

1. NAME OF THE MEDICINAL PRODUCT

YESCARTA

Patient safety information card

The marketing of YESCARTA is subject to a risk management plan (RMP) including a 'patient safety information card'. The "patient safety information card", emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment

Prescriber guide

This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

0.4 – 2 x 10⁸ cells dispersion for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

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

2.2 Qualitative and quantitative composition

Each patient specific single infusion bag of YESCARTA contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 x 10⁶ anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 x 10⁶ – 2 x 10⁶ cells/kg), with a maximum of 2 x 10⁸ anti-CD19 CAR T cells.

Excipients with known effect

Each bag of YESCARTA contains 300 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for intravenous infusion.

A clear to opaque, white to red suspension of cells for infusion, supplied in an infusion bag, individually packed in a metal cassette.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

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

4.2 Posology and method of administration

YESCARTA must be administered in a qualified clinical setting.

YESCARTA therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with YESCARTA. A minimum of four doses of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion of YESCARTA.

Posology

YESCARTA is intended for autologous use only (see section 4.4).

A single dose of YESCARTA contains 2×10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag.

The availability of YESCARTA must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² intravenous and fludarabine 30 mg/m² intravenous should be administered on the 5th, 4th, and 3rd day before infusion of YESCARTA.

Pre-medication

- Paracetamol 500-1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour before YESCARTA infusion is recommended.
- Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of YESCARTA.

Monitoring

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Special populations

Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection

There is no clinical experience in patients with active HIV, HBV or HCV infection.

Paediatric population

The safety and efficacy of YESCARTA in children and adolescents below 18 years of age have not yet been established. No data are available.

Elderly

No dose adjustment is required in patients ≥ 65 years of age. Efficacy was consistent with the overall treated patient population.

Method of administration

YESCARTA is to be administered via intravenous infusion.

YESCARTA must not be irradiated. Do NOT use a leukodepleting filter.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified human blood cells. Healthcare professionals handling YESCARTA should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation of YESCARTA

- Verify that the patient's identity (ID) matches the patient identifiers on the YESCARTA cassette.
- The YESCARTA bag must not be removed from the cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the YESCARTA bag from the cassette.
- Check that the patient information on the cassette label matches that on the bag label.
- Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines (or immediately contact Kite).
- 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. YESCARTA should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, YESCARTA is stable at room temperature (20°C-25°C) for up to 3 hours. YESCARTA infusion should begin within 30 minutes of thaw completion and the total YESCARTA infusion time should not exceed 30 minutes.

Administration

- For autologous use only.
- Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration of YESCARTA.
- Verify the patient ID again to match the patient identifiers on the YESCARTA bag.
- Prime the tubing with 0.9% sodium chloride solution (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during YESCARTA infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with 0.9% sodium chloride solution (0.154 mmol sodium per mL) to ensure all YESCARTA is delivered.

For special precautions for disposal, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

General

Due to the risks associated with YESCARTA treatment, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection.
- Active graft-versus-host disease (GVHD).

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

YESCARTA is intended solely for autologous use and must not 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.

Concomitant disease

Patients with active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Primary central nervous system (CNS) lymphoma

There is no experience of use of YESCARTA in patients with primary CNS lymphoma. Therefore, the risk/benefit of YESCARTA has not been established in this population. YESCARTA is not indicated for the treatment of patients with primary or secondary central nervous system lymphoma.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, including life-threatening and fatal reactions, was very commonly observed with YESCARTA with a time to onset of 1 to 12 days (see section 4.8).

Ensure that a minimum of 4 doses of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, are available for each patient prior to infusion of YESCARTA.

Monitor patients daily for signs and symptoms of CRS for at least 10 days following infusion at the qualified clinical facility. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS occur. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on YESCARTA. These include the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental

oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

YESCARTA should not be administered to patients with active infections or inflammatory disease until these conditions have resolved.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS.

YESCARTA continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of YESCARTA-associated CRS.

