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', emphasises 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.

$0.4 – 2 \times 10^8$ cells dispersion for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Yescarta (axicabtagene ciloleucel) is a genetically modified autologous cell-based product containing T cells transduced *ex vivo* using a retroviral vector expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (ScFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of Yescarta contains axicabtagene ciloleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells per kg of body weight (range: $1 \times 10^6 – 2 \times 10^6$ cells/kg), with a maximum of 2×10^8 anti-CD19 CAR-positive viable T cells suspended in a cryopreservative solution.

Each infusion bag contains approximately 68 mL of dispersion for infusion.

Excipients with known effect

Each bag of Yescarta contains 300 mg sodium and 3.4 mL of dimethyl sulfoxide (DMSO). Yescarta may contain residual amounts of gentamicin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for intravenous infusion.

A clear to opaque, white to red dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory (r/r) 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 treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Yescarta. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Posology

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

Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one infusion bag. The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (within a range of $1 \times 10^6 – 2 \times 10^6$ cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above.

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/m^2 intravenous and fludarabine 30 mg/m^2 intravenous must be administered prior to infusing Yescarta. The recommended days are 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 must 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 is to be monitored at the physician's discretion.
- Patients must 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 limited clinical experience in patients with active HIV, HBV or HCV infection.

Elderly
No dose adjustment is required in patients ≥ 65 years of age.

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.

Method of administration

Yescarta is to be administered via intravenous infusion.

Yescarta must not be irradiated. A leukodepleting filter must not be used.

Before administration, it must be confirmed that the patient's identity (ID) matches the unique patient information on the Yescarta infusion bag and cassette.

Administration
- A leukodepleting filter must not be used.
- Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period.
- Yescarta is intended for autologous use only, it must be confirmed that the patient's identity matches the patient identifiers on the Yescarta bag.
- Once the tubing has been primed, the entire content of the Yescarta bag must be infused within 30 minutes by either gravity or a peristaltic pump.

For detailed instructions on preparation, administration, accidental exposure and disposal of Yescarta, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to gentamicin (a possible trace residue).

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the product.

Autologous use

Yescarta is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the Yescarta infusion bag and cassette. Yescarta must not be administered if the information on the patient-specific infusion bag and cassette label does not match the patient's identity.

Monitoring after infusion

Patients must 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/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient is to be monitored at the physician's discretion.

Patients are to be counselled to remain within the proximity of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Vital signs and organ function must be monitored depending on the severity of the reaction.

Reasons to delay treatment

Due to the risks associated with Yescarta treatment, infusion must 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).

Serological testing

Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Yescarta (see section 4.2).

Blood, organ, tissue and cell donation

Patients treated with Yescarta must not donate blood, organs, tissues, or cells for transplantation.

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 in ZUMA-1 and ZUMA-7, and 1 to 11 days in ZUMA-5 (see section 4.8). CRS should be managed at the physician's discretion, based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 1. Interleukin-6 (IL-6) receptor inhibitor based therapy such as tocilizumab has been administered for moderate or severe CRS associated with Yescarta.

At least 1 dose of tocilizumab per patient must be on site and available for administration prior to Yescarta infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Patients must be monitored 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 is to be monitored at the physician's discretion.

Patients are to be counselled 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) must 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 must 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 must be managed by standards of critical care and measures such as echocardiography are to be considered.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. In the event of febrile neutropenia, infection is to be considered and managed with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) is to 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, or if no response to second or subsequent doses of tocilizumab, consider alternate measures for treatment of cytokine release syndrome.	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, also known as immune effector cell-associated neurotoxicity syndrome (ICANS), 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 must be monitored for signs and symptoms of neurologic adverse reactions (Table 2). Patients must be monitored at least daily for 10 days at the qualified clinical facility following infusion for signs and symptoms of neurologic toxicity/ICANS. After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion. Patients are to be counselled 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/ICANS occur. Vital signs and organ functions must be monitored depending on the severity of the reaction.

Patients who experience Grade 2 or higher neurologic toxicities /ICANS must be monitored with continuous cardiac telemetry and pulse oximetry. Intensive-care supportive therapy must be provided for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines are to be considered for seizure prophylaxis 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/ICANS 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 must 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, infection is to be considered and managed 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 must be performed 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. Blood counts are to be monitored after treatment with Yescarta.

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 DMSO or residual gentamicin in Yescarta.

Secondary malignancies

Patients treated with Yescarta may develop secondary malignancies. Patients are to be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company is to be contaced 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 must be monitored and events managed according to standard guidelines.

CD19-negative disease

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.

There are limited data available on CD19-negative patients treated with Yescarta and it is possible that CD19-negative patients may have less benefit compared with CD19-positive patients. Patients with CD19-negative status by immunohistochemistry may still express CD19 and have been shown to benefit from treatment with Yescarta. The potential risks and benefits associated with treatment of CD19-negative patients with Yescarta should be considered.

