EU Risk Management Plan for YESCARTA® (axicabtagene ciloleucel)

EU Risk Management Plan for YESCARTA (axicabtagene ciloleucel)

RMP version to be assessed as part of this submission:

Version number:	Data lock point for this RMP:	Date of final sign-off:
12.0	**Clinical:** ZUMA-1: 18 March 2021 ZUMA-5: 14 September 2020 ZUMA-7: 18 March 2021 **Post-marketing:** 05 March 2024	07 Oct 2025

Rationale for submitting an updated RMP: EMEA/H/C/004480/WS2771/0084 closing sequence.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant Changes to RMP
Part I		Not applicable
Part II Safety Specification	Part II: Module SI - Epidemiology of the Indication(s) and Target Populations(s)	Not applicable
	Part II: Module SII - Nonclinical Part of the Safety Specification	Not applicable
	Part II: Module SIII - Clinical Trial Exposure	Not applicable
	Part II: Module SIV - Populations Not Studied in Clinical Trials	Not applicable
	Part II: Module SV – Post-authorization Experience	Not applicable
	Part II: Module SVI - Additional EU Requirements for the Safety Specification	Not applicable
	Part II: Module SVII - Identified and Potential Risks	Not applicable
	Part II: Module SVIII - Summary of the Safety Concerns	Not applicable
Part III Pharmacovigilance Plan		The objectives of Study KT-US-982-0910 ‘Molecular profiling of tissue samples from patients who received a Kite-manufactured gene-modified cell therapy and have developed a

Part	Module/Annex	Significant Changes to RMP
		secondary malignancy of T-cell origin' were updated.
Part IV Plan for Post-authorization Efficacy Studies		Not applicable
Part V Risk Minimization Measures		Aligned with the RMP updates
Part VI Summary of the Risk Management Plan		Aligned with the RMP updates.
Part VII Annexes	Annex 2, and Annex 3	Aligned with the RMP updates.

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
v11.3	23 September 2025	EMA/VR/0000301490

Details of the currently approved RMP:

Version Number	Approved with Procedure	Date of Approval (Opinion Date)
12.0	EMEA/H/C/004480/WS2771/0084	18 September 2025

QPPV name:	Rainer Heissing
QPPV signature:	The RMP has been reviewed and approved by the QPPV and the electronic signature is on file.

Abbreviations: QPPV = qualified person of pharmacovigilance.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

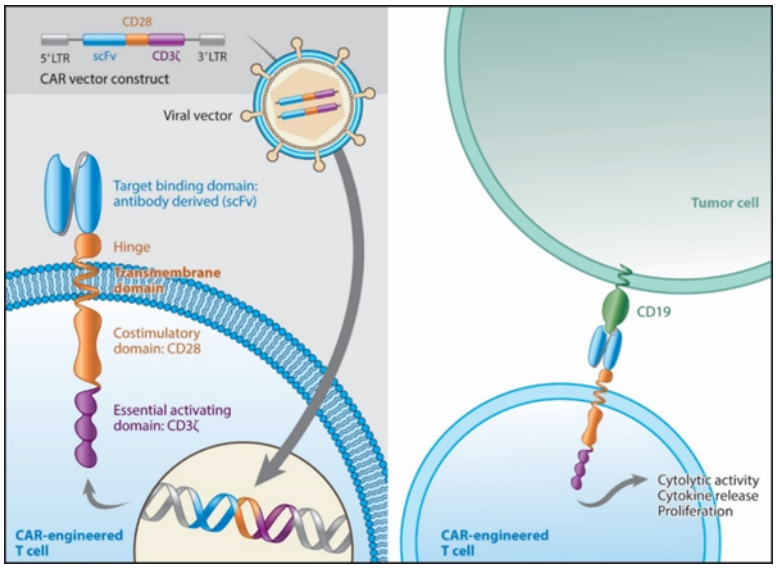
ADR	Adverse drug reaction
allo-HSCT	Allogeneic haematopoietic stem-cell transplant
ASCT	Autologous stem cell transplant
ASIR	Age-standardized incidence rate
ATMP	Advanced therapy medicinal product
CAR	Chimeric antigen receptor
CAR T	Chimeric antigen receptor T cells
CHIP	Clonal hematopoiesis of indeterminate potential
CHRS	Clonal hematopoiesis risk score
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRS	Cytokine release syndrome
DHL/THL	Double-hit or triple-hit
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FL	Follicular lymphoma
GBD	Global Burden of Disease
GvHD	Graft versus host disease
HCP	Healthcare professional
HGBL	High-grade B-cell lymphoma
IARC	International Agency for Research on Cancer
ICANS	Immune effector cell-associated neurotoxicity syndrome
iNHL	Indolent non-Hodgkin lymphoma
IPI	International prognostic index
LBCL	Large B-cell lymphoma
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin lymphoma
PAC	Patient alert card
PCR	Polymerase chain reaction
PI3K	Phosphatidylinositol 3-kinase
PL	Package leaflet
PMBCL	Primary mediastinal B-cell lymphoma
PSUR	Periodic safety update report
RCR	Replication-competent retrovirus
RMP	Risk management plan

SmPC	Summary of product characteristics
TLS	Tumor lysis syndrome
US	United States
VIS	Vector integration site
WHO	World Health Organization

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Axicabtagene ciloleucel
Pharmaco-therapeutic group(s) (ATC Code):	L01XL03
Marketing Authorization Applicant	Kite Pharma EU B.V.
Medicinal products to which this RMP refers:	1
Invented name(s) in the EEA	Yescarta
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class**: Not applicable
	Summary of mode of action: Axicabtagene ciloleucel is an autologous treatment by which a patient's own T cells are harvested and genetically engineered ex vivo by retroviral transduction of a construct encoding an anti-CD19 CAR. As axicabtagene ciloleucel is an autologous cell -based product, it has no defined chemical properties. The anti-CD19 CAR construct used in the production of axicabtagene ciloleucel comprises 3 regions: 1) an anti-human CD19 scFv derived from the FMC63 murine hybridoma; 2) a partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28; and 3) the cytoplasmic portion of the human CD3-ζ molecule, including its intracellular signaling domain. Following CAR engagement with $CD19^{+}$ target cells, the CD3ζ domain activates the downstream signaling cascade that leads to T cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity. The intracellular signaling domain of CD28 provides a co-stimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including IL2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct killing of CD19 expressing target cells. In addition, activated T cells secrete cytokines, chemokines and other molecules that can recruit and activate additional anti-tumor immune cells {Restifo 2012}. A schematic describing the axicabtagene ciloleucel construct and the mode of action of the product is shown in Figure Part I.1.

	Figure Part I.1. Axicabtagene Ciloleucel CAR Construct and Mechanism of Action  **Important information about its composition**: For production of axicabtagene ciloleucel, the anti-CD19 CAR construct is cloned into a retroviral vector and packaged into retroviral particles. T cells from patients are transduced with the anti-CD19 CAR-containing murine γ-retrovirus. Transduced cells are expanded and cryopreserved to generate the axicabtagene ciloleucel product. Cryopreserved product is then shipped under controlled conditions to a qualified treatment center, where the cells are thawed and infused to the patient.
Hyperlink to the Product Information	1.3.1 Product Information - English
Indication(s) in the EEA	**Current**: Yescarta is indicated for the treatment of adult patients with DLBCL and 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 DLBCL and PMBCL, after two or more lines of systemic therapy. Yescarta is indicated for the treatment of adult patients with relapsed or refractory FL after three or more lines of systemic therapy.
	Proposed: Not applicable
Dosage in the EEA	**Current**: Single infusion product, for autologous and intravenous use only. Each patient specific single infusion bag of Yescarta contains a dispersion for infusion CAR-positive variable T cells in one infusion bag. The target dose is 2×10^6 CAR-positive viable T cells/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.
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	**Current**: Dispersion for infusion. A clear to opaque, white to red dispersion. 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 of 2×10^6 CAR-positive viable T cells/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.
	Proposed: Not applicable
Is/Will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = anatomical therapeutic chemical; CAR = chimeric antigen receptor; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; $CD19^+$ = cluster of differentiation 19-positive; CD28 = cluster of differentiation 28; CD3ζ = cluster of differentiation 3ζ; DLBCL = diffuse large B-cell lymphoma; EEA = European Economic Area; EU = European Union; FL = follicular lymphoma; HGBL = high grade B-cell lymphoma; INN = international non-proprietary name; PMBCL = primary mediastinal large B-cell lymphoma; RMP = risk management plan; scFv = single chain variable region fragment.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI- EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. 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, or is refractory to, first-line chemoimmunotherapy. In addition, Yescarta is indicated for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy as well as adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy.