Table 1: CRS grading and management guidance

CRS Grade (a)	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
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.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
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	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days. If not improving, manage as Grade 4 (below).
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above. Consider alternate immunosuppressants if no improvement or if condition worsens.

N/A = not available/not applicable

(a) Lee et al 2014.

(b) Refer to Table 2 for management of neurologic adverse reactions.

(c) Refer to tocilizumab summary of product characteristics for details.

Neurologic adverse reactions

Severe neurologic adverse reactions have been very commonly observed in patients treated with YESCARTA, which could be life-threatening or fatal (see section 4.8). Patients with a history of CNS disorders such as seizures or cerebrovascular ischaemia may be at increased risk. Fatal and serious cases of cerebral oedema have been reported in patients treated with YESCARTA. Patients should be monitored for signs and symptoms of neurologic adverse reactions (Table 2). Patients should be monitored at least daily for 10 days at the qualified healthcare facility following infusion for signs and symptoms of neurologic toxicity. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of neurologic toxicity occur. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction.

Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines should be considered as

clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on YESCARTA. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

Table 2: Neurologic adverse reaction grading and management guidance

Grading assessment	Concurrent CRS	No concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Infections and febrile neutropenia

Serious infections have been very commonly observed with YESCARTA (see section 4.8). Patients should be monitored for signs and symptoms of infection before, during, and after YESCARTA infusion and treated appropriately. Prophylactic anti-microbials should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after YESCARTA infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

HBV reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells. Screening for HBV, HCV, and HIV should be performed in accordance with clinical guidelines before collection of cells for manufacturing of YESCARTA.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. Grade 3 or higher prolonged cytopenias following YESCARTA infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia. Monitor blood counts after YESCARTA infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with YESCARTA. Hypogammaglobulinaemia has been very commonly observed in patients treated with YESCARTA. Immunoglobulin levels should be monitored after treatment with YESCARTA and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

Hypersensitivity reactions

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

Secondary malignancies

Patients treated with YESCARTA may develop secondary malignancies. Monitor patients life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

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

Prior treatment with anti-CD19 therapy

There is limited experience with YESCARTA in patients exposed to prior CD19-directed therapy. YESCARTA is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Excipients

This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with YESCARTA.

Live vaccines

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of child bearing potential must be verified before starting YESCARTA treatment.

See the prescribing information for lymphodepleting chemotherapy 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.

Pregnancy

There are no available data with YESCARTA use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with YESCARTA to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if YESCARTA has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after YESCARTA therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborns of mothers treated with YESCARTA should be considered.

Breast-feeding

It is unknown whether YESCARTA is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should be advised of the potential risk to the breast-fed child.

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.

4.7 Effects on ability to drive and use machines

YESCARTA has major influence on the ability to drive and use machines. Due to the potential for neurologic events, including altered mental status, or seizures, patients should refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

The safety data described in this section reflect exposure to YESCARTA in ZUMA-1, a Phase 1/2 study in which 108 patients with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) received CAR-positive T cells based on a recommended dose which was weight-based. The median duration of follow up was 27.4 months.

The most significant and frequently occurring adverse reactions were CRS (93%), encephalopathy (58%), and infections (39%).

Serious adverse reactions occurred in 56% of patients. The most common serious adverse reactions included encephalopathy (22%), unspecified pathogen infections (16%), bacterial infections (6%), febrile neutropenia (6%), viral infections (5%), and pyrexia (5%).

The most common Grade 3 or higher adverse reactions included encephalopathy (31%), unspecified pathogen infections (19%), CRS (11%), bacterial infection (9%), aphasia (7%), viral infection (6%), delirium (6%), hypotension (6%), and hypertension (6%).

