a specialized clinical facility for at least 4 weeks and to seek immediate medical attention, should signs or symptoms of CRS occur at any time (see **7 Warnings and Precautions, Monitoring and Laboratory Tests**). An algorithm has been developed to guide the management of CRS in patients treated with YESCARTA (Table 2). At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

Management of CRS

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. Manage CRS according to the recommendations in Table 2. Patients with Grade 1 CRS should be managed with vigilant supportive care and monitored for infection and fluid balance. 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. Patients with medically significant cardiac dysfunction should be managed by standards of critical care. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 2 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 not improving after 24 hours, administer tocilizumab per Grade 2 below.	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). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS. If improving, manage as Grade 1 above.	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.

CRS Grade[a]	Tocilizumab	Corticosteroids
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 D, Gardner R, Porter D, et al. How I treat: current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195*
b. *Refer to Table 3 for management of neurologic adverse reactions.*
c. *Refer to tocilizumab Product Monograph for details.*
d. *Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, intravenous immunoglobulin (IVIG) and anti-thymocyte globulin (ATG)*

Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. Hypogammaglobulinemia was reported in 15% of patients with LBCL and 19% of patients with FL (20% of patients with iNHL overall). In ZUMA-1, B-cell aplasia was observed in 60% and 77% of a subset of patients with LBCL who had evaluable blood samples at baseline and at 3 months, respectively. Among 141 patients in ZUMA-7 with evaluable samples at baseline, 57% had detectable B-cells. Three months after YESCARTA treatment, the proportion of patients with detectable B-cells decreased to 38%, B-cell aplasia was observed in 24% and 54% of FL patients with evaluable blood samples at baseline and at 3 months, respectively. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement in case of recurrent infections.

Due to prolonged hypogammaglobulinemia and B-cell aplasia, it is not known if patients will respond to vaccination following treatment with YESCARTA. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live viral 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 (see **9 Drug interactions**).

Hypersensitivity reactions

Allergic reactions may occur with the infusion of YESCARTA (see **8 Adverse Reactions**). Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO; a component of Cryostor* CS10) or residual gentamicin in YESCARTA. All patients should be monitored closely during the infusion period.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In LBCL patients, Grade 3 or higher prolonged cytopenias (still present at Day 30 or with an onset at Day 30 or beyond) included neutropenia (26%), thrombocytopenia (13%), and anemia (6%). In FL/overall iNHL patients, Grade 3 or higher prolonged cytopenias included neutropenia (FL: 27%; iNHL: 28%), thrombocytopenia (FL: 10%; iNHL: 9%), and anemia (FL: 6%; iNHL: 7%). Monitor blood counts after YESCARTA infusion.

Serious infections

Severe or life-threatening infections occurred in patients after YESCARTA infusion. Infections (all grades) occurred in 41% of patients with LBCL and 52 % of patients with FL (53% of patients with iNHL overall). Grade 3 or higher infections occurred in 19% of patients with LBCL and 15% of patients with FL (18% of patients with iNHL overall), including infections with an unspecified pathogen, bacterial infections, and viral infections. YESCARTA should not be administered to patients with clinically significant active infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines.

Febrile neutropenia was observed in 15% of patients with LBCL and 2% of patients with FL/iNHL overall after YESCARTA infusion and may be concurrent with CRS. Differences observed between populations may be in part due to changes in reporting of febrile neutropenia between studies. 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, life-threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations should be performed.

Viral reactivation

Reactivation of viruses, including hepatitis B virus (HBV), human polyomavirus 2 (JC virus; the cause of progressive multifocal leukoencephalopathy [PML]) and human herpesvirus 6 (HHV-6) 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.

Monitoring and Laboratory Tests

- Monitor patients at least daily for 7 days following infusion at the specialized healthcare/clinical facility where the infusion was administered for signs and symptoms of CRS and neurologic adverse reactions (Table 2 and Table 3). Healthcare

professionals can consider hospitalization for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events.

- CRS and neurologic adverse reactions can occur more than 7 days after the infusion. Instruct patients to remain within proximity of a specialized treatment centre or appropriately trained healthcare facility for at least 4 weeks following infusion. If the post-infusion monitoring of patients takes place in a healthcare facility that is not the treatment centre, it must meet the same requirements as the specialized treatment centre regarding the availability of emergency equipment and tocilizumab, the capacity to manage CAR T adverse reactions, as well as appropriately trained staff with expertise in CAR T therapy adverse reaction recognition and management. Educate patients and their caregivers for signs and symptoms of CRS and neurologic adverse reactions. Advise patients and their caregivers to immediately contact the designated health professional if CRS or neurologic adverse reactions are suspected.

Neurologic

Neurologic adverse reactions

Severe neurologic adverse reactions (including immune effector cell-associated neurotoxicity syndrome [ICANS]), have been very commonly observed in patients treated with YESCARTA, which could be life-threatening or fatal. Neurologic adverse reactions occurred in 62% of patients with LBCL and 56% of patients with FL (59% of patients with iNHL overall), with 25% of patients with LBCL and 15% of patients with FL (19% of patients with iNHL overall) experiencing Grade 3 or higher (severe or life threatening) adverse reactions. The median time to onset was 6 days (range 1 to 133 days) for patients with LBCL and 7 days (1 to 177 days) for patients with FL/iNHL overall. The median duration was 10 days for patients with LBCL and 14 days for patients with FL/iNHL overall, with resolution occurring within 3 weeks for 66% of patients with LBCL (range: 1 – 191 days) and 59% of patients with FL/iNHL overall (range: 1 -177 days). The most common signs or symptoms (>10%) associated with neurologic adverse reactions include: tremor (29%); confusional state (24%); encephalopathy (23%); aphasia (18%); and somnolence (12%). Serious adverse reactions including: encephalopathy; aphasia; delirium; seizures; spinal cord edema; myelitis; quadriplegia; and dysphagia have been reported in patients administered YESCARTA. Fatal and serious cases of cerebral edema have been reported in patients treated with YESCARTA.

In a subsequent cohort of LBCL patients (ZUMA-1 Cohort 4), corticosteroids were administered at the onset of Grade 1 toxicities (see Table 3). Neurologic adverse reactions occurred in 61% of patients and 17% had Grade 3 neurologic adverse reactions with no patients experiencing a Grade 4 or 5 event. The median time to onset of neurologic adverse reactions was 6 days with a median duration of 8 days (range: 1 to 144 days). The most common neurologic adverse reactions were consistent with the overall LBCL population treated with YESCARTA.

Patients with a history of CNS disorders such as seizures or cerebrovascular ischemia may be at increased risk and were not enrolled in ZUMA-1 (see **14 Clinical Trials**).

Management of neurologic adverse reactions

Monitor patients for signs and symptoms of neurologic adverse reactions/ICANS (Table 3). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic adverse reactions should be monitored with continuous cardiac telemetry and pulse oximetry. An algorithm has been developed to guide the management of neurologic adverse

reactions in patients treated with YESCARTA (Table 3). Treat moderate, severe or life-threatening neurologic adverse reactions with tocilizumab (if with concurrent CRS) and/or corticosteroids. Provide intensive care supportive therapy for severe or life threatening neurologic adverse reactions. Consider levetiracetam for seizure prophylaxis for any grade of neurologic adverse reactions. Patients should be monitored at least daily for 7 days at the specialized healthcare facility following infusion for signs and symptoms of neurologic toxicity. Physicians can consider hospitalization for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events. Counsel patients to remain within proximity of a specialized clinical facility for at least 4 weeks following infusion, and to seek immediate medical attention should signs or symptoms of neurologic toxicity/ICANS occur at any time.

Table 3 Neurologic Adverse Reaction/ICANS Grading and Management Guidance

<table>
<tr><th>Grading Assessment[a]</th><th>Concurrent CRS</th><th>No concurrent CRS</th></tr>
<tr><td rowspan="2">Grade 1

Examples include:
Somnolence-mild drowsiness or sleepiness
Confusion-mild disorientation
Encephalopathy-mild limiting of ADLs</td><td>If CRS symptoms not improving after 24 hours, administer tocilizumab per Grade 2 below.
Administer one dose of dexamethasone 10 mg intravenously.
If not improving after 2 days, repeat dexamethasone 10 mg intravenously.</td><td>Administer one dose of dexamethasone 10 mg intravenously.
If not improving after 2 days, repeat dexamethasone 10 mg intravenously.</td></tr>
<tr><td>Dysphasia-not impairing ability to communicate</td><td colspan="2">Consider levetiracetam for seizure prophylaxis.</td></tr>
<tr><td>Grade 2

Examples include:
Somnolence—moderate, limiting instrumental
Activities of daily living (ADL)
Confusion—moderate disorientation
Encephalopathy—limiting instrumental ADLs
Dysphasia—moderate impairing ability to communicate spontaneously
Seizure(s)</td><td>Administer tocilizumab[b] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).
Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen.
Limit to a maximum of 3 doses in a 24-hour period; Maximum total of 4 doses if no clinical improvement in the signs and symptoms of 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 still not improving, manage as appropriate grade below.</td><td>Administer dexamethasone 10 mg intravenously four times a day.

If improving, continue dexamethasone use until the severity is Grade 1 or less, then quickly taper as clinically appropriate.
If still not improving, manage as appropriate grade below.</td></tr>
</table>

<table>
<tr><th>Grading Assessment[a]</th><th>Concurrent CRS</th><th>No concurrent CRS</th></tr>
<tr><td></td><td colspan="2">Consider levetiracetam for seizure prophylaxis.</td></tr>
<tr><td rowspan="2">Grade 3

Examples include:
Somnolence—obtundation or stupor
Confusion—severe disorientation
Encephalopathy—limiting self-care ADLs
Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly</td><td>Administer tocilizumab per Grade 2 above.

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.</td><td>Administer methylprednisolone 1000 mg 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.</td></tr>
<tr><td colspan="2">Consider levetiracetam for seizure prophylaxis. Consider the possibility of cerebral edema.</td></tr>
<tr><td rowspan="2">Grade 4

Life-threatening consequences
Urgent intervention indicated
Requirement for mechanical ventilation</td><td>Administer tocilizumab per Grade 2 above.
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.[c]</td><td>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.[c]</td></tr>
<tr><td colspan="2">Consider levetiracetam for seizure prophylaxis. Consider the possibility of cerebral edema.</td></tr>
</table>

Abbreviation: ADLs, activities of daily living.

(a) Severity based on Common Terminology Criteria for Adverse Events
(b) Refer to tocilizumab Product Monograph for details
(c) Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG

Reproductive Health: Female and Male Potential

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. Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) after YESCARTA administration.

Sexually active males who have received YESCARTA should use a condom during intercourse with females of reproductive potential or pregnant women.

If either partner has received YESCARTA, pregnancy should be discussed with the treating physician.

See the Product Monographs 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.

Fertility

No clinical data on the effect of YESCARTA on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

Special Populations

7.1.1 Pregnant Women

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.

7.1.2 Breast-feeding

It is unknown if YESCARTA is excreted in human milk. Because many drugs are excreted in human milk, precaution should be exercised for breast-feeding. The developmental and health benefits of breast-feeding 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Generally, safety and efficacy were similar between patients ≥ 65 years and patients overall treated with YESCARTA. No dose adjustment is required in patients ≥ 65 years of age.