SI.1.1. Incidence

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers originating primarily in B lymphocytes and, to a lesser extent, in T lymphocytes and natural killer cells. Large B-cell lymphoma (LBCL) is an aggressive subset of B-cell NHL, representing 30% to 40% of NHL cases {Chaganti 2016, Morton 2006, Sehn 2015}. The most common LBCL subtype is DLBCL (including DLBCL not otherwise specified), which accounts for more than 80% of LBCL cases {Sehn 2021}. In 2016, the World Health Organization (WHO) introduced HGBL as a new category of LBCLs {Swerdlow 2016}. HGBL represents up to 13% of LBCL cases {Rosenwald 2019, Willenbacher 2020}.

The average age-standardized incidence rate (ASIR) of NHL in Europe between 2019-2020 ranged from 8.6 to 8.8 per 100,000 population (Table SI 1) ({Global Health Data Exchange (GHDx) 2019, World Health Organization (WHO) 2020}); ranging from 2.8 per 100,000 population in North Macedonia to 13.2 per 100,000 population in Slovenia {World Health Organization (WHO) 2020}. During the period from 2019 through 2020, countries in the central and eastern regions of Europe had the lowest ASIRs in comparison to countries in the Western or Northern region of Europe {Global Health Data Exchange (GHDx) 2019, World Health Organization (WHO) 2020}.

DLBCL, an aggressive subtype, is the most common subtype of B-cell NHL, accounting for approximately 30% to 40% of all cases {Chaganti 2016, Morton 2006, Sehn 2015}. Between 2000-2002, the crude incidence of NHL in Europe was reported as 3.8/100,000 population {Sant 2010}. However, neither Global Burden of Disease (GBD) nor International Agency for Research on Cancer (IARC) directly report rates for DLBCL. Thus, the ASIR for DLBCL was derived by using the highest proportion (i.e. 40%) of NHL cases (listed in Table SI 1) diagnosed as DLBCL {Global Health Data Exchange (GHDx) 2019, World Health Organization (WHO) 2020}. Consequently, the derived ASIR for DLBCL in Europe was 3.5 per 100,000 population in 2019 and 3.4 per 100,000 population in 2020.

There is no published information about the incidence of HGBL.

PMBCL is also an aggressive subtype of DLBCL that represents approximately 2% to 4% of patients diagnosed with NHL {Bhatt 2015, Dabrowska-Iwanicka 2014, Savage 2006, Sehn 1998}. Again, neither GBD nor IARC directly report rates for PMBCL. Using the above mentioned approach, the highest proportion (i.e. 4%) of NHL cases (listed in Table SI 1) diagnosed as PMBCL, the derived average ASIR of PMBCL in Europe during the period 2019-2020 was 0.4 per 100,000 population ({Global Health Data Exchange (GHDx) 2019, World Health Organization (WHO) 2020}).

FL is the most common indolent (slow-growing) form of B-cell NHL, accounting for approximately 20% to 30% of all NHL cases. Some patients with FL will transform histologically to DLBCL, i.e. Transformed Follicular Lymphoma, which is more aggressive and is associated with a worse outcome than FL {Casulo 2015}. Between 2000-2002, the crude incidence rate of FL in Europe was reported as 2.2 per 100,000 population {Sant 2010}. Similar to the above-mentioned approach, of using the highest proportion of FL estimated from NHL (i.e. 30%), the average ASIR of FL in the Europe for the period 2019-2020 was derived to be 2.8 per 100,000 population.

Table SI 1. ASIR of NHL, DLBCL, PMBCL and FL per 100, 000 in Europe, 2019-2020

	GBD, 2019			IARC, 2020		
	Overall	**Male**	**Female**	**Overall**	**Male**	**Female**
NHL[a]	8.8	10.7	6.8	8.6	10.4	6.7
DLBCL[b]	3.5	4.3	2.7	3.4	4.2	2.7
PMBCL[b]	0.4	0.4	0.3	0.3	0.4	0.3
FL[b]	2.6	2.6	2.6	2.6	2.6	2.6

Abbreviations: ASIR = age-standardized incidence rate; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; GBD = global burden of disease; IARC = International Agency for Research on Cancer; NHL = non-Hodgkin's lymphoma; PMBCL = primary mediastinal B-cell lymphoma.

a NHL data are based on European estimates for 2019-2020 from the {Global Health Data Exchange (GHDx) 2019} and {World Health Organization (WHO) 2020}

b DLBCL, PMBCL and FL estimates were calculated by using the highest proportion of NHL cases diagnosed as DLBCL (40%), PMBCL (4%) and FL (30%)

SI.1.2. Prevalence

In 2020, the average 1-, 3- and 5-year crude prevalence rate of NHL in Europe ranged from 13.3 to 52.0 per 100,000 population (Table SI 2) {World Health Organization (WHO) 2020}.

Table SI 2. Crude Prevalence Rates of NHL in Europe, 2020

	Crude Prevalence Rates per 100,000 population		
	Overall	**Male**	**Female**
1-year	13.3	15.2	11.6
3-year	34.7	39.3	30.4
5-year	52.0	58.5	45.9

Abbreviations: NHL = non-Hodgkin lymphoma.
NHL data are based on European estimates from the {World Health Organization (WHO) 2020}

Table SI 3. Prevalence Estimates for HGBL Double Hit or Triple Hit and HGBL, Not Otherwise Specified

Data source	Source population, year	Prevalence reported per 10,000 persons (A)	Derived HGBL DHL/THL prevalence estimates per 10,000 persons (B=A*4%)	Derived HGBL, NOS prevalence estimates per 10,000 persons (C= A*60%*2.2%)	Computed HGBL prevalence estimate per 10,000 persons (B+C)
GBD	NHL, 2017	9.9	0.40[a]	0.13[b]	0.53

Abbreviations: GBD = Global burden of disease (http://ghdx.healthdata.org/gbd-results-tool); HGBL NOS = high-grade B-cell lymphoma, not otherwise specified; HGBL DHL/THL = high-grade B-cell lymphoma double-hit or triple-hit; NHL = non-Hodgkin lymphoma.
Note:
[a] HGBL DHL/THL = A * 4% (source population is NHL).
[b] HGBL, NOS = (A * 60%) * 2.2% (source population is NHL).

SI.1.3. Demographics of the Population in the Approved Indication

SI.1.3.1. Age

The literature indicates NHL incidence is strongly related to age, with the highest incidence rates being observed in the older population {CancerMPact 2021}. The median age of diagnosis for NHL is 67 years, there is variability in the age of diagnosis among NHL subtypes with median age at diagnosis of 64, 37, and 59 years of age for DLBCL, PMBCL, and FL, respectively {Armitage 1998, Smith 2015}.