Tabulated list of adverse reactions

Adverse reactions reported from clinical trials and post-marketing setting are presented below. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse drug reactions identified with YESCARTA

System Organ Class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Unspecified pathogen infections Viral infections Bacterial infections
	Common	Fungal infections
Blood and lymphatic system disorders		
	Very common	Leukopenia Neutropenia Anaemia Thrombocytopenia
	Common	Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome Hypogammaglobulinaemia
	Common	Hypersensitivity Histiocytosis Haematophagic
Metabolism and nutrition disorders		
	Very common	Dehydration Decreased appetite Hypophosphataemia Hyponatraemia Weight decrease
	Common	Hypocalcaemia Hypoalbuminaemia
Psychiatric disorders		
	Very common	Delirium Anxiety
	Common	Insomnia
Nervous system disorders		
	Very common	Encephalopathy Headache Tremor Dizziness Aphasia
	Common	Ataxia Neuropathy Seizure Dyscalculia Myoclonus
	Uncommon	Spinal cord oedema

System Organ Class (SOC)	Frequency	Adverse reactions
		Myelitis Quadriplegia
Cardiac disorders		
	Very common	Tachycardia Arrhythmia
	Common	Cardiac arrest Cardiac failure
Vascular disorders		
	Very common	Hypotension Hypertension
	Common	Thrombosis Capillary leak syndrome
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Dyspnoea Hypoxia Pleural effusion
	Common	Pulmonary oedema
Gastrointestinal disorders		
	Very common	Diarrhoea Nausea Vomiting Constipation Abdominal pain Dry mouth
	Common	Dysphagia*
Skin and subcutaneous tissue disorders		
	Common	Rash
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction Pain in extremity Back pain Arthralgia Muscle pain
Renal and urinary disorders		
	Common	Renal insufficiency
General disorders and administration site conditions		
	Very common	Fatigue Pyrexia Oedema Chills
Investigations		
	Very common	Alanine aminotransferase increased Aspartate aminotransferase increased
	Common	Bilirubin increased

Only cytopenias that resulted in (i) new or worsening clinical sequelae or (ii) that required therapy or (iii) adjustment in current therapy are included in Table 3.

* Dysphagia has been reported in the setting of neurologic toxicity and encephalopathy

Description of selected adverse reactions

Cytokine release syndrome

CRS occurred in 93% of patients. Eleven percent (11%) of patients experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 2 days (range: 1 to 12 days) and the median duration was 7 days (range: 2 to 29 days). Ninety-eight percent (98%) of patients recovered from CRS.

The most common signs or symptoms associated with CRS included pyrexia (83%), hypotension (44%), tachycardia (24%), hypoxia (23%), and chills (20%). Serious adverse reactions that may be

associated with CRS included acute kidney injury, atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, capillary leak syndrome, hypotension, hypoxia, and HLH/MAS. See section 4.4 for monitoring and management guidance.

Neurologic adverse reactions

Neurologic adverse reactions occurred in 67% of patients. Thirty-two percent (32%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 5 days (range: 1 to 17 days). The median duration was 13 days (range: 1 to 191 days). Most patients recovered from neurologic adverse reactions, with the exception of 4 patients who had ongoing neurologic adverse reactions at the time of death; the deaths were due to other causes.

The most common signs or symptoms associated with neurologic adverse reactions included encephalopathy (58%), headache (40%), tremor (31%), dizziness (21%), aphasia (18%), and delirium (17%). Serious adverse reactions including encephalopathy (22%), aphasia (4%), delirium (4%), and seizures (1%) have been reported in patients administered YESCARTA.

Other neurologic adverse reactions have been reported less frequently in clinical trials and included dysphagia (5%), myelitis (0.2%), and quadriplegia (0.2%).

Spinal cord oedema was reported, in the context of neurologic toxicity in the post-marketing setting.

See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections

Febrile neutropenia was observed in 36% of patients after YESCARTA infusion. Infections occurred in 39% of patients in ZUMA-1. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 26% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 19%, 9%, and 6% of patients respectively. The most common site of infection was in the respiratory tract. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias

Grade 3 or higher neutropenia (including febrile neutropenia), anaemia, and thrombocytopenia occurred in 80%, 45%, and 40% of patients, respectively. Prolonged (still present at Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher neutropenia, thrombocytopenia, and anaemia occurred in 26%, 24%, and 10% of patients, respectively. Grade 3 or higher neutropenia, thrombocytopenia, and anaemia present after Day 93 occurred in 11%, 7%, and 3% of patients, respectively. See section 4.4 for management guidance.