8 Adverse Reactions

8.1. Adverse Reaction Overview

The following adverse reactions are described under **7 Warnings and Precautions**:

- Cytokine Release Syndrome
- Neurologic Adverse Reactions
- Hypersensitivity Reactions
- Serious Infections
- Prolonged Cytopenias
- Hypogammaglobulinemia

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The adverse reactions described in this section reflect exposure to YESCARTA in one randomized, open-label study (ZUMA-7) and one open-label, single-arm study (ZUMA-1) in which 170 and 108 adult patients, respectively, with relapsed or refractory LBCL, and 148 patients with relapsed/refractory iNHL (including FL [n = 124]), who received CAR-positive T cells based on the recommended dose which was weight-based (see **14 Clinical Trials**). The median duration of follow-up for patients treated with YESCARTA was 19.6 months in ZUMA-7, 15.4 months in ZUMA-1 and 19.7 months in iNHL patients.

Relapsed or Refractory LBCL

ZUMA-7

The safety of YESCARTA was evaluated in ZUMA-7, a study in which patients with primary refractory or first relapsed LBCL (predominantly DLBCL or HGBL), after first line chemoimmunotherapy, received YESCARTA (N=170) or standard of care therapy (SOCT, n=168). SOCT was defined as 2 to 3 cycles of second-line chemoimmunotherapy (R-ICE, R-DHAP, R-ESHAP, or R-GDP), with responders being eligible to receive high-dose therapy (HDT, n=64) followed by an autologous stem cell transplant (ASCT, n=62) (see **14 Clinical Trials**). Only patients who intended to proceed to HDT and ASCT (if a response to second-line therapy was attained) were eligible. Patients with a history of central nervous system (CNS) disorders (such as seizures or cerebrovascular ischemia), serious or uncontrolled infection, or autoimmune disease requiring systemic immunosuppression were ineligible. The study required ANC ≥ 1000/mm^3, platelet count ≥ 75,000/mm^3, creatinine clearance ≥ 60 mL/min, AST/ALT ≤ 2.5 x ULN, and total bilirubin ≤ 1.5 mg/dL.

The median age of the study population was 59 years (range: 21 to 81 years); 66% were male. The baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 54% of patients and 1 in 46% of patients.

The most common non-laboratory adverse reactions (incidence ≥ 20%) occurring in the YESCARTA treatment arm include fever, CRS, fatigue, encephalopathy, hypotension, tachycardia, diarrhea, headache, nausea, musculoskeletal pain, chills, cough, tremor, transaminases increased, unspecified pathogen infections, dizziness, decreased appetite,

hypoxia, edema, abdominal pain, and constipation. Serious adverse reactions occurred in 51% of patients. The most common serious adverse reactions (> 2%) included CRS, fever, encephalopathy (including aphasia, confusional state, somnolence), hypotension, unspecified pathogen infections (including pneumonia), B-cell lymphoma, viral infection, neutropenia, tremor, and arrhythmia.

The most common (≥ 10%) Grade 3 or higher reactions included leukopenia, neutropenia, lymphopenia, anemia, thrombocytopenia, encephalopathy, hyponatremia, hyperglycemia, and hypotension.

Fatal treatment emergent adverse events occurred in 4% of YESCARTA treated patients and 1% of SOCT patients (reporting until day 150 post-randomization or until the initiation of new lymphoma therapy, whichever occurred first). Deaths due to adverse events in the YESCARTA treatment arm, without regard for relationship to treatment, were due to myocardial infarction, progressive multifocal leukoencephalopathy, hepatitis B reactivation, sepsis, and COVID-19; and in the SOCT arm were due to cardiac arrest and acute respiratory distress syndrome.

Sixty-six percent (112/170) of patients received tocilizumab after infusion of YESCARTA.

Table 4 summarizes the adverse reactions that occurred in at least 10% of patients treated with YESCARTA and Table 7 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients.

Table 4 Summary of Adverse Reactions Observed in at Least 10% of Patients Treated with YESCARTA in ZUMA-7

System organ class/preferred term	YESCARTA N=170		Standard of Care Therapy N=168	
	Any Grade n (%)	Grade 3 or Higher n (%)	Any Grade n (%)	Grade 3 or Higher n (%)
Cardiac Disorders				
Tachycardia [a]	74 (44)	4 (2)	25 (15)	1 (1)
Arrhythmia [b]	25 (15)	5 (3)	10 (6)	0 (0)
Gastrointestinal Disorders				
Diarrhea [c]	71 (42)	5 (3)	68 (40)	11 (7)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)
Abdominal pain [d]	34 (20)	6 (4)	45 (27)	2 (1)
Constipation	34 (20)	0 (0)	58 (35)	0 (0)
Vomiting	33 (19)	0 (0)	55 (33)	1 (1)
General Disorders and Administration Site Conditions				
Fever [e]	158 (93)	15 (9)	43 (26)	1 (1)
Fatigue [f]	88 (52)	11 (6)	95 (57)	5 (3)
Chills	47 (28)	1 (1)	14 (8)	0 (0)
Edema [g]	38 (22)	2 (1)	41 (24)	2 (1)
Hepatobiliary Disorders				
Transaminases increased [h]	44 (26)	3 (2)	19 (11)	4 (2)
Immune System Disorders				

System organ class/preferred term	YESCARTA N=170		Standard of Care Therapy N=168	
	Any Grade n (%)	Grade 3 or Higher n (%)	Any Grade n (%)	Grade 3 or Higher n (%)
Cytokine release syndrome	157 (92)	11 (6)	0 (0)	0 (0)
Immunoglobulins decreased [i]	19 (11)	0 (0	1 (1)	0 (0)
Infections and Infestations				
Infections with pathogen unspecified	44 (26)	13 (8)	36 (21)	11 (7)
Viral infections	25 (15)	6 (4)	8 (5)	1 (1)
Bacterial infections	17 (10)	8 (5)	18 (11)	11 (7)
Fungal infections	17 (10)	1 (1)	7 (4)	1 (1)
Metabolism and Nutrition Disorders				
Decreased appetite	42 (25)	7 (4)	42 (25)	6 (4)
Hypoalbuminemia	23 (14)	1 (1)	12 (7)	0 (0)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain [j]	67 (39)	2 (1)	64 (38)	7 (4)
Motor dysfunction [k]	26 (15)	6 (4)	13 (8)	0 (0)
Nervous System Disorders				
Encephalopathy [l]	83 (49)	33 (19)	13 (8)	0 (0)
Headache	70 (41)	5 (3)	43 (26)	2 (1)
Tremor	44 (26)	2 (1)	1 (1)	0 (0)
Dizziness [m]	43 (25)	6 (4)	31 (18)	11 (7)
Neuropathy peripheral [n]	18 (11)	4 (2)	27 (16)	0 (0)
Psychiatric Disorders				
Insomnia	21 (12)	0 (0)	26 (15)	1 (1)
Delirium [o]	18 (11)	7 (4)	10 (6)	1 (1)
Renal and Urinary Disorders				
Renal impairment [p]	19 (11)	4 (2)	32 (19)	4 (2)
Respiratory, Thoracic and Mediastinal Disorders				
Cough [q]	46 (27)	1 (1)	19 (11)	0 (0)
Hypoxia [r]	37 (22)	16 (9)	13 (8)	7 (4)
Skin and Subcutaneous Tissue Disorders				
Rash [s]	27 (16)	1 (1)	26 (15)	3 (2)
Vascular Disorders				
Hypotension [t]	80 (47)	19 (11)	29 (17)	5 (3)

The following events were also counted in the incidence of CRS: coagulopathy, tachycardia, arrhythmia, cardiac failure, diarrhea, nausea, vomiting, fever, fatigue, chills, edema, transaminases increased, decreased appetite, hyponatremia, musculoskeletal pain, headache, tremor, dizziness, renal impairment, cough, hypoxia, dyspnea, pleural effusion, respiratory failure, rash, hypotension, and hypertension.

a. Tachycardia includes tachycardia, postural orthostatic tachycardia syndrome, sinus tachycardia.
b. Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block , bradycardia, bundle branch block right, electrocardiogram QT prolonged, extra systoles, heart rate increased, heart rate irregular, sinus bradycardia, supraventricular extra systoles, supraventricular tachycardia, ventricular arrhythmia, ventricular extra systoles, ventricular tachycardia.
c. Diarrhea includes diarrhea, colitis, enteritis.

d. Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, abdominal pain upper, dyspepsia.
e. Fever includes pyrexia.
f. Fatigue includes fatigue, asthenia, malaise.
g. Edema includes edema, face edema, generalized edema, localized edema, edema peripheral, swelling, peripheral swelling, pulmonary edema, swelling, fluid overload, hypervolemia, edema genital.
h. Transaminases increased includes transaminases increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased.
i. Immunoglobulins decreased includes hypogammaglobulinemia, blood immunoglobulin G decreased.
j. Musculoskeletal pain includes musculoskeletal pain, arthralgia, arthritis, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity.
k. Motor dysfunction includes muscle contractions involuntary, muscle spasms, muscle spasticity, muscle tightness, muscle twitching, muscular weakness.
l. Encephalopathy includes encephalopathy, altered state of consciousness, amnesia, aphasia, apraxia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dysarthria, dysgraphia, dyskinesia, dyspraxia, hypersomnia, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, metabolic encephalopathy, slow speech, somnolence, stupor, toxic encephalopathy.
m. Dizziness includes dizziness, dizziness postural, presyncope, syncope, vertigo.
n. Neuropathy peripheral includes hyperesthesia, hypoesthesia, lumbar radiculopathy, neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy.
o. Delirium includes delirium, agitation, delusion, disorientation, hallucination, restlessness.
p. Renal impairment includes blood creatinine increased, acute kidney injury.
q. Cough includes cough, productive cough, upper-airway cough syndrome.
r. Hypoxia includes hypoxia, oxygen saturation decreased.
s. Rash includes rash, application site rash, dermatitis, dermatitis allergic, dermatitis bullous, erythema, pruritus, rash erythematous, rash macular, rash maculo-papular, rash pruritic.
t. Hypotension includes hypotension, capillary leak syndrome, diastolic hypotension, orthostatic hypotension.

ZUMA-1

The most common non-hematological adverse reactions (in ≥ 20%) include: CRS (93%); fever (87%); encephalopathy (58%); hypotension (57%); tachycardia (57%); fatigue (45%); headache (44%); decreased appetite (43%); chills (37%); diarrhea (37%); hypoxia (32%); nausea (32%); tremor (31%); cough (30%); unspecified pathogen infection (28%); vomiting (26%); arrhythmia (22%); dizziness (22%); edema (21%); and constipation (20%).

Serious adverse reactions occurred in 55% of patients. The most common serious adverse reactions (≥ 2%) include: encephalopathy (19%); lung infection (7%); pyrexia (7%); pneumonia (6%); confusional state (5%); febrile neutropenia (5%); aphasia (4%); atrial fibrillation (4%); cardiac arrest (4%); urinary tract infection (4%); acute kidney injury (3%); agitation (3%); ejection fraction decreased (3%); hypotension (3%); hypoxia (3%); neutropenia (3%); somnolence (3%); atrial flutter (2%); and delirium (2%). Seventeen (16%) patients required intensive care unit admission.