Excipients (sodium)

This medicinal product contains 300 mg sodium per infusion bag, 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. As a precautionary measure, 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 must be advised on the potential risks to the foetus. Pregnancy after Yescarta therapy must be discussed with the treating physician.

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

Breast-feeding

It is unknown whether Yescarta is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women must 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 must 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 are from a total of 397 adult patients treated with Yescarta in three multi-centre pivotal clinical studies (ZUMA-1, ZUMA-5 and ZUMA-7 and post-marketing experience. Adverse reactions are adverse events from pivotal clinical studies and post-marketing experience medically assessed as reasonably attributed to axicabtagene ciloleucel) .

Relapsed or refractory DLBCL, PMBCL and DLBCL arising from follicular lymphoma after two or more lines of systemic therapy
Safety data from ZUMA-1 reflects exposure to Yescarta in a Phase 1/2 study in which 108 patients received CAR-positive T cells based on a recommended dose which was weight-based. The data described are from the 54-month follow-up analysis where the median actual duration of follow up was 23.5 months (range: 0.3 to 68.2 months).

The most significant and frequently occurring adverse reactions were CRS (93%), encephalopathy (60%), and infections (40%).

Serious adverse reactions occurred in 51% of patients. The most common (≥ 5%) serious adverse reactions included encephalopathy (22%), unspecified pathogen infections (15%), bacterial infection (6%), viral infection (6%), febrile neutropenia (5%), and fever (5%).

The most common (≥5%) Grade 3 or higher non-haematological adverse reactions included encephalopathy (31%), unspecified pathogen infections (19%), CRS (11%), bacterial infection (9%), delirium (6%), hypertension (6%), hypotension (6%), transaminases increased (6%), and viral infection (6%). The most common Grade 3 or higher haematological adverse reactions included lymphopenia (99%), leukopenia (96%), neutropenia (94%), anaemia (65%), and thrombocytopenia (56%).

DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy
Safety data from ZUMA-7 reflects exposure to Yescarta in a Phase 3 study in which 170 patients received CAR-positive T cells based on a recommended dose which was weight-based. The data described are from an analysis where the median actual duration of follow-up was 23.2 months (range: 1.5 to 41.3 months).

The most significant and frequently occurring adverse reactions were CRS (92%), encephalopathy (49%), and infections (45%).

Serious adverse reactions occurred in 54% of patients. The most common (≥ 5%) serious adverse reactions included CRS (17%), encephalopathy (16%), unspecified pathogen infections (8%), fever (6%) and viral infection (5%).

The most common (≥ 5%) Grade 3 or higher non-haematological adverse reactions included encephalopathy (19%), unspecified pathogen infections (8%), CRS (6%), and bacterial infection (5%). The most common Grade 3 or higher haematological adverse reactions included lymphopenia (99%), leukopenia (95%), neutropenia (94%), anaemia (41%), and thrombocytopenia (26%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in patients exposed to Yescarta in ZUMA-1 (n=108), ZUMA-5 (n=119), and ZUMA-7 (n=170) and from post-marketing reports. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). 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		

System Organ Class (SOC)	Frequency	Adverse reactions
	Very common	Unspecified pathogen infections Viral infection Bacterial infection
	Common	Fungal infection
Blood and lymphatic system disorders		
	Very common	Febrile neutropenia[#] Neutropenia[#] Lymphopenia[#] Leukopenia[#] Anaemia[#] Thrombocytopenia[#]
	Common	Coagulopathy[a]
Immune system disorders		
	Very common	Cytokine Release Syndrome Immunoglobulins decreased[b]
	Common	Hypersensitivity
	Uncommon	Haemophagocytic Lymphohistiocytosis[**]
Metabolism and nutrition disorders		
	Very common	Hyponatraemia[#] Hypophosphataemia[#] Hyperuricemia[#***] Hyperglycaemia[#] Decreased appetite[c]
	Common	Hypokalaemia[#] Hypocalcaemia[#] Hypoalbuminaemia[#] Dehydration[d] Weight decreased
Psychiatric disorders		
	Very common	Delirium[e] Insomnia
	Common	Anxiety Affective disorder[f]
Nervous system disorders		
	Very common	Encephalopathy[g] Tremor[h] Headache[i] Dizziness[j]
	Common	Ataxia[k] Seizures, including status epilepticus Hemiparesis Facial paralysis[l] Neuropathy peripheral[m] Myoclonus
	Uncommon	Quadriplegia Spinal cord oedema Myelitis Dyscalculia
Cardiac disorders		
	Very common	Tachycardia[n] Arrhythmia[o]
	Common	Cardiac arrest Cardiac failure[p]
Vascular disorders		
	Very common	Hypotension[q] Hypertension
	Common	Thrombosis[r]
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough[s]