SI.1.3.2. Sex

In Europe, both incidence and prevalence rates for NHL are higher in males than in females {Global Health Data Exchange (GHDx) 2019, World Health Organization (WHO) 2020}. The estimated ASIR of NHL in 2020 was 10.4 per 100,000 in males and 6.7 per 100,000 in females (male to female ratio 1.55:1) (Table SI 1) {World Health Organization (WHO) 2020}. The male to female ratio for the estimated 5-year prevalence rate of NHL in 2020 was 1.2:1 with males having a higher prevalence rate per 100,000 population than females. There is variability in sex distribution across NHL subtypes with 55%, 34%, and 42% males being observed in DLBCL, PMBCL, and FL patients, respectively {Armitage 1998}.

MYC/BCL2 HGBL double-hit or triple-hit is observed in older patients, with a slight male predominance. In studies with patients ranging from 17 to 87 years, the median age observed was approximately 60 years, with 60% to 65% of patients being male {Li 2016, Oki 2014, Petrich 2014}.

SI.1.3.3. Racial and/or Ethnic Origin

There is a paucity of research on the variation in NHL incidence by ethnicity in Europe. However, United States (US) data shows that since 1992, NHL rates have been significantly higher in non-Hispanic whites than in blacks {Howlader 2015}.

SI.1.3.4. Risk Factors

A family history of lymphoma, autoimmune disease, HIV infection, hepatitis C virus seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors of DLBCL {Tilly 2015}.

There are no identified risk factors for PMBCL; however, a familial case of PMBCL has been described in Finland, probably related to the 5533C > A mutation in the myeloid/lymphoid or mixed-lineage leukemia gene {Dabrowska-Iwanicka 2014}.

First-degree family history of NHL, higher body mass index as a young adult, and work as a spray painter were associated with increased risk of FL {Chihara 2015}.

SI.1.4. Main Existing Treatment Options

SI.1.4.1. Relapsed/refractory DLBCL and PMBCL

The recommended DLBCL and PMBCL treatment strategies based on the European Society for Medical Oncology (ESMO) guidelines are summarized in Table SI 4 {Tilly 2015}. The efficacy of treatment regimen for HGBL has not been fully assessed. It should be noted that the current ESMO guidelines, published in 2015 {Tilly 2015}, prior to the revision of the WHO classification do not include treatment recommendations for this specific subgroup of LBCL, potentially due to the lack of differentiated treatment options.

Therapeutic options for relapsed/refractory DLBCL and PMBCL are shown in Table SI 5.

Table SI 4. ESMO recommended treatment strategies for relapsed/refractory DLBCL and PMBCL

	Eligible for transplant	Not eligible for transplant
First relapse/progress	Platinum-based chemotherapy regimens (i.e., R-DHAP, R-ICE, R-GDP) as salvage treatment. For chemo sensitive patients: R-HDCT with ASCT as remission consolidation. Consider allogenic transplantation in patient relapsed after R-HDCT with ASCT or in patient with poor-risk factors at relapse.	Platinum- and/or gemcitabine-based regimens. Clinical trials with novel drugs.
>2 relapse/progress	Allogenic transplantation Clinical trials with novel drugs	Clinical trials with novel drugs. Palliative care.

Abbreviations: ASCT = autologous stem-cell transplantation; DLBCL = diffuse large B-cell lymphoma; ESMO = European Society for Medical Oncology; PMBCL = primary mediastinal B-cell lymphoma; R-GDP = rituximab-gemcitabine, dexamethasone, cisplatin; R-HDCT = rituximab-high-dose chemotherapy; R-DHAP = rituximab-dexamethasone, high dose cytarabine, cisplatin; R-ICE = rituximab-ifosfamide, carboplatin, etoposide.

Table SI 5. Therapeutic options for relapsed/refractory DLBCL and PMBCL

Class	Medicinal Product Brand name (generic name)	Safety Profile	Reference
Antibody-drug conjugates	Polivy (Polatuzumab vedotin)	The main warning and precautions for Polivy are: myelosuppression, peripheral neuropathy, infections, progressive multifocal leukoencephalopathy, TLS, infusion-related reactions, embryo-fetal toxicity, and hepatic toxicity. The most frequently-reported (≥ 30%) ADRs in patients treated with Polivy in combination with bendamustine and rituximab were anemia (31.8%), thrombocytopenia (32.5%), neutropenia (45.7%), diarrhea (35.8%), nausea (33.1%), and peripheral neuropathy (30.5%). The most common serious ADRs were febrile neutropenia (10.6%), sepsis (9.9%), infusion-related reactions (11.3%), pneumonia (8.6%), and pyrexia (7.9%).	{Polivy 2020}
mAbs Anti CD19	Monjuvi (Tafasitamab)	The main warning and precautions for Monjuvi: myelosuppression, infections, infusion-related reactions, and embryo-fetal toxicity. The most common adverse reactions (≥20%) are neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.	{MONJUVI 2020}
Topoisomerase II inhibitor	Pixuvri (pixantrone)	The most common toxicity is bone marrow suppression, particularly of the neutrophil lineage. Other toxicities such as nausea, vomiting, and diarrhea were generally infrequent, mild, reversible, manageable. Decreased ejection fraction (19.1%). Cardiac failure events (8.8%). Tachycardia, arrhythmia, sinus tachycardia, or bradycardia (4.4%).	{Pixuvri 2012}
CAR T	Kymriah	The main warning and precautions for Kymriah are: CRS, neurological adverse reactions, infections and febrile neutropenia, prolonged cytopenias, secondary malignancies, hypogammaglobulinemia, and TLS.	{Kymriah 2020}

Class	Medicinal Product Brand name (generic name)	Safety Profile	Reference
		The most common non-hematological adverse reactions were CRS (57%), infections (58%), pyrexia (35%), diarrhea (31%), nausea (29%), fatigue (27%), and hypotension (25%). The most common hematological adverse reactions were decreased lymphocytes (100%), decreased white blood cells (99%), decreased hemoglobin (99%), decreased neutrophils (97%), and decreased platelets (95%).	
	Breyanzi	The main warning and precautions for Breyanzi are: CRS, neurological adverse reactions, infections and febrile neutropenia, viral reactivation, prolonged cytopenias, hypogammaglobulinemia, secondary malignancy, TLS, hypersensitivity, and prior stem cell transplantation. The most common adverse reactions of any grade were neutropenia (67%), anemia (48%), CRS (39%), fatigue (38%), and thrombocytopenia (37%). The most common serious adverse reactions were CRS (17%), encephalopathy (11%), infection with an unspecified pathogen (6%), neutropenia (4%), thrombocytopenia (4%), aphasia (4%), pyrexia (4%), bacterial infectious disorders (4%), delirium (4%), tremor (4%), febrile neutropenia (3%), and hypotension (3%).	{Breyanzi 2021}

Abbreviations: ADR = adverse drug reaction; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; mAb = monoclonal antibody; PMBCL = primary mediastinal B-cell lymphoma; TLS = tumor lysis syndrome.

SI.1.4.2. Relapsed/refractory FL

The approach is generally based on whether relapse was early (progression of disease within 24 months of treatment with chemo-immunotherapy) or later, prior therapies and biopsy of a site of suspected relapse to determine the presence of transformation {Casulo 2019}. Treatment options include chemo-immunotherapy, single agent rituximab, kinase inhibitors, obinutuzumab, and stem cell transplant.

In 2014, a phosphatidylinositol 3-kinase (PI3K) δ inhibitor, idelalisib, was approved for use by the European Medicines Agency (EMA) in patients who have relapsed with FL based on published data {Gopal 2014, Zydelig 2021}.