The most common Grade 3 or higher adverse reactions include: encephalopathy (30%); unspecified pathogen infection (19%); hypotension (15%); fever (14%); CRS (12%); hypoxia (10%); bacterial infection (8%); aphasia (7%); arrhythmia (6%); viral infection (6%); delirium (6%); and hypertension (6%). Grade 5 (fatal) adverse events were reported in 4 patients: (anoxic brain injury [secondary to cardiac arrest which occurred in the setting of CRS]; histiocytosis haematophagic (HLH); intracranial hemorrhage in the setting of thrombocytopenia; and pulmonary embolism.

In ZUMA-1, 68% of patients received prophylactic allopurinol for TLS and 46% of patients received tocilizumab and/or corticosteroids for the treatment of adverse reactions (including CRS and neurologic adverse reactions), including 32% who required 2 or more doses of tocilizumab.

Table 5 summarizes the adverse reactions that occurred in at least 10% of patients treated with YESCARTA.

Table 5 Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in ZUMA-1

System organ class/preferred term	Any Grade n (%) N = 108	Grade 3 or Higher n (%) N = 108
Cardiac Disorders		
Tachycardia[a]	62 (57)	2 (2)
Arrhythmia[b]	24 (22)	6 (6)
Gastrointestinal Disorders		
Diarrhea	40 (37)	5 (5)
Nausea	35 (32)	0 (0)
Vomiting	28 (26)	1 (1)
Constipation	22 (20)	0 (0)
Abdominal pain[c]	16 (15)	2 (2)
Dry mouth	12 (11)	0 (0)
General Disorders and Administration Site Conditions		
Fever	94 (87)	15 (14)
Fatigue[d]	49 (45)	3 (3)
Chills	40 (37)	0 (0)
Edema[e]	23 (21)	1 (1)
Immune System Disorders		
Cytokine release syndrome	100 (93)	13 (12)
Hypogammaglobulinemia[f]	18 (17)	0 (0)
Infections and Infestations		
Infections-pathogen unspecified	30 (28)	20 (19)
Viral infections	21 (19)	6 (6)
Bacterial Infections	15 (14)	9 (8)
Metabolism and Nutrition Disorders		
Hypoalbunemia	106 (98)	8 (7)
Decreased appetite	46 (43)	2 (2)
Weight decreased	16 (15)	0 (0)
Dehydration	12 (11)	3 (3)
Musculoskelatal and Connective Tissue Disorders		
Motor dysfunction[g]	18 (17)	1 (1)
Pain in extremity[h]	18 (17)	1 (1)
Back pain	15 (14)	1 (1)
Muscle pain	15 (14)	1 (1)

System organ class/preferred term	Any Grade n (%) N = 108	Grade 3 or Higher n (%) N = 108
Arthralgia	11 (10)	0 (0)
Nervous System Disorders		
Encephalopathy[i]	63 (58)	32 (30)
Headache[j]	48 (44)	1 (1)
Tremor	33 (31)	2 (2)
Dizziness[k]	24 (22)	1 (1)
Aphasia[l]	19 (18)	8 (7)
Psychiatric Disorders		
Delirium[m]	18 (17)	7 (6)
Anxiety	11 (10)	1 (1)
Renal and Urinary Disorders		
Renal Insufficiency	13 (12)	5 (5)
Respiratory, Thoracic and Mediastinal Disorders		
Hypoxia[p]	35 (32)	11 (10)
Cough[n]	32 (30)	0 (0)
Dyspnea[o]	21 (19)	3 (3)
Pleural effusion	14 (13)	2 (2)
Vascular Disorders		
Hypotension[q]	62 (57)	16 (15)
Hypertension	16 (15)	6 (6)

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxia, renal insufficiency, and hypotension. MedDRA version 19.0, CTCAE version 4.03.

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. Fatigue includes fatigue, malaise.
e. Edema includes face edema, generalized edema, localized swelling, localized edema, edema, edema genital, edema peripheral, periorbital edema, peripheral swelling, scrotal edema.
f. Hypogammaglobulinemia includes hypogammaglobulinemia, blood immunoglobulin D decreased, blood immunoglobulin G decreased.
g. Motor dysfunction includes muscle spasms, muscular weakness.
h. Pain in extremity includes pain not otherwise specified, 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.
j. Headache includes headache, head discomfort, sinus headache, procedural headache.
k. Dizziness includes dizziness, presyncope, syncope.
l. Aphasia includes aphasia, dysphasia.
m. Delirium includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness.
n. Cough includes cough, productive cough, upper-airway cough syndrome.
o. Dyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress.
p. Hypoxia includes hypoxia, oxygen saturation decreased.
q. Hypotension includes diastolic hypotension, hypotension, orthostatic hypotension.

No new safety concerns were identified in the 24-month analysis, which included a median duration of follow-up of 27.4 months.

Relapsed or Refractory iNHL, including FL: ZUMA-5

Assessment of adverse reactions reflects exposure to YESCARTA in ZUMA-5, a Phase 2 study that included 148 patients with iNHL (124 FL patients)) who received CAR-positive T cells based on a recommended dose which was weight-based. The median duration of follow up was 20.3 months for patients with FL and 19.7 months for all patients with iNHL.

The most common adverse reactions (incidence ≥ 20%) included fever (85%), CRS (82%), hypotension (52%), fatigue (50%), encephalopathy (49%), unspecified pathogen infections (46%), headache (45), tachycardia (44%), musculoskeletal pain (41%), nausea (41%), tremor (30%), chills (29%), diarrhea (29%), constipation (28%), vomiting (26%), decreased appetite (26%), cough (25%), hypoxia (24%), arrhythmia (22%), dizziness (21%), immunoglobulins decreased (20%) and rash (20%). Serious adverse reactions occurred in 50% of patients. The most common serious adverse reactions (> 2%) included encephalopathy (17%), fever (14%), unspecified pathogen infections (14%), CRS (14%), bacterial infection (4%), febrile neutropenia (3%), hypoxia (3%), hypotension (3%), and viral infection (3%).

The most common (≥ 10%) Grade 3 or higher reactions included, neutropenia (93%), leukopenia (93%), thrombocytopenia (35%), anemia (31%), hypophosphatemia (25%), lymphopenia (22%), encephalopathy (16%), unspecified pathogen infections (12%), hyperglycemia (10%) and hyponatremia (10%).

Table 6 summarizes the adverse reactions, excluding laboratory terms, that occurred in at least 10% of patients treated with YESCARTA and Table 9 describes Grade 3 or 4 laboratory abnormalities that developed or worsened in at least 10% of patients.

Table 6 Summary of Adverse Reactions Observed in at Least 10% of iNHL Patients Treated with YESCARTA in ZUMA-5

System organ class/preferred term	Any Grade n (%) N = 148	Grade 3 or Higher n (%) N = 148
Cardiac Disorders		
Tachycardia [a]	65 (44)	2 (1)
Arrhythmia [b]	32 (22)	3 (2)
Gastrointestinal Disorders		
Nausea	60 (41)	0
Diarrhea	43 (29)	1 (1)
Constipation	41 (28)	0
Vomiting	38 (26)	1 (1)
Abdominal pain [c]	25 (17)	0
General Disorders and Administration Site Conditions		
Fever[d]	126 (85)	11 (7)
Fatigue [e]	74 (50)	1 (1)
Chills	43 (29)	0
Edema [f]	20 (14)	2 (1)
Pain	20 (14)	1 (1)
Hepatobiliary Disorders		
Transaminases increased	20 (14)	7 (5)
Immune System Disorders		
Cytokine release syndrome	121 (82)	10 (7)
Immunoglobulins decreased [g]	29 (20)	1 (1)
Infections and Infestations		
Unspecified pathogen infections	68 (46)	21 (14)
Viral Infection	26 (18)	4 (3)
Fungal infection	17 (11)	3 (2)
Metabolism and Nutrition Disorders		
Decreased appetite [h]	39 (26)	2 (1)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain [i]	61 (41)	2 (1)
Motor dysfunction [j]	26 (18)	3 (2)
Nervous System Disorders		
Encephalopathy [k]	72 (49)	24 (16)
Headache	67 (45)	2 (1)
Tremor	45 (30)	1 (1)
Dizziness [l]	31 (21)	0
Aphasia	20 (14)	6 (4)
Neuropathy peripheral [m]	18 (12)	0
Ataxia [n]	16 (11)	0
Psychiatric Disorders		
Insomnia	25 (17)	0
Delirium [o]	23 (16)	8 (5)
Affective disorder [p]	15 (10)	1 (1)

System organ class/preferred term	Any Grade n (%) N = 148	Grade 3 or Higher n (%) N = 148
Respiratory, Thoracic and Mediastinal Disorders		
Cough [q]	37 (25)	0
Hypoxia	36 (24)	12 (8)
Nasal inflammation	22 (15)	0
Dyspnea [r]	17 (11)	2 (1)
Skin and Subcutaneous Tissue Disorders		
Rash [s]	29 (20)	4 (3)
Vascular Disorders		
Hypotension [t]	77 (52)	6 (4)
Hypertension	19 (13)	9 (6)
Thrombosis [u]	19 (13)	7 (5)

a. Tachycardia includes tachycardia, sinus tachycardia.
b. 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.
c. Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, dyspepsia, epigastric discomfort.
d. Fever includes pyrexia, hyperthermia.
e. Fatigue includes asthenia, fatigue, decreased activity, malaise.
f. Edema includes edema, face edema, generalized edema, localized edema, edema peripheral, peripheral swelling, pulmonary edema, fluid overload, swelling face.
g. Immunoglobulins decreased includes hypogammaglobulinemia, blood immunoglobulin G decreased.
h. Decreased appetite includes decreased appetite, hypophagia.
i. Musculoskeletal pain includes musculoskeletal pain, arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, myalgia, neck pain, osteoarthritis, pain in extremity.
j. Motor dysfunction includes motor dysfunction, muscle rigidity, muscle spasms, muscle strain, muscular weakness.
k. Encephalopathy includes agraphia, amnesia, aphasia, 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.
l. Dizziness includes dizziness, presyncope, syncope, vertigo.
m. Neuropathy peripheral includes allodynia, cervical radiculopathy, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, parosmia, peripheral sensory neuropathy.
n. Ataxia includes ataxia, balance disorder, gait disturbance, vestibular disorder.
o. Delirium includes agitation, delirium, hallucination, restlessness.
p. Affective disorder includes anxiety, depression, impulsive behavior, mania, panic attack.
q. Cough includes cough, productive cough, upper-airway cough syndrome.
r. Dyspnea includes dyspnea, dyspnea exertional.
s. Rash includes dermatitis bullous, erythema, pruritus, rash, rash macular, rash maculo-papular, Stevens-Johnson syndrome, urticaria, rash erythematous, rash pustular, blister, dermatitis, dermatitis acneiform.
t. Hypotension includes capillary leak syndrome, hypotension, hypoperfusion, orthostatic hypotension.
u. Thrombosis includes deep vein thrombosis, embolism, peripheral embolism, peripheral ischemia, pulmonary embolism, thrombosis in device, vascular occlusion, jugular vein thrombosis.