System Organ Class (SOC)	Frequency	Adverse reactions
	Common	Respiratory failure[t] Hypoxia[u] Pleural effusion Pulmonary oedema Dyspnoea[v] Nasal inflammation[w]
Gastrointestinal disorders		
	Very common	Vomiting Diarrhoea[x] Constipation Abdominal pain[y] Nausea
	Common	Dysphagia**** Dry mouth[z]
Hepatobiliary disorders		
	Very common	Transaminases increased[aa]
	Common	Hyperbilirubinaemia[bb]
Skin and subcutaneous tissue disorders		
	Very common	Rash[cc]
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction[dd] Musculoskeletal pain[ee]
	Uncommon	Rhabdomyolysis
Renal and urinary disorders		
	Common	Renal impairment[ff]
General disorders and administration site conditions		
	Very common	Fever[gg] Oedema[hh] Fatigue[ii] Chills
	Common	Pain
	Uncommon	Multiple organ dysfunction syndrome
Eye Disorders		
	Common	Visual impairment[jj]

* Adverse drug reactions were identified from a pooled analysis of 397 adult patients treated with Yescarta in ZUMA-1, ZUMA-5, and ZUMA-7 and from post-marketing experience.
** Haemophagocytic lymphohistiocytosis has been reported in the setting of CRS.
*** Hyperuricemia was identified from a pooled analysis of 227 adult patients treated with Yescarta in ZUMA-1 and ZUMA-5.
**** Dysphagia has been reported in the setting of neurologic toxicity and encephalopathy.
[#] Frequency based on Grade 3 or higher laboratory parameter.

a. Coagulopathy includes Coagulopathy, Blood fibrinogen decreased, Blood fibrinogen increased, Disseminated intravascular coagulation, Hypofibrinogenaemia, International normalized ratio increased, Prothrombin level decreased, Prothrombin time prolonged
b. Immunoglobulins decreased includes Blood immunoglobulin G decreased, Hypogammaglobulinaemia
c. Decreased appetite includes Decreased appetite, Hypophagia
d. Dehydration includes Dehydration, Hypovolaemia
e. Delirium includes Delirium, Agitation, Delusion, Disorientation, Hallucination, Restlessness
f. Affective disorder includes Impulsive behavior, Mood altered, Depression, Panic attack
g. Encephalopathy includes Encephalopathy, Agraphia, Altered state of consciousness, Amnesia, Aphasia, Aphonia, Apraxia, Cognitive disorder, Confusional state, Depressed level of consciousness, Disturbance in attention, Dysarthria, Dysgraphia, Dyskinesia, Dyspraxia, Hypersomnia, Immune effector cell-associated neurotoxicity syndrome, Lethargy, Leukoencephalopathy, Loss of consciousness, Memory impairment, Mental impairment, Mental status changes, Metabolic encephalopathy, Neurotoxicity, Slow speech, Somnolence, Speech disorder, Stupor, Toxic encephalopathy
h. Tremor includes Tremor, Head titubation
i. Headache includes Headache, Head discomfort, Tension headache
j. Dizziness includes Dizziness, Dizziness postural, Presyncope, Syncope, Vertigo
k. Ataxia includes Ataxia, Balance disorder, Gait disturbance
l. Facial paralysis includes Facial paralysis, Facial paresis
m. Neuropathy peripheral includes Neuropathy peripheral, Allodynia, Cervical radiculopathy, Hyperaesthesia, Hypoaesthesia, Lumbar radiculopathy, Paraesthesia, Peripheral sensory neuropathy, Peroneal nerve palsy
n. Tachycardia includes Tachycardia, Postural orthostatic tachycardia syndrome, Sinus tachycardia
o. Arrhythmia includes Arrhythmia, Atrial fibrillation, Atrial flutter, Atrioventricular block, Bradycardia, Bundle branch block right, Electrocardiogram QT prolonged, Extrasystoles, Heart rate increased, Heart rate irregular, Sinus bradycardia,