In 2017, a second PI3K inhibitor (PI3Kδ and PI3Kα inhibitor), copanlisib, received an accelerated approval by the Food and Drug Administration (FDA) in patients who have relapsed with FL based on published data {ALIQOPA 2017, Dreyling 2017}.

SI.1.5. Natural History of the Indicated Condition including Mortality and Morbidity

Most commonly, DLBCL patients present with a rapidly enlarging, painless, lymph node. In up to 40% of patients, the initially identified site is extranodal, commonly involving the skin, gastrointestinal tract, central nervous system (CNS), lungs, genitourinary tract, or the bones. Approximately 15% of patients present with bone marrow involvement, about one-third have B symptoms (fever, night sweats, and weight loss), nearly one-half have Ann Arbor system stage III/IV disease, and more than one-half have an elevated serum lactate dehydrogenase level {Flowers 2010}.

FL has similar symptoms. Untreated patients' survival may be measured in weeks to months {Cultrera 2012}. PMBCL typically presents as a large, fast-growing tumor with invasion usually limited to the anterior-upper mediastinum although it tends to infiltrate adjacent thoracic structures like the chest wall, pleura, lungs, pericardium, and heart causing pleural/pericardial effusion in approximately 30–50% of cases. The disease is mainly locally advanced. Eighty percent of patients have clinical stage I and II and 75% of them have bulky disease with a tumor mass exceeding 10 cm. Enlarged lymph nodes localized outside the mediastinum are rarely found. Bone marrow infiltration is seen in few cases. Recurrent disease tends to spread to distant extranodal organs like the kidneys, adrenal glands, liver, CNS, and less frequently to the lymph nodes. Typical symptoms such as cough, tachypnea, vein thrombosis, chest pain, or dysphagia are related to the tumor mass infiltration or compression, with a history of complaints for usually less than three months. Approximately half of the patients present with upper vena cava syndrome. Systemic symptoms, mainly weight loss and fever, are relatively rare and they affect less than 20% of patients {Dabrowska-Iwanicka 2014}.

While patients with HGBL double-hit or triple-hit (DHL/THL) do not have a specific clinical presentation, the disease usually exhibits an aggressive behaviour. The diagnosis typically occurs mostly in elderly patients or patients with advanced stage (III/IV), frequent extranodal disease including bone marrow and CNS involvement, higher International Prognostic Index (IPI) score, elevated levels of lactate dehydrogenase, and elevated chemo-immuno-refractoriness {Johnson 2009, Le Gouill 2007, McPhail 2018, Niitsu 2009, Oki 2014, Snuderl 2010, Sun 2015, Tomita 2009}. HGBL DHL/THL also presents a high risk of CNS relapse in the brain parenchyma and leptomeningeal compartment; although this feature could potentially be related to the higher rate of unfavourable IPI score when compared to DLBCL, not other specified and the aggressive features of the disease itself {Evrard 2019, Le Gouill 2007, Petrich 2014}.

SI.1.5.1. Mortality

The average crude mortality rate for NHL in the Europe, between 2019-2020 ranged from 6.7 to 7.2 per 100,000 population with a male to female ratio of 1.2:1. In 2020, the estimated age-standardized mortality rate for NHL was 2.7 per 100,000 population with a male to female ratio of 1.8:1 (Table SI 6). Similar to the incidence rate, countries in the central and eastern

regions of Europe had lower mortality rates in comparison to countries in the Western or Northern region of Europe, although the highest mortality rate was reported in Slovenia (4.5 per 100,000 population) {World Health Organization (WHO) 2020}.

Table SI 6. Crude and Age-standardized Mortality Rates for NHL in the EU, 2019-2020

	Crude Mortality Rate per 100,000 population			Age-standardized mortality rate per 100,000 population		
	Overall	**Male**	**Female**	**Overall**	**Male**	**Female**
GBD, 2019	7.2	7.8	6.6	-	-	-
IARC, 2020	6.7	7.5	5.8	2.7	3.5	1.9

Abbreviations: EU = European Union; GBD = global burden of disease; IARC = International Agency for Research on Cancer NHL = non-Hodgkin's lymphoma
NHL data are based on European estimates for 2019-2020 for the Global Burden of Disease and International Agency for Cancer Research registers ({Global Health Data Exchange (GHDx) 2019, World Health Organization (WHO) 2020})

SI.1.6. Important Co-morbidities

A population-based study of severity of comorbidity among patients with NHL showed that 70% to 80% of patients with NHL are older than 60 years of age and had one or more comorbid condition at the time of cancer diagnosis, and 40% to 50% of these had high impact comorbidity such as:

- Heart-related conditions
- Chronic obstructive pulmonary disease (COPD)
- Diabetes
- Previous cancer
- Renal failure

About 65% of systematically treated patients with aggressive NHL suffered from treatment related toxicity, hematological toxicity being the most predominant. Among patients with aggressive NHL, the chance of dying for those with high impact comorbidity was twice as high compared with those without comorbidity {Janssen-Heijnen 2005}.

Hester and colleagues reported that the following were the most prevalent comorbidities {Hester 2017}.

- Diabetes (25%)
- COPD (16%)
- Congestive heart failure (12%)

PART II: MODULE SII- NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Currently, no in vivo models are available for accurately assessing the nonclinical characteristics of a human autologous T-cell-based product such as axicabtagene ciloleucel. A relevant animal model would need to fulfil all the following criteria: 1) accurate expression of human CD19 in B cells, 2) presence of a fully competent and intact human immune system and repertoire; and 3) ability to support engraftment of a CD19-expressing human B-cell cancer cell line that would allow testing of the product candidate axicabtagene ciloleucel.

Further, according to both US and European Union (EU) regulatory guidance documents ({U.S. Department of Health & Human Services 2013} and {European Medicines Agency 2008a}) the traditional battery of nonclinical studies establishing pharmacology, pharmacokinetics, and toxicity employed to support drug products, such as a targeted small-molecule or a biomolecule, are not applicable to an autologous cellular therapy such as axicabtagene ciloleucel.

Additionally, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines stipulate that therapeutics such as axicabtagene ciloleucel that are intended to treat patients with advanced cancer are exempted from the requirement for carcinogenicity and genotoxicity studies {European Medicines Agency 2008b}.

Based on the nature of axicabtagene ciloleucel and the guidance documents cited above, assessment of safety pharmacology endpoints, overall toxicology, reproductive and developmental toxicity, carcinogenicity, and genotoxicity using in vitro and in vivo models were not conducted.

In vivo data using surrogate anti-murine CD19 chimeric antigen receptor T cells (CAR T) and a syngeneic mouse model of lymphoma demonstrated the ability of anti-murine CD19 CAR T cells to eradicate a $CD19^+$ murine lymphoma. Anti-murine CD19 CAR T cells measured by flow cytometry were found in the blood of treated animals up to one week following the infusion. In the animal studies, B-cell aplasia was observed, but animals showed no overt signs of other toxicity {Kochenderfer 2010}. B-cell aplasia may lead to infections and cytopenias which are considered Important Identified Risks.

Axicabtagene ciloleucel product manufacturing relies on a replication deficient murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T cell genome. Although there is a theoretical risk of oncogenesis via insertional mutagenesis (i.e., dysregulated activation of oncogenic genes at the site of vector integration in the host chromosome), no genotoxic/oncogenic effects manifested by transformation and clonal expansion resulting in T-cell malignancies have been observed in either animals or human subjects treated with γ-retrovirally transduced mature polyclonal T cells. Support for the safety of this vector is based on additional data representing a period of up to approximately 5 years of follow-up for patients with solid tumours {Brentjens 2013, Robbins 2015} and 11 years (540-patient-years) for patients with HIV infection {Scholler 2012}. These studies have shown no evidence of long-term genotoxicity of T-cell therapies produced using γ-retroviral vectors. In addition, no evidence of long-term genotoxicity has been observed in subjects treated with the anti-CD19 CAR T cell products {Cappell 2020, Kochenderfer 2017a, Kochenderfer 2017b, Locke 2019}.