8.3. Less Common Clinical Trial Adverse Reactions

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

Relapsed or Refractory LBCL:

ZUMA-7

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 (9%)
- *Cardiac disorders:* Cardiac failure (1%)[a]; cardiac arrest (1%)
- *Immune system disorders*: Hypersensitivity (1%)
- *Infections and infestations*: Sepsis (4%), pneumonia (8%); hepatitis B reactivation (1%)
- *Nervous system disorders:* Ataxia (5%), seizure (3%), myoclonus (2%), facial paralysis (1%)
- *Respiratory, thoracic and mediastinal disorders:* Dyspnea (8%), pleural effusion (6%), respiratory failure (2%)
- *Vascular disorders:* Hypertension (9%), thrombosis (8%)

a. Cardiac failure includes cardiac failure, acute left ventricular failure, ejection fraction decreased.

ZUMA-1

- *Blood and lymphatic system disorders:* Coagulopathy (2%);
- *Cardiac disorders:* Cardiac failure (6%) and cardiac arrest (4%); ejection fraction decreased (4%);
- *Immune system disorders*: Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%);
- *Infections and infestations disorders:* Fungal infections (6%); human herpesvirus 6 infection (1%);
- *Metabolism and nutrition disorders:* metabolic acidosis (5%);
- *Nervous system disorders:* Ataxia (6%); neuropathy (4%); seizure (4%); dyscalculia (2%); and myoclonus (2%);
- *Respiratory, thoracic and mediastinal disorders:* Pulmonary edema (9%);
- *Skin and subcutaneous tissue disorders:* Rash (3%); and
- *Vascular disorders:* Thrombosis (6%); capillary leak syndrome (3%)

Relapsed or Refractory iNHL, including FL and MZL subtypes: ZUMA-5:

- *Blood and lymphatic system disorders:* Coagulopathy [a] (6%), febrile neutropenia (3%)
- *Cardiac disorders:* Cardiac failure [b] (2%)
- *Eye disorders:* Visual impairment [c] (5%)
- *Gastrointestinal disorders:* Dysphagia (5%)
- *General disorders and administration site conditions:* Multiple organ dysfunction syndrome (1%)
- *Infections and infestations:* Bacterial infection (9%)
- *Musculoskeletal and connective tissue disorders:* Rhabdomyolsis (1%)
- *Nervous system disorders:* Seizure (2%), hemiparesis (2%)
- *Renal and urinary disorders:* Renal insufficiency[d] (7%)
- *Respiratory, thoracic and mediastinal disorders:* Respiratory failure (1%)

a. Coagulopathy includes coagulopathy, blood fibrinogen decreased, international normalized ratio increased, activated partial thromboplastin time prolonged.

b. Cardiac failure includes cardiac failure, ejection fraction decreased, stress cardiomyopathy.
c. Visual impairment includes vision blurred, visual acuity reduced.
d. Renal insufficiency includes blood creatinine increased, acute kidney injury, renal failure.

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 7, Table 8, and Table 9 describe the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients in ZUMA-7, ZUMA-1, and ZUMA-5, respectively.

Relapsed or Refractory LBCL

ZUMA-7

Table 7 Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in ZUMA-7 Following Treatment with YESCARTA (N = 170)

	YESCARTA N=170	**Standard of Care Therapy N=168**
	Grades 3 or 4 n (%)	**Grades 3 or 4 n (%)**
Leukopenia	159 (94)	94 (56)
Neutropenia	156 (92)	85 (51)
Lymphopenia	144 (85)	101 (60)
Anemia	64 (38)	73 (43)
Thrombocytopenia	43 (25)	105 (63)
Hyponatremia	20 (12)	3 (2)
Hyperglycemia	19 (11)	7 (4)

ZUMA-1

Table 8 Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in ZUMA-1 Following Treatment with YESCARTA based on CTCAE (N=108)

Lab Abnormality	Grades 3 or 4 n (%)
Lymphopenia	107 (99)
Leukopenia	104 (96)
Neutropenia	100 (93)
Anemia	68 (63)
Thrombocytopenia	61 (56)
Hypophosphatemia	56 (52)
Hypokalemia	34 (32)
Hyponatremia	25 (23)
Uric Acid increased	16 (15)
Direct bilirubin increased	14 (13)
Alanine Aminotransferase increased	13 (12)
Aspartate aminotransferase increased	11 (10)

Relapsed or Refractory iNHL, including FL and MZL subtypes: ZUMA-5

Table 9 Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in ZUMA-5 Following Treatment with YESCARTA (N = 148)

Lab Abnormality	Grades 3 or 4 n (%)
Leukopenia	137 (93)
Neutropenia	137 (93)
Thrombocytopenia	52 (35)
Anemia	46 (31)
Hypophosphatemia	37 (25)
Lymphopenia	33 (22)
Hyponatremia	15 (10)
Hyperglycemia	15 (10)
Hypocalcemia*	14 (9)
Hypokalemia*	7 (5)
Hypoalbuminemia*	2 (1)

* Other clinically important Grade 3 or Grade 4 laboratory abnormalities that occurred in less than 10% of patients in ZUMA-5 following treatment with YESCARTA.

8.5. Post-Market Adverse Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post-marketing use of YESCARTA. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Immune System Disorders

Infusion related reaction. One Grade 5 event possibly related to an IRR was reported during routine surveillance.

Nervous System Disorders

Spinal cord edema, myelitis, quadriplegia, dysphagia (see **7 Warnings and Precautions**), and status epilepticus.

Vascular Disorders

Hemorrhage - gastrointestinal hemorrhage, cerebral hemorrhage, pulmonary hemorrhage, hemorrhage intracranial, shock hemorrhagic, hemorrhage, cystitis hemorrhagic and subarachnoid hemorrhage.

One hundred twenty cases of serious hemorrhage were reported in the post-marketing setting. Of the 120 cases, 39 cases included hemorrhage events with fatal outcomes.

9 Drug Interactions

9.2. Drug Interactions Overview

No formal interaction studies have been performed with YESCARTA.

9.3. Drug-Behaviour Interactions

The interaction of YESCARTA with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

Pharmacokinetic Interactions

No pharmacokinetic drug interaction studies have been performed with YESCARTA. T-cells are known to be susceptible to immune-suppressive agents. The benefit/risk of immuno-suppressive agents including but not limited to corticosteroids, cytotoxic chemotherapy, immunophilins, mTOR inhibitors, should be considered as these can be lymphotoxic and may reduce the effectiveness of YESCARTA (see **10 Clinical Pharmacology- Pharmacokinetics**).

Pharmacodynamic Interactions

The immunization with vaccines during or following YESCARTA treatment has not been studied. The effectiveness of vaccines may be affected by prolonged B-cell aplasia and hypogammaglobulinemia (see **7 Warnings and Precautions**). The safety of live viral vaccines has not been investigated in patients treated with YESCARTA; vaccination with live viral 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.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1. 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 elimination of CD19-expressing cells.

10.2. 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, YESCARTA treatment can result in a period of B-cell aplasia and hypogammaglobulinemia, as described in WARNINGS AND PRECAUTIONS.

LBCL

Among patients with LBCL with an ongoing response at primary analysis data cutoff in ZUMA-7, 21 of 61 evaluable patients (34%) had no detectable B cells at baseline, and the majority of patients at Month 3 (43 of 69 evaluable patients [62%]) and Month 6 (8 of 13 evaluable patients [62%]) had no detectable B cells. At Month 24, 20 of 24 evaluable patients (83%) with an ongoing response had detectable B cells.

Among patients with LBCL with an ongoing response at 24 months in ZUMA-1, 13 of 29 (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.

10.3. Pharmacokinetics

Following infusion of YESCARTA in adult patients with LBCL, 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.

LBCL

Among patients with LBCL in ZUMA-7 (n=162 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 peak levels in responders (n=142) were 275% higher compared to the corresponding level in nonresponders (n=20) (28.9 cells/µL vs 10.5 cells/µL). Median AUC Day 0 - 28 in responding patients (n=142) was 418% of the corresponding level in nonresponders (n=20) (292.9 days × cells/µL vs. 70.1 days × cells/µL).

Among patients with LBCL in ZUMA-1, the number of anti-CD19 CAR T cells in blood was positively associated with objective response, CR or PR. The median anti-CD19 CAR T-cell peak levels in responders (n=71) were 216% of the corresponding level in nonresponders (n=27) (43.6 cells/µL vs 20.2 cells/µL). Median AUC Day 0-28 in responding patients (n=71) was 253% of the corresponding level in nonresponders (n=27) (561.96 days × cells/µL vs. 222.04 days × cells/µL).

Table 10 Cellular Kinetic parameters of YESCARTA in adult patients with relapsed or refractory large B-cell lymphoma

	ZUMA-7		ZUMA-1	
Parameter n, Median (Min, Max)	**Responding Patients N =149**	**Non-Responding Patients N = 21**	**Responding Patients N = 73**	**Non-Responding Patients N = 28**
Peak (cells/µL)	n=142, 28.9 (0.04 to 1173.25)	n=20, 10.5 (0.09 to 622.50)	n=71, 43.55 (0.84, 1513.69)	n=27, 20.2 (1.25, 167.42)
T_{peak} (day)	n=142, 8 (2, 233)	n=20, 8 (8, 106)	n=71, 8 (8, 29)	n=27, 8 (8, 78)
Median $AUC_{0\text{-}28d}$ (days x cells/ µL)	n=142, 292.9 (0.00 to 1.65 × 10^4)	n=20, 70.1 (0.00 to 8541.63)	n=71, 561.96 (14.44, 14329.29)	n=27, 222.04 (5.09, 2112.82)

N is equal to the total number of patients and n is the number of patients with evaluable PK parameter.
Response data are based on central read per Cheson 2007.
Peak is defined as the maximum number of CAR T cells measured post infusion.
Area under curve (AUC) is defined as the area under curve in a plot of number of CAR T cells against scheduled visit from Day 0 to Day 28.
Time-to-peak is defined as number of days from YESCARTA infusion to the date when the CAR T cells in blood firstly reached the maximum post-baseline level.

Relapsed or Refractory iNHL, including FL: ZUMA-5

Among patients with FL, the median peak anti-CD19 CAR T-cell levels in responders (n=79) versus nonresponders (n=3) were 37.62 cells/µL and 35.31 cells/µL, respectively. The median AUC_{0-28} in responders versus nonresponders were 451.17 cells/µL•days and 247.14 cells/µL•days, respectively.

Table 11 Cellular Kinetic parameters of YESCARTA in adult patients with relapsed or refractory follicular lymphoma

Parameter n, Median (Min, Max)	Responding Patients	Non-Responding Patients
Peak (cells/µL)	N=79, 37.62 (0.49, 1415.40)	n=3, 35.31 (1.80, 60.24)
Median AUC_{0-28d} (days x cells/ µL)	n=79, 451.17 (5.93, 1.99E+04)	n=3, 247.14 (23.61, 804.42)

N is equal to the total number of patients and n is the number of patients with evaluable PK parameter.
Response data are based on central read per Cheson 2014.
Peak is defined as the maximum number of CAR T cells measured post infusion.
Area under curve (AUC) is defined as the area under curve in a plot of number of CAR T cells against scheduled visit from Day 0 to Day 28 (or from Day 0 to Day 90).
Time-to-peak is defined as the number of days from YESCARTA infusion to the date when the CAR T cells in blood first reached the maximum post-baseline level.