Supraventricular extrasystoles, Supraventricular tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular tachycardia
p. Cardiac failure includes Cardiac failure, Acute left ventricular failure, Ejection fraction decreased, Stress cardiomyopathy
q. Hypotension includes Hypotension, Capillary leak syndrome, Diastolic hypotension, Hypoperfusion, Orthostatic hypotension
r. Thrombosis includes Thrombosis, Axillary vein thrombosis, Brachiocephalic vein thrombosis, Deep vein thrombosis, Device occlusion, Embolism, Jugular vein thrombosis, Peripheral embolism, Peripheral ischaemia, Pulmonary embolism, Splenic vein thrombosis, Thrombosis in device
s. Cough includes Cough, Productive cough, Upper-airway cough syndrome
t. Respiratory failure includes Respiratory failure, Acute respiratory failure
u. Hypoxia includes Hypoxia, Oxygen saturation decreased
v. Dyspnoea includes Dyspnoea, Dyspnoea exertional
w. Nasal inflammation includes Rhinitis allergic, Rhinorrhoea
x. Diarrhoea includes Diarrhoea, Colitis, Enteritis
y. Abdominal pain includes Abdominal pain, Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Dyspepsia, Epigastric discomfort
z. Dry mouth includes Dry mouth, Lip dry
aa. Transaminases increased includes Transaminases increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Hypertransaminasaemia
bb. Hyperbilirubinaemia increased includes Hyperbilirubinemia, Blood bilirubin increased
cc. Rash includes Rash, Application site rash, Dermatitis, Dermatitis allergic, Dermatitis bullous, Erythema, Pruritus, Rash erythematous, Rash macular, Rash maculo-papular, Rash pruritic, Rash pustular, Urticaria
dd. Motor dysfunction includes Motor dysfunction, Muscle contractions involuntary, Muscle rigidity, Muscle spasms, Muscle spasticity, Muscle strain, Muscle tightness, Muscle twitching, Muscular weakness
ee. Musculoskeletal pain includes Musculoskeletal pain, Arthralgia, Arthritis, Back pain, Bone pain, Flank pain, Groin pain, Musculoskeletal chest pain, Myalgia, Neck pain, Osteoarthritis, Pain in extremity
ff. Renal impairment includes Acute kidney injury, Blood creatinine increased, Renal failure
gg. Fever includes Hyperthermia, Pyrexia
hh. Oedema includes Oedema, Face oedema, Generalized oedema, Localized oedema, Oedema genital, Oedema peripheral, Peripheral swelling, Swelling
ii. Fatigue includes Fatigue, Asthenia, Decreased activity, Malaise
jj. Visual impairment includes Visual impairment, Hemianopia, Vision blurred, Visual acuity reduced

Description of selected adverse reactions

Cytokine release syndrome
In ZUMA-1 and ZUMA-7, CRS occurred in 92% of patients. Eight percent (8%) of patients experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 3 days (range: 1 to 12 days) and the median duration was 7 days (range: 2 to 58 days). Ninety-nine percent (99%) of patients recovered from CRS. No CRS was reported by patients treated with standard of care therapy (SOCT) in ZUMA-7.

In ZUMA-5, CRS occurred in 77% of patients. Six percent (6%) of patients experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 4 days (range: 1 to 11 days) and the median duration was 6 days (range: 1 to 27 days). Ninety-nine percent (99%) of patients recovered from CRS.

The most common adverse reactions (≥ 20%) that may be associated with CRS included pyrexia (89%), hypotension (50%), tachycardia (47%), chills (30%), and hypoxia (24%). Serious adverse reactions that may be associated with CRS included pyrexia (12%), hypotension (5%), hypoxia (3%), arrhythmia (3%), cardiac failure (2%), fatigue (2%), headache (2%), tachycardia (2%), cardiac arrest (1%), dyspnoea (1%), and tachypnoea (1%). See section 4.4 for monitoring and management guidance.

Neurologic adverse reactions
In ZUMA-1 and ZUMA-7, neurologic adverse reactions occurred in 63% of patients. Twenty-five percent (25%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. Neurologic toxicities occurred within the first 7 days of infusion for 75% of patients. The median time to onset was 6 days (range: 1 to 133 days). The median duration was 10 days, with resolution occurring within 3 weeks for 66% of patients following infusion.

In ZUMA-5, neurologic adverse reactions occurred in 57% of patients. Sixteen percent (16%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. Neurologic toxicities occurred within the first 7 days of infusion for 65% of patients. The median time to onset was

7 days (range: 1 to 177 days). The median duration was 14 days, with resolution occurring within 3 weeks for 60% of patients, following infusion.

The most common (≥ 5%) neurologic adverse reactions included encephalopathy (51%), tremor (28%), and delirium (14%). Serious neurologic adverse reactions reported in patients included encephalopathy (18%), tremor (2%), delirium (2%), hemiparesis (1%) and seizure (1%). In ZUMA-7, encephalopathy and tremor were reported in 49% and 25% of patients treated with Yescarta compared to 8% and 1% treated with SOCT, respectively.

Other neurologic adverse reactions have been reported less frequently in clinical trials and included dysphagia (3%), myelitis (0.2%), and quadriplegia (0.2%).

See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 10% of patients after Yescarta infusion. Infections occurred in 48% of patients. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 19% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 12%, 6%, and 5% of patients respectively. The most common site of unspecified pathogen infection was in the respiratory tract. In ZUMA-7, febrile neutropenia and viral infection were reported in 2% and 16% of patients treated with Yescarta compared to 27% and 5% treated with SOCT, respectively. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Grade 3 or higher neutropenia (including febrile neutropenia), anaemia, and thrombocytopenia occurred in 68%, 31%, and 23% 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%, 12%, and 6% of patients, respectively. In ZUMA-1, at the time of the 24-month follow-up analysis, Grade 3 or higher neutropenia, thrombocytopenia, and anaemia present after Day 93 occurred in 11%, 7%, and 3% of patients, respectively. In ZUMA-7, Grade 3 or higher neutropenia and thrombocytopenia were reported in 94% and 26% of patients treated with Yescarta compared to 51% and 63% treated with SOCT, respectively. See section 4.4 for management guidance.