Additionally, a comprehensive summary of replication-competent retrovirus (RCR) data derived from patients treated with γ-retrovirally transduced T-cell products was performed on 629 follow-up samples ranging from 1 month to 8 years after infusion {Bear 2012}. The data demonstrated a lack of RCR events in patient samples across 29 clinical trials including HIV-infected patients. Furthermore, in the 2-year follow-up of subjects treated with axicabtagene ciloleucel in the ZUMA-1 study, no cases of RCRs or secondary cancers related to axicabtagene ciloleucel were observed {Locke 2019}; this remained true as of the 4-year follow-up of the ZUMA-1 study as well {Jacobson 2020}. Similarly, no cases of RCR or secondary malignancies related to KTE-X19 (Tecartus), which utilizes the same retroviral vector, producer clone, and anti-CD19 single chain variable region fragment construct used in the manufacture of axicabtagene ciloleucel, were reported in the ZUMA-2 study {Wang 2020}.

Although the murine γ-retroviral vector cannot replicate, vector integration sites (VIS) were assessed in anti-CD19 CAR T cells manufactured from healthy donor T cells transduced with the same vector used in the manufacture of axicabtagene ciloleucel. Results showed: 1) VIS were found preferentially near transcriptional start sites, which is consistent with VIS mapping for other murine γ-retroviral vectors reported in literature {Biasco 2011, Chang 2016}; and 2) strong distance association between VIS and T cell-related genes, as expected of transcriptionally active chromatin at the time of vector integration, consistent with previous reports in the literature. The VIS characterisation studies indicate that T-cell transformation due to murine γ-retroviral insertional mutagenesis would be an extremely rare event that likely requires the contribution of multiple additional factors beyond the integration site of the viral vector.

Although studies to investigate the systematic viral site integration analysis of the anti-CD19 chimeric antigen receptor (CAR) construct in the axicabtagene ciloleucel T-cell product could provide information on the proximity of the CAR transgene to certain genes or genomic regions, there is no evidence that this could be used as a prediction factor for a possible clonal or oligoclonal secondary expansion. Additionally, as a technical limitation, the particular T-cell clone may not be detected in the infusion product due to a limitation of the sampling material or because of a combination of the relative abundance of the clone of interest and the resolution obtained with the available technologies. Interestingly, only 2 cases of clonal expansion due to viral integration in specific genomic regions of T cells have been reported to date in patients treated with retrovirally engineered CAR T cell therapies in 2 independent clinical studies. In both cases, lentiviral vectors were used and both cases were characterised by a delayed clonal expansion of CAR T cells that contracted as the tumour was eliminated, without evidence of malignant transformation {Fraietta 2018, Shah 2019}. Notably, both CAR T cell products were polyclonal at the end of manufacturing and the T cell clones responsible for the delayed expansion post-treatment were not detected in the infusion bags of either patient. Thus, after careful review of the published literature regarding use of T-cell products produced using γ-retroviral vectors, Kite has concluded that additional VIS studies would not provide meaningful data.

All Kite clinical studies of axicabtagene ciloleucel employ a robust monitoring plan to assess the presence of RCR and the expansion and persistence of anti-CD19 CAR T cells in peripheral blood of subjects treated with axicabtagene ciloleucel. This will reveal the occurrence of engineered T-cell expansion and allow for retrospective analysis to determine whether a

transformation event due to γ-retroviral insertion underlies the increased proliferative capacity of a particular T cell clone. The clinical monitoring plan includes follow-up assessments for RCR at Months 3, 6, and 12 for all subjects; additionally, subjects who have a positive RCR test result during the first year will be monitored annually thereafter for 15 years; samples will be collected from all subjects for up to 15 years regardless of RCR test result. Further, quantitative polymerase chain reaction (PCR) will be utilised to monitor for secondary expansion of anti-CD19 CAR T cells in blood at multiple time points after infusion as defined in the study-specific protocol schedule of assessments. If such an event occurs, insertional sites will be characterised in detail utilizing methods such as linear amplification-mediated PCR and next-generation sequencing to fully characterize the location and nature of the integration site(s).

Based upon a theoretical possibility ‘Secondary malignancy of T-cell origin’ is considered an important identified risk.

PART II: MODULE SIII- CLINICAL TRIAL EXPOSURE

Overall, approximately 811 subjects have been administered axicabtagene ciloleucel in the clinical trial programme. Table SIII.1 provides the cumulative number of subjects exposed to axicabtagene ciloleucel in ongoing and completed clinical trials.

Table SIII.1. Estimated Cumulative Subject Exposure in Gilead-Sponsored Interventional Clinical Trials with Axicabtagene Ciloleucel (as of 22 August 2022)

Study	Number of subjects
ZUMA-1	277
ZUMA-2	10
ZUMA-5	152
ZUMA-6	34
ZUMA-7 (Axicabtagene ciloleucel/standard of care)	170/168
ZUMA-9	84*
ZUMA-11	12
ZUMA-12	40
ZUMA-14	26
ZUMA-19	6
Total number of subjects treated with axicabtagene ciloleucel	811

Note: Data from ongoing studies as of 22 August 2022.
Non-investigational drugs, excluding placebo, were presented as "Other".
If a subject was dosed with axicabtagene ciloleucel and non-investigational drugs, then the subject was counted once in the rows of "Subjects treated with axicabtagene ciloleucel" and "Other" categories, and counted once in the row of "Total Unique Subjects".
Compassionate use subjects are not included in the exposure estimation.
*ZUMA-9 (KTE-C19-109) - 59 subjects in Cohort 2 of the study were from the postmarketing setting per the approved protocol, were treated with axicabtagene ciloleucel and are included in the clinical trial exposure estimation.
Data Source: ADSL Program Name: t_ex Output Generated: 20220908T11:53

Table SIII.2. Cumulative Subject Exposure to Axicabtagene Ciloleucel from Ongoing Clinical Trials by Age and Sex (as of 22 August 2022)

Age (Years)	Male (N=515)	Female (N=296)	Total (N=811)
< 18	0	0	0
18 to 65	371	205	576
> 65	144	91	235
Total	515	296	811

Note: Data from ongoing studies as of 22 August 2022.
N = Subjects treated with axicabtagene ciloleucel.
Compassionate use subjects are not included in the exposure estimation.
Data Source: ADSL Programme Name: t_ex_age_sex Output Generated: 20220908T11:53.

Table SIII.3. Cumulative Subject Exposure to Axicabtagene Ciloleucel from Ongoing Clinical Trials by Racial Group (as of 22 August 2022)

Racial group	Number of subjects
White	669
Other	69
Asian	37
Black or African American	33
Native Hawaiian or other pacific islander	2
American Indian or Alaska native	1
Total	811

Note: Data from ongoing studies as of 22 August 2022.
Compassionate use subjects are not included in the exposure estimation.
Data Source: ADSL Programme Name: t_ex_race Output Generated: 20220908T11:53.