Special Populations and Conditions

- **Geriatrics**

  The anti-CD19 CAR T cell peak level and AUC Day_{0-28} were not significantly influenced by age in LBCL patients or FL patients.

- **Sex**

  The anti-CD19 CAR T cell peak level and AUC Day_{0-28} were not significantly influenced by sex in LBCL patients or FL patients.

- **Hepatic Insufficiency**

  No specific studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of YESCARTA.

- **Renal Insufficiency**

  No specific studies have been conducted to determine the effect of renal impairment on the pharmacokinetics of YESCARTA.

10.4. Immunogenicity

There is a potential for immunogenicity with YESCARTA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. The screening assay is an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. This ELISA was employed to rapidly identify positive samples. Eleven patients (4%) tested positive for pre-dose anti-FMC63 antibodies at baseline in ZUMA-7 and ZUMA-1, and one patient (1%) who had a negative test result at baseline had a positive test result after Day 0 in the screening ELISA in ZUMA-7. In ZUMA-5, 20 patients (14%) were antibody-positive at baseline, and 4 patients (3%) who had negative test results at baseline had positive test results after Day 0 in the screening ELISA. The YESCARTA treated patients who tested antibody-positive from the screening ELISA were

tested negative by a confirmatory cell-based assay, which leverages a properly folded and expressed extracellular portion of the CAR (ScFv, hinge and linker). There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, were altered in these patients in the clinical studies.

11 Storage, Stability and Disposal

Storage

- YESCARTA must be stored in the VAPOUR PHASE of liquid nitrogen (≤ −150°C) and it must remain frozen until the patient is ready for treatment to assure viable live autologous cells are available for patient administration.
- Thawed product should NOT be refrozen.

Stability

- Final product is stable for 12 months when stored frozen in the vapour phase of liquid nitrogen.
- Final product is stable for up to 3 hours after thawing.

Disposal

- Unused medicine must be disposed of in compliance with local guidelines for the disposal of medicinal products containing blood borne pathogens and genetically modified cells.

12 Special Handling Instructions

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

PART 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance: axicabtagene ciloleucel

Physicochemical properties: axicabtagene ciloleucel is a clear to opaque, white to red suspension of cells for infusion.

Product Characteristics
YESCARTA is prepared from the patient's peripheral blood cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells, which are enriched for T cells, are 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 **4 Dosage and Administration**, **11 Storage, Stability and Disposal**, **12 Special Handling Instructions**).

In addition to T cells, YESCARTA may contain NK and NK-T cells. The formulation contains 5% dimethylsulfoxide (DMSO; a component of Cryostor* CS10) and 2.5% albumin (human). YESCARTA is manufactured with gentamicin.

14 Clinical Trials

14.1. Clinical Trials by Indication

Relapsed or Refractory Large B-Cell Lymphoma

Table 12 Summary of Patient Demographics for the Clinical Trial in Relapsed or Refractory Large B-Cell Lymphoma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
ZUMA-7 (Phase 3)	Randomized, open-label, multicenter trial	Single intravenous infusion of YESCARTA at a target dose of 2 × 10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2 × 10^8 cells) or SOCT (defined as 2 to 3 cycles of standard of care chemo-immunotherapy followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT) in those with disease response)	Total randomized: 359 YESCARTA: 180 randomized; 178 patients underwent leukapheresis; 172 patients treated with conditioning chemotherapy; 170 received YESCARTA SOCT: 179 randomized; 168 received at least 1 dose of salvage chemotherapy; 62 received HDT and ASCT	Overall study population: 59 years (range: 21 to 81)	Overall study population: 237 (66%) males 122 (34%) females
ZUMA-1 (Phase 2)	Single-arm, open-label, multicenter trial	Single intravenous infusion of YESCARTA at a target dose of 2 × 10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2 × 10^8 cells)	111 patients underwent leukapheresis; 103 patients treated with conditioning chemotherapy; 101 received YESCARTA	Leukapheresed and Treated groups: 56 years (range: 23 to 76)	Leukapheresed: 77 (69%) males 34 (31%) females Treated: 68 (67%) males 33 (33%) females

ZUMA-7: Axicabtagene ciloleucel vs. Standard of care treatment in patients with DLBCL or HGBL that is refractory to, or relapsed within 12 months of, first-line chemoimmunotherapy

A Phase 3 randomized, open-label, multicenter trial evaluated the efficacy of YESCARTA compared to standard of care treatment (SOCT) in adult patients with large B-cell lymphoma (LBCL) (predominantly diffuse large B-cell lymphoma [DLBCL] or high-grade B-cell lymphoma [HGBL]), that was refractory to, or relapsed within 12 months following first-line rituximab and anthracycline-based chemotherapy. Only patients who intended to proceed to HDT and ASCT (if response to second-line therapy was achieved) were eligible. Patients with PMBCL were not eligible. Other exclusions were patients with history or presence of central nervous system (CNS) lymphoma or other CNS disorders (such as seizures or cerebrovascular ischemia), disease requiring urgent therapy due to tumour mass effects, active or serious infections, prior hematopoietic stem cell transplantation (HSCT), and/or ECOG performance status of 2 or greater.

In total, 359 patients were randomized in a 1:1 ratio to receive a single infusion of YESCARTA, or SOCT defined as 2 to 3 cycles of standard of care chemoimmunotherapy. Patients who achieved complete or partial response were then eligible to undergo HDT and ASCT. Randomization was stratified by response to first-line therapy (primary refractory, vs relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (IPI) (0 to 1 vs 2 to 3) as assessed at the time of screening.

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 were administered on the fifth, fourth, and third day before YESCARTA. Bridging therapy, limited to non-disease modifying corticosteroid treatment, administered between leukapheresis and lymphodepleting chemotherapy was permitted for patients at the discretion of the investigator.

In the overall study population, the median age was 59 years (range: 21 to 81 years), 66% were male, and 83% were white. Diagnoses per investigator were: DLBCL not otherwise specified (NOS) (63%), double expressor lymphoma (22%), high grade B-cell lymphoma (HGBL) with or without *MYC* and *BCL-2* and/or *BCL-6* gene rearrangement (including double/triple hit) (19%), and large cell transformation from FL (13%). Seventy-four percent of patients had primary refractory disease and 26% of patients had relapsed within 12 months of first-line therapy. Patients had a second-line age-adjusted IPI score of 0-1 (55%) or 2-3 (45%) and an ECOG performance status of 0 (54%) or 1 (46%).

Of the 180 patients randomized to receive YESCARTA, 178 underwent leukapheresis and 170 were treated with YESCARTA. Of the patients treated, 60 (33%) received bridging corticosteroid therapy. YESCARTA was successfully manufactured for all 178 patients who underwent leukapheresis. Eight patients (4%) were not treated following leukapheresis, primarily due to progressive disease, serious adverse events, or death. Among infused patients, the median time from leukapheresis to product release was 13 days (range 10 to 24 days), leukapheresis to product delivery was 18 days (range: 13 to 49 days), and leukapheresis to YESCARTA infusion was 26 days (range: 16 to 52 days). Among the 170 patients who received YESCARTA, 166 (98%) received within 10% of the planned dose (for patients weighing ≤ 100 kg: target dose of 2.0×10^6 anti-CD19 CAR-positive viable T cells/kg; for patients weighing >100 kg: target flat

dose of 2 x 10^8 anti-CD19 CAR T cells). All 170 patients who received YESCARTA were monitored at a healthcare facility for a minimum of 7 days post-infusion.

Of the 179 patients randomized to receive SOCT, 168 received any SOCT treatment, and 62 patients (37%) received HDT and on-protocol ASCT. Lack of response to salvage chemotherapy was the most common reason for not proceeding with HDT and ASCT.

The primary endpoint for efficacy was event-free survival (EFS) as determined by a blinded independent review committee. At the time of the primary EFS analysis, the median follow-up time was 24.9 months. Key secondary endpoints included objective response rate (ORR) and overall survival (OS). The primary analysis of OS was performed at a protocol-specified timepoint of five years from the first subject enrolled. The summary of efficacy results demonstrating a statistically significant benefit of YESCARTA over SOCT is shown in Table 13, and the Kaplan-Meier curves for EFS and OS are shown in Figure 1 and Figure 2, respectively.

Table 13 Summary of Efficacy Results for ZUMA-7

Outcome[a]	**YESCARTA N = 180**	**SOCT N = 179**
Event-Free Survival		
Number of events (%)	108 (60)	144 (80)
Median, months [95% CI][b]	8.3 [4.5, 15.8]	2.0 [1.6, 2.8]
Stratified hazard ratio [95% CI]	0.40 [0.31, 0.51]	
Stratified log-rank p-value[c]	<0.0001	
Overall Survival		
Number of events (%)	82 (46)	95 (53)
Median OS, months [95% CI][b]	NR (28.6, NE)	31.1 (17.1, NE)
Stratified hazard ratio [95% CI]	0.73 (0.54, 0.98)	
Stratified log-rank p-value[c,d]	0.017	
Objective Response Rate (%) [95% CI]	83 [77.1, 88.5]	50 [42.7, 57.8]
Difference in ORR (95% CI)	33.1 (23.2, 42.1)	
Stratified CMH test p-value[c, e]	<0.0001	
Complete Response Rate (%) [95% CI]	65 [57.6, 71.9]	32 [25.6, 39.8]
Partial Response Rate (%) [95% CI]	18 [13.0, 24.8]	18 [12.6, 24.3]

CI, confidence interval; NE, not estimable; NR, not reached; SOCT = Standard of Care Therapy; CMH, Cochran-Mantel-Haenszel.

a. Per the International Working Group Lugano Classification (Cheson 2014), as assessed by the independent review committee.
b. Kaplan-Meier method.
c. The p values obtained from the stratified log-rank test or the stratified CMH test were one-sided. The stratification factors were response to first-line therapy (primary refractory, vs relapse within 6 months of first-line therapy vs relapse within > 6 but ≤ 12 months) and second-line age-adjusted International Prognostic Index (0 to 1 vs 2 to 3).
d. P-value was compared with the one-sided efficacy boundary 0.0249 for the primary OS analysis.
e. To control for type I error, statistical testing of the primary and key secondary efficacy endpoints followed a hierarchical scheme: first, EFS was tested, followed by ORR if EFS was significant, then OS if both EFS and ORR were significant.

Based on the primary OS analysis after five years (median follow-up time 47.2 months), 72% and 49% of patients received subsequent therapy after no response or relapse in the SOCT arm and the YESCARTA arm, respectively.