Hypogammaglobulinaemia

In ZUMA-1, hypogammaglobulinaemia occurred in 16% of patients. Cumulatively, 33 (31%) of 108 subjects received intravenous immunoglobulin therapy at the time of the 24-month analysis. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for anti-FMC63 prior to being treated with YESCARTA. An impact of these antibodies on efficacy or safety was not discernible.

Special population

There is limited experience with YESCARTA in patients ≥ 75 years of age. Generally, safety and efficacy were similar between patients ≥ 65 years and patients < 65 years of age treated with YESCARTA. Outcomes were consistent between patients with Eastern Cooperative Oncology Group (ECOG) of 0 and 1 and by sex.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>. Additionally, adverse events can be reported to the registration holder by email (DrugSafety.Israel@gilead.com).

4.9 Overdose

There are no data regarding the signs of overdose with YESCARTA.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: **not yet assigned**

Mechanism of action

YESCARTA, an engineered autologous T-cell immunotherapy product, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling 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 apoptosis and necrosis of CD19-expressing target cells.

Pharmacodynamic effects

In phase 2 of ZUMA-1, 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 IL2R α were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days.

Due to the on-target, off-tumour effect of YESCARTA, a period of B-cell aplasia is expected following treatment. Among 73 patients with evaluable samples at baseline, 40% had detectable B-cells; the B-cell aplasia observed in the majority of patients at baseline was attributed to prior therapies. Following YESCARTA treatment, the proportion of patients with detectable B-cells decreased: 20% had detectable B-cells at Month 3, and 22% had detectable B-cells at Month 6. The initiation of B-cell recovery was first noted at Month 9, when 56% of patients had detectable B-cells. This trend of B-cell recovery continued over time, as 64% of patients had detectable B-cells at Month 18, and 77% of patients had detectable B-cells at Month 24. Patients were not required to be followed after they progressed; thus, the majority of patients with evaluable samples were responders.

Analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of IL-15, as well as IL-6, were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS.

Clinical efficacy and safety

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

A total of 108 patients were treated with YESCARTA in a phase 1/2 open-label, multicentre, single-arm study in patients with relapsed or refractory aggressive B-cell NHL. Efficacy was based on 101 patients in phase 2, including histologically confirmed DLBCL (N = 77), PMBCL (N = 8), or DLBCL arising from follicular lymphoma, (N = 16) based on the 2008 WHO-classification. DLBCL in ZUMA-1 included patients with DLBCL NOS, other DLBCL subtypes, and high-grade B-cell lymphoma (HGBCL) based on the 2016 WHO-classification. Forty-seven patients were evaluable for MYC, BCL-2, and BCL-6 status. Thirty were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 5 were found to have HGBCL with MYC, BCL-2 or BCL-6 gene rearrangement (double- and triple-hit); and 2 were found to have HGBCL 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.

Eligible patients were ≥ 18 years of age with refractory disease defined as progressive disease (PD) or stable disease (SD) as best response to last line of therapy, or disease progression within 12 months after autologous stem cell transplant (ASCT). Patients who were refractory to chemotherapy or who relapsed after two or more lines of systemic therapy were generally ineligible for haematopoietic stem cell transplantation. Patients must have received at least prior anti-CD20 antibody therapy and an anthracycline containing regimen. Patients with CNS lymphoma, 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 median duration of follow up was 27.1 months (still ongoing). A summary of the patient demographics is provided in Table 4.