Hypogammaglobulinaemia
Hypogammaglobulinaemia was reported in 15% of patients treated with Yescarta. Cumulatively, 36 (33%) of 108 patients in ZUMA-1 received intravenous immunoglobulin therapy by the time of the 54-month analysis, 28 (16%) of 170 patients in ZUMA-7 received intravenous immunoglobulin therapy by the time of the 23.2 month analysis and 33 (28%) of 119 subjects in ZUMA-5 received intravenous immunoglobulin therapy at the time of the 24-month follow-up analysis. In ZUMA-7, immunoglobulins decreased was reported in 11% of patients treated with Yescarta compared to 1% of patients treated with SOCT. 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. Eleven out of 278 patients (4%) tested positive for anti-FMC63 antibodies prior to being treated with Yescarta in ZUMA-1 and ZUMA-7, and 1 patient (1%) in ZUMA-7 who had a negative test result prior to treatment, had a positive test result after treatment in the screening ELISA. Results of a confirmatory cell-based assay, leveraging a properly folded and expressed extracellular portion of the CAR (ScFv, hinge and linker) demonstrated that all patients treated with Yescarta that had a positive result in the screening ELISA were antibody negative at all time points tested. There is no evidence that the kinetics of initial expansion and persistence of Yescarta, or the safety or effectiveness of Yescarta, was altered in these patients. In ZUMA-5, 13 out of 116 patients (11%) tested positive for antibodies in the ELISA screening assay prior to being treated with Yescarta, and 2 subjects who had negative results prior to treatment had positive test results after treatment. Results of a confirmatory

cell-based assay demonstrated that all patients treated with Yescarta that had an ELISA positive result were antibody negative, before, during and after treatment.

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.

Post-marketing experience

Adverse reactions reported in the post-marketing setting include status epilepticus (0.3%), spinal cord oedema and ICANS.

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: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX70

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

After Yescarta infusion, pharmacodynamic responses were evaluated by measuring transient elevation of cytokines, chemokines, and other molecules in blood over a 4-week interval. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and IL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days.

Analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher post-infusion levels (peak and AUC at 1 month) of multiple immune-modulatory and pro-inflammatory analytes were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS in ZUMA-1, ZUMA-7 and ZUMA-5.

Due to the on-target, off-tumour effect of Yescarta, a period of B-cell aplasia is expected following treatment. Among 73 patients in ZUMA-1 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. Among 141 patients in ZUMA-7 with evaluable samples at baseline, 57% had detectable B-cells. Following Yescarta treatment, the proportion of patients with detectable B-cells decreased: 38% had detectable B-cells at Month 3, and 41% had detectable B-cells at Month 6. The initiation of B-cell recovery was apparent at Month 9, when 58% 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 84% of patients had detectable B-cells at Month 24.
Among 113 ZUMA-5 patients with evaluable samples at baseline, 75% of patients had detectable B-cells. Following Yescarta treatment, the proportion of patients with detectable B-cells decreased: 40% of patients had detectable B-cells at Month 3. B-cell recovery was observed over time, with 61% of patients having 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.

Clinical efficacy and safety

Relapsed or refractory DLBCL, PMBCL and DLBCL arising from follicular lymphoma after two or more lines of systemic therapy (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 r/r 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 HGBL based on the 2016 WHO-classification. Forty-seven patients were evaluable for MYC, BCL-2, and BCL-6 status. Thirty were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 5 were found to have HGBL with MYC, BCL-2 or BCL-6 gene rearrangement (double- and triple-hit); and 2 were found to have HGBL not otherwise specified. Sixty-six patients were evaluable for cell-of-origin classifications (germinal center B-cell type [GCB] or activated B-cell type [ABC]). Of these, 49 patients had GCB-type and 17 patients had ABC-type.

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 63.1 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)**
Age (years)		
Median (min, max)	58 (23, 76)	58 (23, 76)
≥ 65	23%	24%

Category	**All leukapheresed (ITT) Cohort 1 + 2 (N = 111)**	**All treated (mITT) Cohort 1 + 2 (N = 101)**
Male gender	69%	67%
Race		
White	85%	86%
Asian	4%	3%
Black	4%	4%
ECOG status		
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/m^2 intravenous cyclophosphamide and 30 mg/m^2 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 OS had not been reached (Table 5). In a 36-month analysis (median study follow-up of 39.1 months) the median OS was 25.8 months with 47 patients (47%*) still alive. In a 48-month analysis (median study follow-up of 51.1

months) the median OS was 25.8 months with 43 patients (44%*) still alive. In a 60-month analysis (median study follow-up of 63.1 months) the median overall survival was 25.8 months with 42 patients (43%*) still alive.
*The Kaplan-Meier estimates of the 3-year, 4-year and 5-year OS rates were 47%, 44% and 43% respectively.