Figure 1. Kaplan-Meier Plot of Event-Free Survival in ZUMA-7

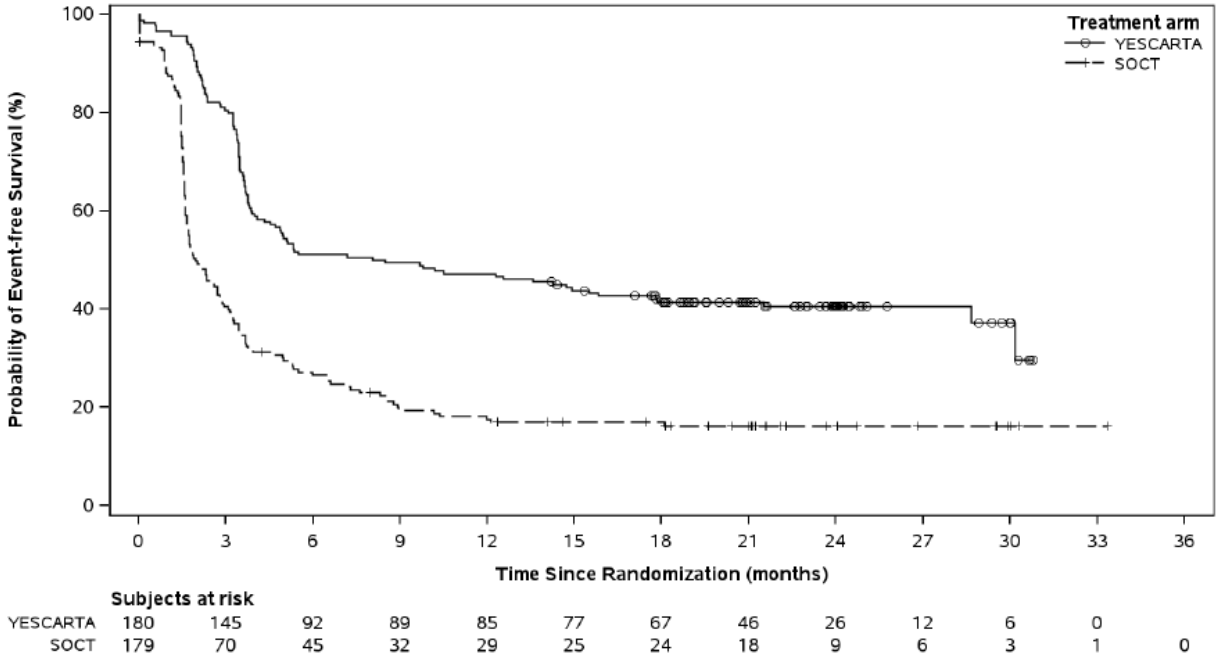
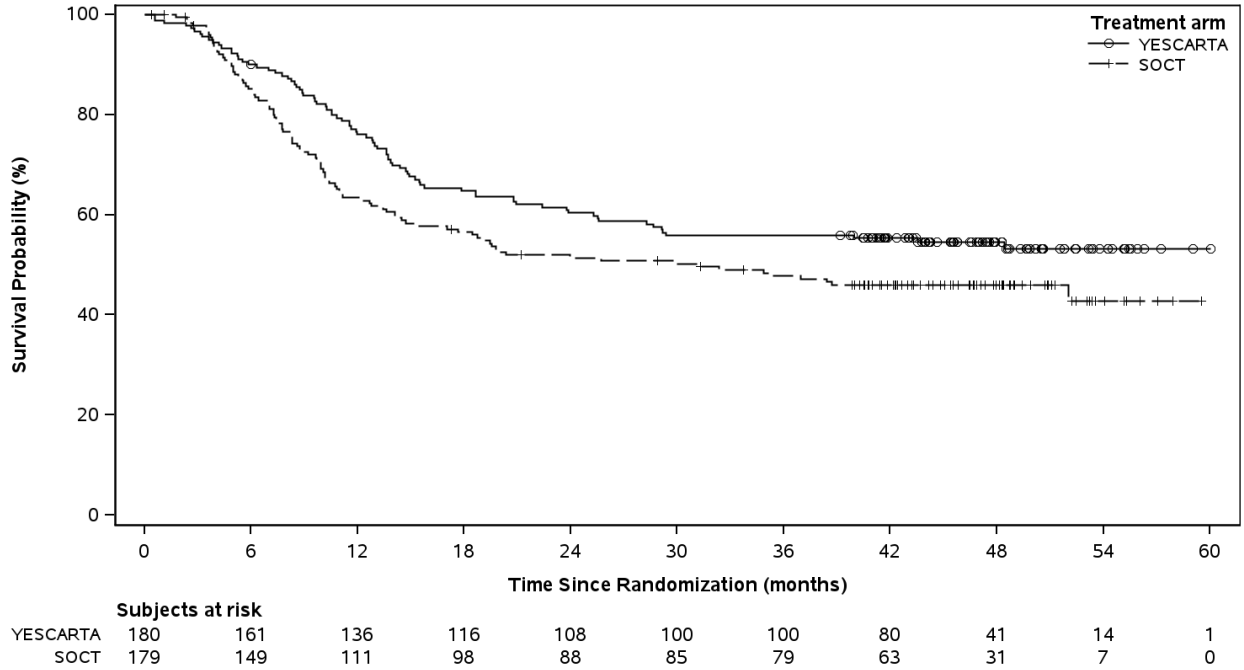


Figure 2. Kaplan-Meier Plot of Overall Survival in ZUMA-7



ZUMA-1 – *single-arm trial of axicabtagene ciloleucel in patients with relapsed or refractory large B-cell lymphoma who received at least 2 prior systemic regimens*

ZUMA-1 is a single-arm, open-label, Phase I/II, multicenter trial that evaluated the efficacy and safety of a single infusion of YESCARTA in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (large B-cell lymphoma) after two or more lines of systemic therapies. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after HSCT. Prior therapies must include anti-CD20 antibody therapy and an anthracycline-containing regimen.

The study excluded patients with prior allogeneic HSCT or CD19-targeting CAR therapy, CNS lymphoma or a history of other CNS disorders (such as seizures or cerebrovascular ischemia), thrombolic events in the last 6 months, 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 room air oxygen saturation of less than 92%, active serious infection or active autoimmune disease requiring systemic immunosuppression.

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 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 5th, 4th, and 3rd day before YESCARTA. No bridging chemotherapy was permitted in the study. All patients were hospitalized for YESCARTA infusion and for a minimum of 7 days afterward.

Of the 111 patients who underwent leukapheresis, 103 patients received conditioning chemotherapy and 101 received YESCARTA (Table 12). Of the 10 patients who underwent leukapheresis but did not receive YESCARTA, 1 was due to manufacturing failure and 9 were due to progressive disease or serious adverse events prior to YESCARTA infusion. 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).

Of the 101 patients treated with YESCARTA, the median age was 58 years (range: 23 to 76), 67% were male, and 86% were white. The baseline ECOG performance status was 42% with ECOG 0, and 58% with ECOG 1. The median number or prior therapies was 3 (range: 1 to 10), 76% of patients had refractory disease to 2 or more lines of therapy, and 21% had relapsed within 1 year of autologous HSCT. There were 46% of patients with International Prognostic Index 3/4 and 85% with disease stage III/IV. Seventy-seven patients had histologically confirmed DLBCL, 8 had PMBCL and 16 had DLBCL arising from follicular lymphoma, based on the 2008 WHO classification. DLBCL in ZUMA-1 included patients with DLBCL not otherwise specified (NOS), other DLBCL subtypes, and high-grade B-cell lymphoma (HGBL) based on the 2016 WHO classification. Forty patients were evaluable for myelocytomatosis viral oncogene homolog (MYC), B-cell lymphoma-2 (BCL-2), and BCL-6 status. Twenty-seven were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 4 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 efficacy of YESCARTA was evaluated in the modified intent-to-treat (mITT) population defined as all patients who received YESCARTA (Table 14). The primary efficacy endpoint was objective response rate (ORR).

Table 14 Summary of Efficacy Results for ZUMA-1 Phase 2 (Primary Analysis; 6 months; independent review) in relapsed or refractory large B-cell lymphoma (mITT population)

Efficacy Endpoints	N =101
Objective Response Rate[a], n (%) (95% CI)	73 (72%) (62, 81)
Complete Remission Rate, n (%) (95% CI)	52 (51%) (41, 62)
Partial Remission Rate, n (%) (95% CI)	21 (21%) (13, 30)
DOR (months)[b] Median[c] (95% CI) Range[d] Probability at 6 months[c] (95% CI)	 9.2 (5.4, NE) 0.0+, 14.4+ 62.0% (48.9%, 72.7%)
DOR if Best Response is CR (months) Median[c] (95% CI) Range[d]	 NE (8.1, NE) 0.4, 14.4+
DOR if Best Response is PR (months) Median[c] (95% CI) Range[d]	 2.1 (1.3, 5.3) 0.03+, 8.4+
Median Follow-up for DOR (Months)[b,c] (95% CI)	7.9 (6.2, 9.6)

CI, confidence interval; CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission; SCT, stem cell transplant.
[a]The objective response was assessed per the revised International Working Group response criteria, Cheson BD et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5).
[b]Among all responders. DOR is measured from the date of first objective response to the date of progression or death from relapse or toxicity. DOR was censored for 60% of patients who achieved a CR or PR, including those who received a new therapy, had SCT, or had an ongoing response. DOR was censored at the time of SCT for patients who received SCT while in response.
[c]Kaplan-Meier estimate.
[d]A + sign indicates a censored value.

Among the 101 patients included in the primary analysis, the best ORR was 72% (73/101) (95% confidence interval [CI]: 62, 81). Fifty-two patients (51%) achieved a CR and 21 patients (21%) achieved PR. The median DOR was 9.2 months (95%CI: 5.4, NE). The median time to response was 0.9 months (range: 0.8 to 6.2 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of PR (Table 14).

Table 15 Summary of Efficacy Results for ZUMA-1 Phase 2 (12-month Analysis; independent review) in relapsed or refractory large B-cell lymphoma (mITT population)

Efficacy Endpoints	N =101
Objective Response Rate[a], n (%) (95% CI)	73 (72%) (62, 81)

Efficacy Endpoints	N =101
Complete Remission Rate, n (%) (95% CI)	52 (51%) (41, 62)
Partial Remission Rate, n (%) (95% CI)	21 (21%) (13, 30)
DOR (months)[b] Median[c] (95% CI) Range Probability at 12 months[c] (95% CI)	 14.0 (8.3, NE) 0.0+, 17.3+ 52.7% (38.6%, 65.0%)
DOR if Best Response is CR (months) Median[c] (95% CI) Range	 NE (11.3, NE) 0.4, 17.3+
DOR if Best Response is PR (months) Median[c] (95% CI) Range	 2.1 (1.3, 5.3) 0.0+, 12.1+
Median Follow-up for DOR (Months)[b,c] (95% CI)	11.1 (10.8, 13.6)

CI, confidence interval; CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission; SCT, stem cell transplant.

[a]The objective response was assessed per the revised International Working Group response criteria, Cheson BD et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5).

[b]Among all responders. DOR is measured from the date of first objective response to the date of progression or death from relapse or toxicity. DOR was censored for 59% of patients who achieved a CR or PR, including those who received a new therapy, had SCT, or had an ongoing response. DOR was censored at the time of SCT for patients who received SCT while in response.

[c]Kaplan-Meier estimate.

[d]A + sign indicates a censored value.

In the 12-month follow-up analysis, the ORR was 72% (73/101) (95% CI: 62, 81). Fifty-two patients (51%) achieved a CR and 21 patients (21%) achieved a PR. The median DOR was 14 months (95% CI: 8.3, NE). The median time to response was 1.0 months (range: 0.8 to 6.3 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of PR (Table 15).