Table 4: Summary of demographics for ZUMA-1 phase 2 (12 month analysis)

Category	All leukapheresed (ITT) Cohort 1 + 2 (N = 111)	All treated (mITT) Cohort 1 + 2 (N = 101)
<i>Age (years)</i>		
Median (min, max)	58 (23, 76)	58 (23, 76)
≥ 65	23%	24%
Male gender	69%	67%
<i>Race</i>		
White	85%	86%
Asian	4%	3%
Black	4%	4%
<i>ECOG status</i>		
ECOG 0	41%	42%
ECOG 1	59%	58%
Median number of prior therapies (min, max)	3 (1, 10)	3 (1, 10)
Patients with refractory disease to ≥ 2 prior lines of therapy	77%	76%
Patients relapsed within 1 year of ASCT	20%	21%
Patients with International Prognostic Index 3/4	46%	46%
Patients with disease stage III/IV	85%	85%

YESCARTA was administered as a single infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg after lymphodepleting chemotherapy regimen of 500 mg/m² intravenous cyclophosphamide and 30 mg/m² intravenous fludarabine on the 5th, 4th, and 3rd day before YESCARTA. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for observation for a minimum of 7 days after YESCARTA infusion.

Of 111 patients who underwent leukapheresis, 101 received YESCARTA. Nine patients were not treated, primarily due to progressive disease or serious adverse events after enrolment and prior to cell delivery. One out of 111 patients did not receive the product due to manufacturing failure. 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 anti-CD19 CAR T cells/kg. ITT was defined as all patients who underwent leukapheresis; mITT was defined as all patients who received YESCARTA.

The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DOR), overall survival (OS), and severity of adverse events. The ORR was prespecified to be tested in the first 92 treated patients and was significantly higher than the prespecified rate of 20% ($P < 0.0001$).

In the primary analysis, based on the mITT population (minimum follow up of 6 months) the ORR was 72% and the complete response (CR) rate was 51%, as determined by an independent review committee. In the 12-month follow-up analysis (Table 5), the ORR was 72% and the CR rate was 51%. 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 partial response (PR). Of the 52 patients who achieved CR, 7 patients had SD and 9 had PR at their initial tumour assessment and converted to CR as late as 6.5 months. The ORR results within PMBCL and DLBCL arising from follicular lymphoma were both 88%. CR rates were 75% and 56%, respectively. Of the 111 patients in the ITT population, the ORR was 66% and the CR was 47%. Other outcomes were consistent with those of the mITT population.

In the 24-month follow-up analysis, based on the mITT population (results from an independent review committee), the ORR and the CR rate were 74% and 54%, respectively. The median time to response was 1.0 months (range: 0.8 to 12.2 months). The DOR was longer in patients who achieved CR compared to patients with a best response of PR (Table 5). Of the 55 patients who achieved CR, 7 patients had SD and 10 had PR at their initial tumour assessment and converted to CR as late as 12 months after YESCARTA infusion. Median duration of response and median overall survival have not been reached (Table 5).

In the phase 1 part of ZUMA-1, 7 patients were treated. Five patients responded, including 4 CRs. At the 12-month follow-up analysis, 3 patients remained in CR 24 months after YESCARTA infusion. At the 24-month follow-up analysis, these 3 patients remained in CR at 30 to 35 months after YESCARTA infusion.

Table 5. Summary of efficacy results for ZUMA-1 phase 2

Category	All leukapheresed (ITT) Cohort 1 + 2 (N = 111)		All treated (mITT) Cohort 1 + 2 (N = 101)	
	12-month analysis	24-month analysis	12-month analysis	24-month analysis
ORR (%) [95% CI]	66 (56, 75)	68 (58, 76)	72 (62, 81)	74 (65, 82)
CR (%)	47	50	51	54
Duration of Response ^a , median (range) in months	14.0 (0.0, 17.3)	NE (0.0, 29.5)	14.0 (0.0, 17.3)	NE (0.0, 29.5)
Duration of Response ^a , CR, median (range) in months	NE (0.4, 17.3)	NE (0.4, 29.5)	NE (0.4, 17.3)	NE (0.4, 29.5)
Overall Survival, median (months) [95% CI]	17.4 (11.6, NE)	17.4 (11.6, NE)	NE (12.8, NE)	NE (12.8, NE)
6 month OS (%) [95% CI]	81.1 (72.5, 87.2)	81.1 (72.5, 87.2)	79.2 (69.9, 85.9)	79.2 (69.9, 85.9)