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)
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 patients 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. Overall survival 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.

DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy (ZUMA-7)
The efficacy and safety of Yescarta in adult patients with r/r large B-cell lymphoma (LBCL) was demonstrated in a Phase 3 randomised, open-label, multicenter study (ZUMA-7). Enrolled patients were predominantly diagnosed with DLBCL and HGBL disease subtypes based on the 2016 WHO-classification and all patients had received first-line rituximab and anthracycline-based chemotherapy. In total, 359 patients were randomised in a 1:1 ratio to receive a single infusion of Yescarta or to receive SOCT (defined as 2 to 3 cycles of standard chemoimmunotherapy [R-ICE, R-

DHAP or R-DHAX, R-ESHAP, or R-GDP] followed by high-dose therapy [HDT] and ASCT in those with disease response). Randomisation 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. The study excluded prior HSCT, detectable cerebrospinal fluid malignant cells or brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater, and any history of central nervous system lymphoma. Patients with active or serious infections were excluded, however patients with simple urinary tract infection and uncomplicated bacterial pharyngitis were permitted if responding to active treatment.

Following lymphodepleting chemotherapy, Yescarta was administered as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR 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. Nondisease modifying bridging therapy limited to corticosteroids, could be administered between leukapheresis and lymphodepleting chemotherapy for patients with high disease burden at screening.

In the overall study population, the median age was 59 years (range: 21 to 81 years); 66% were male, and 83% were white. Seventy-four percent of patients had primary refractory LBCL 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%). The median study duration was 24.9 months.

Patients in the Yescarta and SOCT arms were categorized as DLBCL NOS/without further classification possible (126 patients and 120 patients, respectively); DLBCL arising from follicular lymphoma (19 patients and 27 patients, respectively); HGBL with *MYC*, *BCL2*, and/or *BCL6* (double- and triple-hit) rearrangements (31 patients and 25 patients, respectively) or HGBL NOS, (1 patient in the SOCT arm); the remaining subjects were categorized under not confirmed, missing, or other.

Of the 180 patients randomised to receive Yescarta, 178 underwent leukapheresis and 170 were treated with Yescarta. Of the patients treated, 60 (33%) received bridging corticosteroid therapy. There were no manufacturing failures. Eight patients (4%) were not treated following leukapheresis, primarily due to progressive disease, serious adverse events, or death. The median time from leukapheresis to product release was 13 days (range: 10 to 24 days), and leukapheresis to Yescarta infusion was 26 days (range: 16 to 52 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All 170 patients who received Yescarta were monitored at a healthcare facility for a minimum of 7 days. Of the 179 patients randomised to receive SOCT, 36% received HDT-ASCT and 56% of patients received cellular immuno-therapy after no response to or relapse after randomisation to SOCT.

The primary endpoint was event-free survival (EFS) as determined by blinded central review. The summary of efficacy results in the overall population is shown in Table 6 and the Kaplan-Meier curve for EFS is shown in Figure 1. The 24-month EFS was 40.5% [95% CI: 33.2, 47.7] in the Yescarta arm and 16.3% [95% CI: 11.1, 22.2] in the SOCT arm. The median progression free survival (PFS) in the Yescarta arm was 14.7 months (95% CI: 5.4, NE) compared with 3.7 months (95% CI: 2.9, 5.3) in the SOCT arm (HR: 0.490 [95% CI: 0.368, 0.652]). Consistent efficacy was observed across selected subgroups including response to first-line therapy, second-line age-adjusted IPI score, ECOG performance status, age, double expressor lymphoma status and HGBL disease subtype. At a pre-specified interim analysis at the time of the primary analysis of EFS, the overall survival data were not mature. Among patients with HGBL per central laboratory, Yescarta demonstrated an improvement in EFS compared to SOCT (HR: 0.285 [95% CI: 0.137, 0.594]). The ORR was 81% (95% CI: 62.5%, 92.5%) and CR rate was 68% (95% CI: 48.6%, 83.3%) in patients treated with Yescarta compared with 42% (95% CI: 23.4%, 63.1%) and 23% (95% CI: 9.0%, 43.6%) respectively in the SOCT arm.