In the 24-month follow-up analysis of ZUMA-1 Phase 2 (independent review; mITT population), the ORR was 74% (75/101) with a median follow-up time of 27.1 months. Fifty-five patients (54%) achieved a CR and 20 patients (20%) achieved a PR. The median DOR was not reached (median follow-up for DOR was 22.9 months). The median time to response was 1.0 month (range: 0.8 to 12.2 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of PR. Of the 55 patients who achieved CR, 7 patients had stable disease (SD) and 10 had PR at their initial tumour assessment and converted to CR as late as 15.3 months after YESCARTA infusion.

In a subsequent, open label, safety management cohort in ZUMA-1 that evaluated the safety and efficacy of YESCARTA with the use of corticosteroids and/or tocilizumab for Grade 1 CRS or neurologic events (see Table 2 and Table 3), a total of 46 patients with relapsed or refractory LBCL were enrolled and 41 patients were treated with YESCARTA. The efficacy outcomes observed in this cohort were comparable to the efficacy outcomes of the ZUMA-1 pivotal cohorts.

Relapsed or Refractory Follicular Lymphoma

Table 16 Summary of Patient Demographics for the Clinical Trial in Relapsed or Refractory Follicular Lymphoma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
ZUMA-5 (Phase 2)	Single-arm, open-label, multicenter trial in adult patients with relapsed or refractory iNHL including follicular lymphoma	Single intravenous infusion of YESCARTA at a target dose of 2×10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2×10^8 cells)	153 patients underwent leukapheresis; 148 patients treated with conditioning chemotherapy; 148 received YESCARTA; 124 patients had follicular lymphoma	Treated: 59.9 years (range: 34 to 79)	Treated: 84 (57%) males 64 (43%) females

The efficacy and safety of YESCARTA in adult patients were evaluated in a phase 2 single-arm, open-label, multicentre study that enrolled patients with r/r indolent B-cell NHL, the majority of whom had r/r FL (n=124/148). Patients with FL grade 3b, transformed lymphoma, lymphoma involving the CNS, or other aggressive lymphomas were not eligible for participation.

Eligible patients were ≥ 18 years of age with relapsed or refractory disease after 2 or more prior lines of systemic therapy and maintained an ECOG status of 0 or 1. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent (single-agent anti-CD20 antibody did not count as line of therapy for eligibility). Patients with stable disease (SD) (without relapse) > 1 year from completion of last therapy were not considered eligible. Patients with a history of allogeneic stem cell transplantation (SCT) or prior anti-CD19 CAR or other genetically modified T-cell therapy were excluded. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia), cardiac ejection fraction of less than 50% or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were ineligible. The study excluded patients with active or serious infections. At the time of the primary analysis, 84 patients with FL in the inferential analysis set (IAS) had an actual median duration of follow up of 17.3 months (range:0.3 to 30.4 months). In the updated 18-month follow-up analysis, the 86 patients with FL in the IAS had an actual median duration of follow-up of 23.26 months (range: 0.3 to 37.7+ months).

At the time of the primary analysis, a total of 151 iNHL patients were enrolled, and 146 patients were treated with YESCARTA including 124 relapsed or refractory FL patients who had received 2 or more lines of prior systemic therapy. YESCARTA was administered as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the 5th, 4th, and 3rd day before YESCARTA. All patients were hospitalized for YESCARTA infusion and for a minimum of 7 days afterward.

The primary analysis was pre-specified to occur when at least 80 FL patients who met the eligibility criteria had a minimum follow-up of 12 months from their first response assessment (termed the Inferential Analysis Set (IAS)). The IAS was a subset of the full analysis set (FAS), which included all FL patients who were enrolled in ZUMA-5. The primary endpoint was the Objective Response Rate (ORR). Secondary endpoints included the CR rate, DOR, and incidence of adverse events. An 18-month follow-up analysis was performed, when at least 80 FL patients had a minimum follow-up of 18 months after infusion.

As of the 18-month follow-up analysis, of 153 iNHL patients (124 r/r FL patients) who underwent leukapheresis, 5 patients were not treated, primarily due to ineligibility or experiencing CR or death prior to the lymphodepleting chemotherapy. No manufacturing failures occurred. The median time from leukapheresis to product release was 12 days (range: 10 to 37 days), leukapheresis to product delivery was 17 days (range: 13 to 72 days) and leukapheresis to YESCARTA infusion was 28 days (range: 19 to 330 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg.

The primary analysis was based on the IAS, which included 84 efficacy evaluable r/r FL patients who received YESCARTA and had the potential to be followed-up for at least 12 months after the first response assessment. Among these 84 r/r FL patients, the ORR was 94% (95%CI: 87, 98) and the CR rate was 79% (95%CI: 68, 87). Among responders, the median time to response was 1 month (range 0.8 to 3.1 months) and the median DOR was not reached (range: 0.0, 25.0+ months). Among the 25 patients with FL who initially achieved a PR, 13 of whom later achieved CR. Subgroup analyses included ORR in patients who were refractory (94%), FLIPI score ≥3 (95%), high tumour burden (95%), progression of disease within 24 months of first immunotherapy (94%) and prior treatment with PI3K inhibitor (96%) (see Table 17).

The efficacy results of the primary analysis, which considered the IAS, were consistent with the ORR and the CR rate observed among the FAS, which included all r/r FL patients without regard for the cut-off date (i.e., patients did not necessarily have the opportunity to be followed for 12 months after the first disease response assessment). The FAS also included patients who were enrolled, but did not receive YESCARTA (n=3). The ORR in the FAS, which included 127 r/r FL patients, was 91% (95%CI: 85, 96), and the CR rate was 75% (95%CI: 66, 82).

Table 17 Primary analysis of efficacy for relapsed/refractory FL patients who received 2 or more prior systemic therapies and had the opportunity to be followed for at least 12 months in study ZUMA-5 (Inferential Analysis Set, IAS[d])

Efficacy Endpoints	**N =84**
Objective Response Rate [a], n (%) (95% CI)	79 (94%) (87%, 98%)
Complete Remission Rate, n (%) (95% CI)	66 (79%) (68%, 87%)
Partial Remission Rate, n (%) (95% CI)	13 (15%) (9%, 25%)
DOR (months)[b] Median[c] (95% CI) Range Event-free rate at 12 months[c] (95% CI)	 NE (20.8, NE) 0.0 +, 25.0 + 77.0% (65.6%, 85.1%)
Median Follow-up for DOR (Months)[b,c] (95% CI)	14.1

Efficacy Endpoints	N =84
	(13.6, 16.7)

CI, confidence interval; CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission.
[a]The objective response was assessed per the revised International Working Group response criteria, Cheson BD et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32 (27): 3059-68.
[b] DOR is defined as the time from the first objective response to disease progression per Lugano Classification (Cheson et al, 2014) or death from any cause. Subjects not meeting the criteria by the analysis data cutoff date will be censored at their last evaluable disease assessment date prior to the data cutoff date or new anticancer therapy start date (including stem cell transplant or retreatment of axicabtagene ciloleucel) whichever is earlier.
[c]Kaplan-Meier estimate.
[d] Inferential Analysis Set [IAS]: defined as having received YESCARTA, met all eligibility criteria, and had the opportunity to be followed at least 12-months [d]
[e]A + sign indicates a censored value.

A descriptive 18-month follow-up analysis that considered the IAS (defined as having received YESCARTA, met all eligibility criteria, and had the opportunity to be followed at least 18-months) included 86 efficacy evaluable r/r FL patients. Among the IAS, the ORR was 94% and the CR rate was 79%. The median DOR was not reached (range: 0.0 + to 25.0 + months) and the proportion of responders who remained in response was 65% at Month 18.

15 Microbiology

Not applicable.

16 Non-Clinical Toxicology

YESCARTA comprises engineered human T-cells, therefore there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for drug development were not performed.

No carcinogenicity or genotoxicity studies have been conducted with YESCARTA.

No studies evaluating the effects of YESCARTA on fertility, reproduction and development have been conducted.

17 Supporting Product Monographs

1) [Pr]ACTEMRA (tocilizumab, 20 mg/mL [Concentrate Solution for Infusion]; 162 mg/0.9 mL [Solution for Injection], Hoffmann-La Roche Limited, Submission Control 198824, Product Monograph, Aug. 30, 2017.
2) [Pr]Fludarabine Phosphate, Teva Canada Limited. Fludarabine Phosphate Sterile Solution for Injection 25 mg/mL (2 mL per vial). Product Monograph. Toronto, Canada. Date of Revision: 01 March. 2016.
3) [Pr]PROCYTOX Cyclophosphamide, Baxter Corporation. [Pr]PROCYTOX Cyclophosphamide Tablets USP: 25 mg, 50 mg Cyclophosphamide for injection: 200 mg, 500 mg, 1000 mg, 2000 mg (powder for injection) per vial. Product Monograph. Mississauga, Ontario. Date of Revision: 07 September. 2012.

4) PrAPO-PREDNISONE, Apotex Inc. PrAPO-PREDNISONE Prednisone Tablets USP 1 mg, 5 mg and 50 mg. Canadian Prescribing Information. Toronto, Canada. Date of Revision: 28 May. 2015.
5) PrDEXAMETHASONE OMEGA UNIDOSE, Omega Laboratories Limited. PrDEXAMETHASONE OMEGA UNIDOSE (Dexamethasone Sodium Phosphate Injection USP) (10 mg/mL). Montreal, Quebec, Canada. Date of Preparation: 12 June. 2012.
6) Pr ZYLOPRIM®, AA Pharma Inc. Allopurinol tablets, 100, 200, and 300 mg. Product Monograph. Vaughan, Ontario Canada. Date of Preparation: 15 September 2010.
7) PrKINERET® (anakinra, solution for injection, 150 mg/mL). Swedish Orphan Biovitrum AB. Product Monograph. Stockholm, Sweden. Date of Approval : March 28, 2018.
8) PrSYLVANT® (siltuximab for injection; 100 mg/vial and 400 mg/vial). Janssen Inc. Product Monograph. Toronto, Ontario, Canada. Date of Approval: 16 March 2018.
9) PrJAKAVI® (ruxolitinib tablets; 5 mg, 10 mg, 15 mg and 20 mg). Novartis Pharmaceuticals Canada Inc. Product Monograph. Dorval, Quebec, Canada. Date of Revision: September 28, 2018.
10) GAMMAGARD LIQUID (Immune Globulin Intravenous [IVIG] 10% Solution for Infusion), Shire Pharma Canada ULC. Toronto, Ontario, Canada. Product Monograph. Date of Approval: May 4, 2018.
11) PrATGAM® (anti-thymocyte globulin [equine]). Pfizer Canada Inc. Concentrate for solution for infusion / sterile solution - 50 mg/mL). Product Monograph. Kirkland, Quebec, Canada. Date of Revision: 28 May 2014.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Yescarta®
(axicabtagene ciloleucel)
This Patient Medication Information is written for the person who will be taking Yescarta. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.
This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about Yescarta, talk to a healthcare professional.