Table SIII.4. Demographics: ZUMA-7, ZUMA-1, and the Pooled Axicabtagene Ciloleucel Population of ZUMA-7 and ZUMA-1 (Safety Analysis Sets)

	Standard of care	Axicabtagene Ciloleucel		
Characteristic	ZUMA-7 (N = 168)	ZUMA-7 (N = 170)	ZUMA-1 (N = 108[b])	Overall (N = 278)
Age (years)				
n	168	170	108	278
Mean (SD)	57.6 (12.0)	57.0 (12.2)	56.1 (12.4)	56.6 (12.3)
Median (Q1, Q3)	60.0 (49.5, 67.0)	58.5 (52.0, 66.0)	58.0 (50.5, 64.5)	58.0 (51.0, 65.0)
Min, Max	29, 81	21, 80	23, 76	21, 80
Age category, n (%)				
≥ 18 and < 65 years	113 (67)	121 (71)	81 (75)	202 (73)
≥ 65 years	55 (33)	49 (29)	27 (25)	76 (27)
Sex, n (%)				
Male	120 (71)	106 (62)	73 (68)	179 (64)
Female	48 (29)	64 (38)	35 (32)	99 (36)
Ethnicity, n (%)				
Hispanic or Latino	8 (5)	8 (5)	19 (18)	27 (10)
Not Hispanic or Latino	158 (94)	159 (94)	89 (82)	248 (89)
Not Reported	2 (1)	3 (2)	0 (0)	3 (1)

Characteristic	Standard of care	Axicabtagene Ciloleucel		
	ZUMA-7 (N = 168)	ZUMA-7 (N = 170)	ZUMA-1 (N = 108[b])	Overall (N = 278)
Race, n (%)				
American Indian or Alaska Native	1 (1)	0 (0)	0 (0)	0 (0)
Asian	8 (5)	11 (6)	3 (3)	14 (5)
Black or African American	6 (4)	9 (5)	5 (5)	14 (5)
Native Hawaiian or Other Pacific Islander	1 (1)	2 (1)	0 (0)	2 (1)
White	145 (86)	138 (81)	92 (85)	230 (83)
Other	7 (4)	10 (6)	8 (7)	18 (6)
Region, n (%)				
North America	120 (71)	132 (78)	107 (99)	239 (86)
Europe	44 (26)	32 (19)	NA	32 (12)
Israel	2 (1)	4 (2)	1 (1)	5 (2)
Australia	2 (1)	2 (1)	NA	2 (1)
Actual follow-up time from Therapy day 0 (months)[a]				
Mean (SD)	16.62 (9.25)	18.87 (8.45)	30.83 (23.82)	23.52 (17.23)
Median (Q1, Q3)	18.02 (8.08, 24.20)	19.56 (12.42, 25.07)	23.52 (7.23, 54.14)	19.83 (10.35, 30.19)
Min, Max	0.9, 37.1	1.5, 36.9	0.3, 67.8	0.3, 67.8

Data cutoff date is 18 March 2021.
Abbreviations: Max = maximum; Min = minimum; N = subjects treated; NA = not applicable; Q1 = first quartile; Q3 = third quartile.
Notes: Percentages are based on the total number of subjects (N) in each column. Age in ZUMA-1 is derived as integer of (total number of months between subject's birthdate and enrollment date)/12, if birthdate is partial or missing, the collected age in the database is used.
a Actual follow up time is calculated as (the death date or the last date known to be alive - the axicabtagene ciloleucel first infusion date or the first dose date of salvage chemotherapy in the SOCT arm in ZUMA-7 + 1)/30.4375.
b ZUMA-1 refers to ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2.
Source: Modified from m5.3.5.3 ISS Table 14.1.4 and Table 14.1.2.1.

Table SIII.5. Baseline Characteristics: ZUMA-7, ZUMA-1, and the Pooled Axicabtagene Ciloleucel Population of ZUMA-7 and ZUMA-1 (Safety Analysis Sets)

Characteristic	Standard of care	Axicabtagene Ciloleucel		
	ZUMA-7 (N = 168)	ZUMA-7 (N = 170)	ZUMA-1 (N = 108[a])	Overall (N = 278)
Disease type[b], n (%)				
DLBCL	110 (65)	103 (61)	84 (78)	187 (67)
HGBL	25 (15)	40 (24)	0	40 (14)
PMBCL	NA	NA	8 (7)	8 (7)
TFL	25 (15)	19 (11)	16 (15)	35 (13)
Other	8 (5)	8 (5)	0	8 (3)
Relapsed/refractory subgroup, n (%)				
Primary refractory	123 (73)	123 (72)	3 (3)	126 (45)
Refractory to 2nd or greater line therapy	0	0	80 (74)	80 (29)
Relapse post ASCT	0	0	25 (23)	25 (9)
Relapse ≤ 6 months of first line therapy	9 (5)	9 (5)	0	9 (3)
Relapse > 6 and ≤ 12 months of first line therapy	36 (21)	38 (22)	0	38 (14)
Number of prior lines of therapy, n (%)				
1	168 (100)	170 (100)	3 (3)	173 (62)
2	0	0	29 (27)	29 (10)
3	0	0	33 (31)	33 (12)
4	0	0	30 (28)	30 (11)
≥5	0	0	13 (12)	13 (5)

Data cutoff date is 18 March 2021.
Source: Table 14.1.5
Abbreviations: ASCT = autologous stem cell transplant; DLBCL = diffuse large B-cell lymphoma; HGBL = high-grade B-cell lymphoma; N = subjects treated; NA = not applicable; PMBCL = primary mediastinal B-cell lymphoma; TFL = transformed follicular lymphoma.
a ZUMA-1 refers to ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2.
b In ZUMA-7, TFL refers to 'large cell transformation from follicular lymphoma' from investigator review; HGBL refers to 'HGBL with or without MYC and BCL2 and/or BCL6 rearrangement' from investigator review; DLBCL refers to 'DLBCL not otherwise specified' from investigator review; all other disease subtypes are assigned as 'Other'
Data Source: ADSL, ADBASE Program Name: t_bchar Output Generated: 20210730T16:07

Table SIII.6. Exposure to Study Treatment: ZUMA-7, ZUMA-1, and the Pooled Axicabtagene Ciloleucel Population of ZUMA-7 and ZUMA-1 (Safety Analysis Sets)

	Axicabtagene Ciloleucel		
	ZUMA-7 (N = 170)	**ZUMA-1 (N = 108[a])**	**Overall (N = 278)**
Axicabtagene ciloleucel Weight-adjusted dose received (x 10^6 CAR T cell/kg) for subjects with weight ≤ 100kg			
n	137	88	225
Mean (SD)	1.98 (0.14)	1.97 (0.14)	1.98 (0.14)
Median (Q1, Q3)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)
Min, Max	1.0, 2.1	1.1, 2.0	1.0, 2.1
Total dose received (x 10^6 CAR T cells) for subjects with weight > 100kg			
n	33	20	53
Mean (SD)	200.00 (0.00)	196.48 (15.52)	198.67 (9.54)
Median (Q1, Q3)	200.00 (200.00, 200.00)	200.00 (199.82, 200.00)	200.00 (200.00, 200.00)
Min, Max	200.0, 200.0	130.6, 201.0	130.6, 201.0
Total number of CAR T cells (x 10^6)			
n	170	108	278
Mean (SD)	161.64 (33.19)	158.81 (33.78)	160.54 (33.39)
Median (Q1, Q3)	170.00 (140.00, 190.00)	164.30 (135.99, 187.15)	165.50 (140.00, 190.00)
Min, Max	58.0, 200.0	63.6, 201.0	58.0, 201.0
Total number of T cells infused (x 10^6)			
n	170	108	278
Mean (SD)	308.35 (90.68)	337.24 (130.39)	319.57 (108.55)
Median (Q1, Q3)	301.52 (242.86, 363.64)	301.68 (256.93, 377.78)	301.68 (246.38, 364.94)
Min, Max	87.9, 633.3	149.5, 894.9	87.9, 894.9

Data cutoff date is 18 March 2021.
Source: Table 14.4.1
Abbreviations: CAR = chimeric antigen receptor; Max = maximum; Min = minimum; N = subjects treated; Q1 = first quartile; Q3 = third quartile.
a ZUMA-1 refers to ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2.
Data Source: ADSL, ADEX Program Name: t_ex Output Generated: 20210730T16:08