Table 6. Summary of Efficacy Results for ZUMA-7 (Primary Analysis)

	Yescarta N = 180	**Standard of Care Therapy N = 179**
Event-Free Survival		
Number of events (%)	108 (60)	144 (80)
Median, months [95% CI][a]	8.3 [4.5, 15.8]	2.0 [1.6, 2.8]
Stratified hazard ratio [95% CI]	0.398 [0.308, 0.514]	
Stratified log-rank p-value	<0.0001	
Objective Response Rate (%) [95% CI]	83 [77.1, 88.5]	50 [42.7, 57.8]
Odds ratio [95% CI]	5.31 [3.08, 8.90]	
Stratified CMH test p-value	<0.0001	
Complete Response Rate (%)	65 [57.6, 71.9]	32 [25.6, 39.8]
Partial Response Rate (%)	18 [13.0, 24.8]	18 [12.6, 24.3]

CI, confidence interval; NE, not estimable; CMH, Cochran-Mantel-Haenszel.

a. Kaplan-Meier method.

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

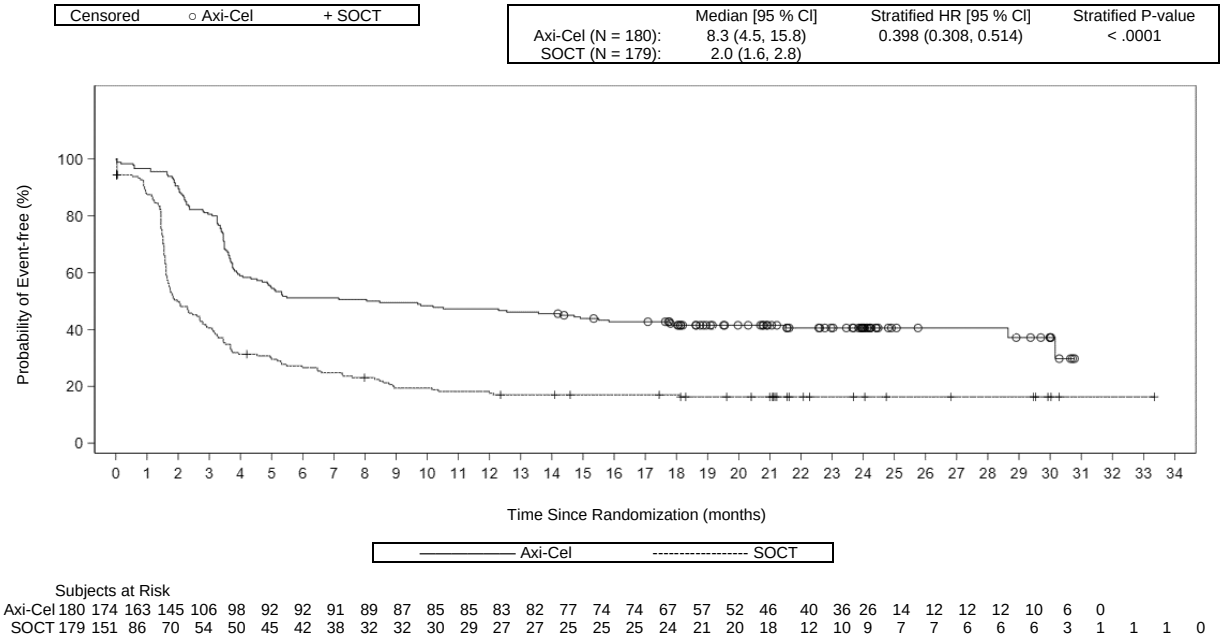
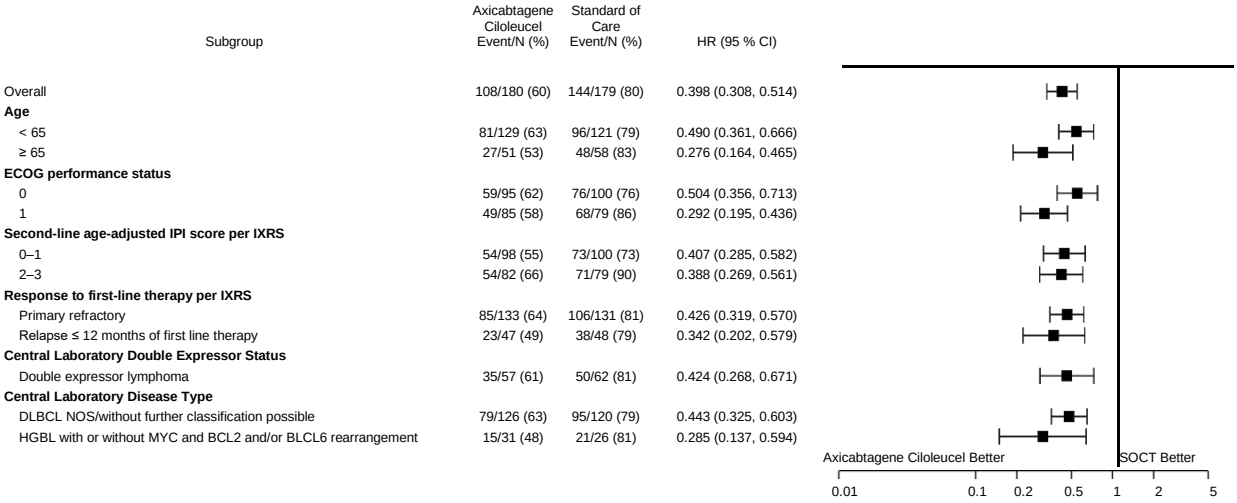


Figure 2. Forest Plot of Event-Free Survival in Selected Subgroups in ZUMA-7



CI, confidence interval; IxRS, interactive voice/web response system.
Disease type by central laboratory was confirmed in 303 of 359 patients, the remaining patients were categorised by the central laboratory as not confirmed, missing or other.