Serious Warnings and Precautions

Yescarta can cause serious side effects that are life-threatening. Sometimes, these serious side effects that are life-threatening can lead to death. The serious adverse effects of Yescarta include the following:

- **Cytokine release syndrome (CRS):** if you have CRS, you may experience one or more of the following symptoms: chills; high fever; feeling weak or very tired; nausea, vomiting; diarrhea; muscle or joint pain; dizziness; headache; cough; shortness of breath; and fast or irregular heartbeat. Talk to your healthcare professional immediately if you have any of these symptoms.
- **Neurologic side effects:** if you have serious neurologic side effects, you may experience one or more of the following symptoms: fit; shaking; difficulty speaking or swallowing; dizziness; confusion; delirium; memory loss, seizure; loss of balance; and decreased or loss of consciousness. Talk to your healthcare professional immediately if you have any of these symptoms.

You will only be given Yescarta by an experienced healthcare professional at specialized treatment centres.

What is Yescarta used for:

- Yescarta is a treatment for your large B-cell lymphoma or follicular lymphoma– two forms of white blood cell cancer.
  - For large B-cell lymphomas, it is used when one other kind of treatment has failed, or the cancer has returned after treatment. It is also used to treat large B-cell lymphoma patients who have received multiple types of treatment when the disease didn't respond or got worse after initially getting better.
  - For follicular lymphoma, it is used when at least two other kinds of treatment have failed or the cancer has returned after treatment.

How Yescarta works:

Yescarta is made from your own white blood cells. Some of these cells are taken from your body and then genetically modified to make Yescarta. Yescarta is given to you by drip (infusion) into a vein. Yescarta recognizes and attacks your lymphoma cells.

The ingredients in Yescarta are:

- Medicinal ingredients: axicabtagene ciloleucel
- Non-medicinal ingredients: Cryostor® CS10, human serum albumin, sodium chloride,

Yescarta comes in the following dosage forms:

Yescarta comes as a cell suspension in one infusion bag. The entire content of the bag should be given to you by drip into a vein as a single, one-time treatment.

Do not use Yescarta if:

- You are allergic to Yescarta or any of the other ingredients of this medicine (Read "The ingredients in Yescarta are" above).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Yescarta. Talk about any health conditions or problems you may have, including if you

- Have a brain tumour or any other types of cancer.
- Have had a stem cell transplant or any other organ transplant in the past.
- Have or have had problems with the heart, blood pressure, lung, liver or kidney.
- Have had blood clots in the body.
- Have any symptoms of CRS (severe systemic inflammation), such as chills, high fever, feeling weak or very tired, nausea, vomiting, diarrhea, muscle or joint pain, dizzy, headache, cough, shortness of breath, or fast or irregular heartbeat.
- Have any symptoms of neurologic problems, such as fits, stroke, shaking, difficulty speaking or swallowing, confusion, delirium, memory loss, seizure, loss of balance, loss of consciousness or decreased level of consciousness.
- Have any symptoms of infection, such as fever (100.4°F/38°C), chill, sore throat, coughing, chest pain, stomach pain, vomiting, and diarrhea.
- Have any symptoms of low red blood cells, such as feeling weak or very tired, and shortness of breath.
- Have any symptoms of low platelets (a type of blood cell), such as bleeding or bruising more easily.
- Had or have hepatitis B or C or HIV (human immunodeficiency virus).
- Had a vaccine in the previous 6 weeks or are planning to have one in the next few months.
- Have any symptoms of severe allergic reactions, such as shortness of breath or trouble breathing, skin rash, swelling of the lips, tongue, or face, chest pain, feeling dizzy or faint.
- Have any symptoms of tumour lysis syndrome, such as nausea, vomiting, diarrhea, muscle cramps or twitches, weakness, numbness or tingling, feeling tired, less urine, irregular heartbeat, confusion, restless, delirium or seizure.
- Are pregnant, think you are pregnant or plan to become pregnant.
- Are a man and you plan to father a child after Yescarta treatment.
- Are breast-feeding or plan to do so.

Other warnings you should know about:

- Do not drive, use heavy machinery, or do other dangerous things for 8 weeks after you get Yescarta because the treatment can cause sleepiness, confusion, weakness, memory and coordination problems.
- Do not donate blood, organs, tissues and cells for transplantation after Yescarta treatment.
- Cases of progressive multifocal leukoencephalopathy (PML) have been reported following Yescarta use. PML is a rare brain infection that can be fatal. Tell your healthcare professional right away if you notice or someone notices in you: progressive weakness on one side of the body; clumsiness of limbs; disturbance of vision; changes in thinking; memory and orientation; confusion; or personality changes. Your healthcare professional may request further testing if PML is suspected.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
The following may interact with Yescarta:

- Corticosteroids, chemotherapy, and other medications that can suppress your immune system: they may make Yescarta less effective.
- Vaccines: Yescarta may make some vaccines less effective. It may not be safe for you to receive a live viral vaccine (a type of vaccine made from weakened virus) during or shortly after Yescarta.

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 remove some of your white blood cells and concentrate them.
- Your blood cells will be sent to a manufacturing centre 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 professional will give it to you through a catheter placed into your vein (intravenous infusion). The treatment usually takes less than 30 minutes.
- Your healthcare professional will recommend that you return to the hospital daily for at least 7 days and will consider whether you need to stay at the hospital as an in-patient for the first 7 days after infusion. This is so your healthcare professional can help you if you have any side effects.
- You should plan to stay close to hospital as discussed with your healthcare professional for at least 4 weeks after getting Yescarta. You may be hospitalized for side effects and your healthcare professional will discharge you if your side effects are under control, and it is safe for you to leave the hospital.
- Your healthcare professional will give you a **Patient Alert Card**. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the healthcare professional when you see them or if you go to hospital.
- Your healthcare professional 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 professional as soon as possible to reschedule.

Usual dose:

Yescarta comes as a cell suspension in one infusion bag. The target dose is 2×10^6 manufactured live T cells (that is CAR T cells) per kg body weight; with a maximum of 2×10^8 CAR T cells (if you weigh 100 kg or higher). The entire content of the bag should be given to you as a single, one-time treatment.

Possible side effects from using Yescarta:

These are not all the possible side effects you may feel when taking Yescarta. If you experience any side effects not listed here, contact your healthcare professional.

Very common:
- Low blood pressure, dizziness
- Headache, difficulty in speaking, agitation, shaking, feeling sick, constipation, diarrhea, pain in the stomach or being sick
- Shortness of breath, cough
- Low levels of antibodies called immunoglobulins, which may lead to infections
- Muscle pains, back pain
- Extreme tiredness
- Dehydration
- Increased levels of liver proteins called transaminases
- Difficulty sleeping
- Loss of interest in activities or feeling depressed
- Stuffy nose

Common:
- Difficulty understanding numbers, memory loss
- Muscle spasms
- Swelling
- Rash
- Itching

Serious side effects and what to do about them

Frequency/Side-effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
Very common			
High fever, chills, difficulty breathing, nausea, vomiting, diarrhea, muscle pain, joint pain, low blood pressure, or dizziness/light headedness (possible symptoms of cytokine release syndrome [CRS])		✓	✓
Fits (seizures), shaking, loss/decreased level of consciousness, confusion, loss of balance or coordination, difficulty self-caring, difficulty reading, writing, and understanding (possible symptoms of neurologic problems)		✓	✓

Seizures lasting 5 minutes or more; or recurrent seizures without recovering between seizures		✓	✓
Feeling warm, fever, chills or shivering; depending on the location of infection, you may also experience cough, difficulty breathing, painful urine or blood in urine, sore throat, or chest pain (possible symptom of infections)		✓	
Weakness, loss of energy, rapid heartbeat, shortness of breath, pale skin, low level of red blood cells in blood test (possible symptoms of low level of red blood cells)		✓	
Spontaneous bleeding or bruising (possible symptoms of low levels of blood platelets or thrombocytopenia)		✓	
Common			
Low number of white blood cells in your blood test; you may or may not have an infection at the same time (neutropenia or febrile neutropenia)		✓	
Changes in functioning or rhythm of the heart (atrial fibrillation, atrial flutter, or ejection fraction decreased)		✓	
Breathlessness, difficulty breathing when lying down (possible symptoms of heart failure)		✓	✓
Loss of consciousness, loss of heartbeat (possible symptoms of cardiac arrest)		✓	✓
Very little or no urine (possible symptoms of acute kidney injury)		✓	
Being anxious, nervous		✓	
Dizziness, light headedness caused by low blood pressure (hypotension)		✓	
Headache or dizziness caused by high blood pressure (hypertension)		✓	
Shortness of breath, fast heartbeat, blue discoloration of lips or extremities (possible symptoms of hypoxia)		✓	
Chest pain, cough, shortness of breath, caused by fluid around the lungs (pleural effusion)		✓	
Extreme shortness of breath or difficulty breathing, feeling suffocated, anxious, restless, cough, frothy sputum with or without blood, blue colored lips, or fast heartbeat, caused by fluid in the lungs (possible symptoms of pulmonary edema)		✓	✓
Leakage of fluids from blood vessels into surrounding tissue (capillary leak syndrome)		✓	
Feeling very tired (somnolence)		✓	
State of severe confusion (delirium)		✓	✓
Extreme activation of the immune system with fever, rash and injury to liver, blood cells and brain (histocytosis hematophagic)		✓	✓
Spontaneous or prolonged and excessive bleeding (coagulopathy)		✓	✓
Blood clots that lower blood flow (thrombosis)		✓	

Reduced level of sodium in the blood, sometimes leading to nausea, headache, drowsiness, restlessness, irritability muscle weakness and cramps (hyponatremia)		✓	
Reduced level of phosphate in the blood, sometime leading to muscle weakness (hypophosphatemia)		✓	
Reduced levels of potassium in the blood, possibly leading to muscle weakness, muscle spasms, abnormal heart rhythm (hypokalemia)		✓	
Nausea, vomiting, fast breathing, and lethargy caused by high levels of acid in the blood (metabolic acidosis)		✓	
Difficulty to swallow (dysphagia)		✓	✓
Uncommon			
Bleeding, which can be severe, called a 'hemorrhage'.		✓	✓
Rare			
Symptoms of new cancer including new lymphoma or leukemia from a type of white blood cells called T-cells. If you have T-cell leukemia this might include symptoms of fever, feeling weak, bleeding gums, bruising. If you have T-cell lymphoma, this might include symptoms of unexplained fever, feeling weak, night sweats, sudden weight loss.		✓	✓
Inflammation and swelling of spinal cord which may cause partial or total paralysis of limbs and torso (myelitis, spinal cord edema and quadriplegia)		✓	✓
Progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, changes in thinking, memory and orientation, confusion, personality changes (Progressive multifocal leukoencephalopathy [PML])		✓	✓
Fever, chills, shivering, nausea, vomiting, tiredness, dizziness, pain where the infusion needle is inserted, blisters, itching, and/or shortness of breath or wheezing during or shortly after infusion (possible infusion-related reaction)		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about Yescarta:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.gilead.ca, or by calling 1-866-207-4267.

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Kite Pharma, Inc.
Santa Monica, CA 90404
USA

Manufactured for:
Gilead Sciences Canada, Inc.
Mississauga, ON L5N 7K2

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