Table SIII.7. Summary of Follow-up Time: ZUMA-7, ZUMA-1, and the Pooled Axicabtagene Ciloleucel Population of ZUMA-7 and ZUMA-1 (Safety Analysis Sets)

	Standard of Care Therapy			Axicabtagene Ciloleucel					
	ZUMA-7 (N=168)			ZUMA-7 (N=170)			ZUMA-1 (N=108[a])		
Duration of follow-up	N	Follow-up (months) mean (SD)	Total Follow-up (months)	N	Follow-up (months) mean (SD)	Total Follow-up (months)	N	Follow-up (months) mean (SD)	Total Follow-up (months)
≥ 1 month	167	16.71 (9.20)	2791.29	170	18.87 (8.45)	3207.89	105	31.70 (23.59)	3328.36
≥ 3 months	159	17.46 (8.79)	2775.59	164	19.49 (7.95)	3195.73	101	32.88 (23.27)	3321.36
≥ 6 months	140	19.20 (7.89)	2687.31	156	20.26 (7.36)	3160.44	84	38.58 (21.38)	3241.07
≥ 9 months	120	21.14 (6.78)	2536.94	143	21.41 (6.55)	3062.05	74	42.77 (19.25)	3164.65
≥ 12 months	104	22.84 (5.58)	2375.72	130	22.50 (5.84)	2924.91	64	47.80 (15.45)	3059.35
≥ 24 months	44	28.17 (3.40)	1239.66	53	28.30 (3.32)	1499.89	54	53.68 (7.56)	2898.69
≥ 36 months	1	37.06 (-)	37.06	1	36.93 (-)	36.93	50	55.37 (4.59)	2768.62
≥ 48 months	0	-	-	0	-	-	47	56.04 (3.81)	2633.95
Overall	168	16.62 (9.25)	2792.15	170	18.87 (8.45)	3207.89	108	30.83 (23.82)	3329.77

Data cutoff date is 18 March 2021.
Source: Table 14.1.2.2.1.1
Abbreviations: N = subjects treated
a ZUMA-1 refers to ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2.
Note: Follow up time from Therapy day 0 is calculated as (the death date or the last date known to be alive - the axicabtagene ciloleucel first infusion date or the first dose date of salvage chemotherapy in the standard of care therapy arm in ZUMA-7 + 1)/30.4375.
Data Source: ADSL Program Name: t_fup Output Generated: 20220214T08:59

Table SIII.8. Summary of Follow-up Time by Gender and Age: ZUMA-7, ZUMA-1, and the Pooled Axicabtagene Ciloleucel Population of ZUMA-7 and ZUMA-1 (Safety Analysis Sets)

	Standard of Care Therapy			Axicabtagene Ciloleucel					
	ZUMA-7 (N=168)			ZUMA-7 (N=170)			ZUMA-1 (N=108[a])		
Duration of follow-up	N	Follow-up (months) mean (SD)	Total Follow-up (months)	N	Follow-up (months) mean (SD)	Total Follow-up (months)	N	Follow-up (months) mean (SD)	Total Follow-up (months)
Male	120	16.43 (9.51)	1971.29	106	17.94 (7.96)	1901.57	73	29.40 (23.88)	2146.37
< 65 Years	83	16.80 (10.28)	1394.07	79	18.04 (8.05)	1424.95	51	28.20 (24.53)	1438.23
≥ 65 Years	37	15.60 (7.56)	577.22	27	17.65 (7.81)	476.62	22	32.19 (22.60)	708.14
Female	48	17.10 (8.66)	820.86	64	20.41 (9.07)	1306.32	35	33.81 (23.77)	1183.41
< 65 Years	30	17.17 (8.85)	515.09	42	19.48 (9.43)	818.27	30	34.96 (23.76)	1048.67
≥ 65 Years	18	16.99 (8.59)	305.77	22	22.18 (8.25)	488.05	5	26.95 (25.29)	134.74

Data cutoff date is 18 March 2021.
Abbreviations: N = subjects treated
a ZUMA-1 refers to ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2.
Source: Table 14.1.2.2.1.2
Note: Follow up time from Therapy day 0 is calculated as (the death date or the last date known to be alive - the axicabtagene ciloleucel first infusion date or the first dose date of salvage chemotherapy in the standard of care therapy arm in ZUMA-7 + 1)/30.4375.
Data Source: ADSL Program Name: t_fup_sex Output Generated: 20220214T09:50

Table SIII.9. Summary of Follow-up Time by Race and Ethnicity: ZUMA-7, ZUMA-1, and the Pooled Axicabtagene Ciloleucel Population of ZUMA-7 and ZUMA-1 (Safety Analysis Sets)

	Standard of Care Therapy			Axicabtagene Ciloleucel					
	ZUMA-7 (N=168)			ZUMA-7 (N=170)			ZUMA-1 (N=108[a])		
Duration of follow-up	N	Follow-up (months) mean (SD)	Total Follow-up (months)	N	Follow-up (months) mean (SD)	Total Follow-up (months)	N	Follow-up (months) mean (SD)	Total Follow-up (months)
Race									
American Indian or Alaska Native	1	17.84 (-)	17.84	0	-	-	0	-	-
Asian	8	19.63 (10.23)	157.01	11	19.86 (7.12)	218.45	3	36.71 (27.65)	110.13
Black or African American	6	21.42 (11.05)	128.53	9	21.03 (4.99)	189.24	5	42.95 (24.28)	214.77
Native Hawaiian or Other Pacific Islander	1	8.67 (-)	8.67	2	15.46 (4.30)	30.92	0	-	-
White	145	16.18 (9.16)	2345.43	138	18.48 (8.53)	2550.11	92	29.26 (23.55)	2692.04
Other	7	19.24 (9.22)	134.67	10	21.92 (11.47)	219.17	8	39.10 (26.05)	312.84
Overall	168	16.62 (9.25)	2792.15	170	18.87 (8.45)	3207.89	108	30.83 (23.82)	3329.77
Ethnicity									
Hispanic or Latino	8	10.07 (8.24)	80.59	8	25.25 (8.32)	201.99	19	31.61 (25.34)	600.61
Not Hispanic or Latino	158	16.96 (9.24)	2679.95	159	18.57 (8.43)	2953.00	89	30.66 (23.63)	2729.17
Not Reported	2	15.80 (6.74)	31.61	3	17.63 (2.80)	52.90	0	-	-
Overall	168	16.62 (9.25)	2792.15	170	18.87 (8.45)	3207.89	108	30.83 (23.82)	3329.77

Data cutoff date is 18 March 2021.
Abbreviations: N = subjects treated
a ZUMA-1 refers to ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2.
Source: Table 14.1.2.2.1.4 & Table 14.1.2.2.1.3
Note: Follow up time from Therapy day 0 is calculated as (the death date or the last date known to be alive - the axicabtagene ciloleucel first infusion date or the first dose date of salvage chemotherapy in the standard of care therapy arm in ZUMA-7 + 1)/30.4375.
Data Source: ADSL Program Name: t_fup_race Output Generated: 20220214T09:18
Data Source: ADSL Program Name: t_fup_ethn Output Generated: 20220214T09:54

ZUMA-5 is a Phase 2 multicenter, open-label, single-arm trial of axicabtagene ciloleucel for the treatment of relapsed/refractory indolent non-Hodgkin lymphoma (iNHL).

In the currently ongoing ZUMA-5 trial, 148 subjects were treated with axicabtagene ciloleucel and represents the safety population for the purposes of this risk management plan (RMP). Of these 148 subjects, 124 subjects had FL and 24 had marginal zone lymphoma (MZL), as of data-cut off of 14 September 2020.