5.2 Pharmacokinetic properties

Yescarta comprises human autologous T cells. The anticipated residual 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.

Cellular kinetics

Following infusion of Yescarta anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 14 days after the day of Yescarta infusion. Age (range: 21 to 80 years) and sex had no significant impact on AUC and peak levels of Yescarta.

Among patients in ZUMA-1, the median peak level of anti-CD19 CAR T cells in the blood was 38.3 cells/μL (range: 0.8 to 1513.7 cells/μL), which decreased to a median of 2.1 cells/μL by 1 month (range: 0 to 167.4 cells/μL) and to a median of 0.4 cells/μL by 3 months (range: 0 to 28.4 cells/μL) after Yescarta infusion. Among patients in ZUMA-7 the median peak level of anti-CD19 CAR T cells in the blood was 25.84 cells/μL (range: 0.04 to 1173.25 cells/μL), which decreased towards baseline in evaluable patients by 3 months (0.35 cells/μL; range: 0.00 to 28.44 cells/μL), but were still detectable in 12 out of 30 evaluable patients until 24 months post-treatment.

Among patients in ZUMA-5, the median peak level of anti-CD19 CAR T cells in the blood was 37.6 cells/μL (range: 0.5 to 1415.4 cells/μL). The median time to peak of anti-CD19 CAR T cells in the blood was 8 days after infusion (range: 8 to 371 days). By 3 months, anti-CD19 CAR T cell levels decreased to near baseline levels to a median of 0.3 cells/μL (range: 0 to 15.8 cells/μL).

Among patients in ZUMA-1, 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 peak level in responders (N = 71) was 216% higher compared to the corresponding level in nonresponders (N = 25) (43.6 cells/μL *versus* 20.2 cells/μL). Median $AUC_{0\text{-}28}$ in responding patients (N = 71) was 253% of the corresponding level in nonresponders (N = 25) (562.0 days × cells/μL *versus* 222.0 days × cells/μL).

Among patients in ZUMA-7 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 peak levels in

responders (n=142) were about 275% higher compared to the corresponding level in nonresponders (n=20) (28.9 cells/µL *versus* 10.5 cells/µL). Median AUC_{0-28} in responding patients (n=142) was about 417% higher compared to the corresponding level in nonresponders (n=20) (292.9 days × cells/µL *versus* 70.1 days × cells/µL).

Among patients in ZUMA-5, the median peak anti-CD19 CAR T-cell levels in responders (n=112) versus nonresponders (n=5) were 38.0 cells/µL and 31.3 cells/µL, respectively. The median AUC_{0-28} in responders versus nonresponders were 454.8 cells/µL•days and 247.1 cells/µL•days, respectively.

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 (contains DMSO)
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 must be stored frozen in the vapour phase of liquid nitrogen (≤ -150 ˚C).

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

6.4 Special precautions for storage

The Yescarta bag must be stored in the vapour phase of liquid nitrogen (≤ -150˚C) and must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration. Do not re-freeze after thawing.

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 with sealed addition tube and two available spike ports, 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 before handling or administering the medicinal product

Yescarta must be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling Yescarta must take appropriate precautions (wearing gloves and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

- Verify that the patient's identity (ID) matches the patient identifiers on the Yescarta cassette.
- The Yescarta bag must not be removed from the metal 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 metal cassette.
- Check that the patient information on the metal 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 for the handling of waste of human-derived material (or immediately contact Kite).

Thawing

- Place the infusion bag inside a second bag.
- 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 must not be washed, spun down, and/or re-suspended in new medium prior to infusion. Thawing takes approximately 3 to 5 minutes.
- Once thawed, Yescarta is stable at room temperature (20 °C-25 °C) for up to 3 hours. However, Yescarta infusion must begin within 30 minutes of thaw completion.

Administration

- A leukodepleting filter must not be used.
- Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period.
- Central venous access is recommended for the administration of Yescarta.
- For autologous use only.
- 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.

Accidental exposure

In case of accidental exposure local guidelines on handling of human-derived materials must be followed. Work surfaces and materials which have potentially been in contact with Yescarta must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Yescarta (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on the handling of waste of human-derived material.

7. MANUFACTURER

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8. REGISTRATION HOLDER

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