Category	All leukapheresed (ITT) Cohort 1 + 2 (N = 111)		All treated (mITT) Cohort 1 + 2 (N = 101)	
	12-month analysis	24-month analysis	12-month analysis	24-month analysis
ORR (%) [95% CI]	66 (56, 75)	68 (58, 76)	72 (62, 81)	74 (65, 82)
9 month OS (%) [95% CI]	69.4 (59.9, 77.0)	69.4 (59.9, 77.0)	69.3 (59.3, 77.3)	69.3 (59.3, 77.3)
12 month OS (%) [95% CI]	59.3 (49.6, 67.8)	59.5 (49.7, 67.9)	60.4 (50.2, 69.2)	60.4 (50.2, 69.2)
24 month OS (%) [95% CI]	Not applicable	47.7 (38.2, 56.7)	Not applicable	50.5 (40.4, 59.7)

NE= Not estimable (not reached)

a Duration of response was censored at the time of SCT for subjects who received SCT while in response.

Note: The 12-month analysis had a median follow-up of 15.1 months. The 24-month analysis had a median follow-up of 27.1 months. OS relates to the time from the leukapheresis date (ITT) or YESCARTA infusion (mITT) to death from any cause.

SCHOLAR-1

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

5.2 Pharmacokinetic properties

Peak levels of anti-CD19 CAR T cells occurred within the first 8 to 15 days after YESCARTA infusion. The median peak level of anti-CD19 CAR T cells in the blood (C_{max}) was 38.3 cells/ μ L (range: 0.8 to 1513.7 cells/ μ L), which decreased to a median of 2.1 cells/ μ L by 1 month (range: 0 to 167.4 cells/ μ L) and to a median of 0.4 cells/ μ L by 3 months (range: 0 to 28.4 cells/ μ L) after YESCARTA infusion.

Age (range: 23 to 76 years) and sex had no significant impact on AUC and C_{max} of YESCARTA.

The number of anti-CD19 CAR T cells in the blood was positively associated with objective response (CR or PR). The median anti-CD19 CAR T cell C_{max} level in responders (N = 71) was 216% higher compared to the corresponding level in nonresponders (N = 25) (43.6 cells/ μ L versus 20.2 cells/ μ L). Median $AUC_{Day\ 0-28}$ in responding patients (N = 71) was 253% of the corresponding level in nonresponders (N = 25) (562.0 days x cells/ μ L versus 222.0 days x cells/ μ L).

YESCARTA comprises human autologous T cells. The anticipated metabolic products are typical cellular degradation products resulting from normal cellular clearance mechanisms. Thus, the infused CAR T cells are expected to be cleared over time. Anti-CD19 CAR T cell levels decreased toward background levels by Month 3 after infusion.

Studies of YESCARTA in patients with hepatic and renal impairment were not conducted.

5.3 Preclinical safety data

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 have been conducted to evaluate the effects of YESCARTA on fertility, reproduction, and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS10
Sodium chloride
Human albumin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

YESCARTA should be stored frozen in the vapour phase of liquid nitrogen ($\leq -150\text{ }^{\circ}\text{C}$).

The stability of YESCARTA upon completion of thawing is up to 3 hours at room temperature ($20\text{ }^{\circ}\text{C}$ to $25\text{ }^{\circ}\text{C}$). However, YESCARTA infusion should begin within 30 minutes of thaw completion and the total YESCARTA infusion time should not exceed 30 minutes. Thawed product should not be refrozen.

6.4 Special precautions for storage

YESCARTA bags must be stored in the vapour phase of liquid nitrogen ($\leq -150\text{ }^{\circ}\text{C}$) and YESCARTA must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are administered to the patient.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ethylene-vinyl acetate cryostorage bag containing approximately 68 mL of cell dispersion.

One cryostorage bag is individually packed in a shipping cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for the disposal of the medicinal product

YESCARTA contains genetically modified human blood cells. Local biosafety guidelines should be followed for unused medicinal products or waste material. All material that has been in contact with YESCARTA (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

7. MANUFACTURER

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8. REGISTRATION HOLDER

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Approved on May 2020

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