All the subjects in the ZUMA-5 safety analysis set received the planned total body surface area adjusted dose of cyclophosphamide (1500 mg/m^2) and fludarabine (90 mg/m^2). Bridging therapy was administered to subjects strictly at the discretion of the treating investigator. In the safety analysis set, 6 subjects (4.3%; 4 subjects with FL and 2 subjects with MZL) received bridging therapy. All of the 6 subjects had documented measurable disease after bridging therapy.

Disease was required to be histologically confirmed of B-cell iNHL, with histological subtype limited to FL Grade 1, Grade 2, or Grade 3a or MZL nodal or extranodal, based on criteria established by the WHO 2016 classification. Subjects were required to have received 2 or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent. Relapsed (defined as those subjects with iNHL who progressed > 6 months from completion of the most recent prior treatment) versus refractory (defined as those subjects with iNHL who progressed within 6 months of completion of the most recent prior treatment) at study entry.

Table SIII.10. Demographics in ZUMA-5

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
Age (years)			
n	124	24	148
Mean (SD)	59.0 (9.9)	64.8 (8.3)	59.9 (9.9)
Median (Q1, Q3)	60.0 (53.0, 67.0)	65.5 (61.0, 71.5)	61.0 (53.0, 67.5)
Min, Max	34, 79	48, 77	34, 79
Age category n (%)			
< 65 Years	86 (69)	11 (46)	97 (66)
>= 65 Years	38 (31)	13 (54)	51 (34)
Sex n (%)			
Male	73 (59)	11 (46)	84 (57)
Female	51 (41)	13 (54)	64 (43)
Ethnicity n (%)			
Hispanic or Latino	6 (5)	2 (8)	8 (5)
Not Hispanic or Latino	118 (95)	21 (88)	139 (94)
Missing	0 (0)	1 (4)	1 (1)
Race n (%)			
Asian	2 (2)	0 (0)	2 (1)
Black or African American	4 (3)	1 (4)	5 (3)
White	115 (93)	22 (92)	137 (93)
Other	3 (2)	1 (4)	4 (3)

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
Country n (%)			
US	114 (92)	24 (100)	138 (93)
France	10 (8)	0 (0)	10 (7)

Data cutoff date: 14 September 2020.
Abbreviations: FL = follicular lymphoma; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; N = subjects treated; Q1 = first quartile; Q3 = third quartile; US = United States.
Note: Percentages are based on the number of subjects in the analysis set.
Data Source: ADSL Program Name: t_dm.sas Output Generated: 20210405T14:16

Table SIII.11. Baseline Characteristics in ZUMA-5

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
Height (cm)			
n	122	23	145
Mean (SD)	171.81 (10.36)	165.52 (8.75)	170.81 (10.35)
Median (Q1, Q3)	172.25 (163.00, 180.00)	162.60 (160.00, 172.70)	170.50 (162.00, 179.00)
Min, Max	149.9, 200.7	149.9, 187.0	149.9, 200.7
Weight (kg)			
n	124	24	148
Mean (SD)	87.00 (19.17)	77.20 (20.32)	85.41 (19.63)
Median (Q1, Q3)	85.25 (72.40, 101.25)	72.40 (64.75, 83.50)	82.97 (71.53, 100.15)
Min, Max	49.4, 137.3	53.0, 127.5	49.4, 137.3
ECOG performance status n (%)			
0	78 (63)	14 (58)	92 (62)
1	46 (37)	10 (42)	56 (38)
Histologically diagnosed disease type per local lab n (%)			
FL	124 (100)	0 (0)	124 (84)
MZL	0 (0)	24 (100)	24 (16)
FL histological category at study entry n (%)			
Grade 1	33 (27)	-	-
Grade 2	61 (49)	-	-
Grade 3a	30 (24)	-	-
MZL histological category n (%)			
Nodal	-	7 (29)	-
Extranodal	-	17 (71)	-

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
Disease stage n (%)			
I	5 (4)	0 (0)	5 (3)
II	13 (10)	2 (8)	15 (10)
III	45 (36)	3 (13)	48 (32)
IV	61 (49)	19 (79)	80 (54)
FLIPI total score n (%)			
0	4 (3)	-	-
1	18 (15)	-	-
2	48 (39)	-	-
3	35 (28)	-	-
4	16 (13)	-	-
5	3 (2)	-	-
Low risk (0 - 1)	22 (18)	-	-
Intermediate risk (2)	48 (39)	-	-
High risk (3 - 5)	54 (44)	-	-
Relapsed/refractory subgroup[a] n (%)			
Relapsed	40 (32)	6 (25)	46 (31)
Refractory	84 (68)	18 (75)	102 (69)
Double refractory subgroup[a] n (%)			
Yes	36 (29)	8 (33)	44 (30)
No	88 (71)	16 (67)	104 (70)
Number of prior lines of therapy[f] n (%)			
1	3 (2)	0 (0)	3 (2)
2	42 (34)	8 (33)	50 (34)
3	32 (26)	7 (29)	39 (26)
4	25 (20)	1 (4)	26 (18)
≥ 5	21 (17)	8 (33)	29 (20)
n	123	24	147
Mean (SD)	3.34 (1.59)	3.63 (1.74)	3.39 (1.62)
Median (Q1, Q3)	3.00 (2.00, 4.00)	3.00 (2.00, 5.00)	3.00 (2.00, 4.00)
Min, Max	1.0, 10.0	2.0, 8.0	1.0, 10.0

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
Response to last line of therapy n (%)			
Complete response	34 (27)	5 (21)	39 (26)
Partial response	24 (19)	3 (13)	27 (18)
Stable disease	25 (20)	3 (13)	28 (19)
Progressive disease	23 (19)	8 (33)	31 (21)
Not evaluable	4 (3)	1 (4)	5 (3)
Unknown	13 (10)	4 (17)	17 (11)
Receiving prior ASCT n (%)			
Yes	30 (24)	3 (13)	33 (22)
No	94 (76)	21 (88)	115 (78)
Time to relapse from first anti-CD20-chemotherapy combination therapy[b] n (%)	123	23	146
≥ 24 months	40 (33)	8 (35)	48 (33)
< 24 months	68 (55)	13 (57)	81 (55)
High tumor bulk as defined by GELF criteria[c] n (%)	64 (52)	10 (42)	74 (50)
Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm	32 (26)	3 (13)	35 (24)
Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm	22 (18)	2 (8)	24 (16)
Presence of B symptoms	8 (6)	2 (8)	10 (7)
Splenomegaly	22 (18)	5 (21)	27 (18)
Pleural effusions or peritoneal ascites	5 (4)	1 (4)	6 (4)
Cytopenias	15 (12)	1 (4)	16 (11)
Leukemia	1 (1)	0 (0)	1 (1)
Prior PI3K inhibitor n (%)			
Yes	34 (27)	9 (38)	43 (29)
No	90 (73)	15 (63)	105 (71)
Prior anti-CD20 single agent[c] n (%)			
Yes	39 (31)	10 (42)	49 (33)
No	85 (69)	14 (58)	99 (67)

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
Prior alkylating single agent n (%)			
Yes	16 (13)	6 (25)	22 (15)
No	108 (87)	18 (75)	126 (85)
Prior anti-CD20 plus alkylating agent n (%)			
Yes	123 (99)	23 (96)	146 (99)
No	1 (1)	1 (4)	2 (1)
Prior lenalidomide n (%)			
Yes	38 (31)	8 (33)	46 (31)
No	86 (69)	16 (67)	102 (69)
Bone marrow assessment at baseline[d] n (%)			
Lymphoma present	33 (27)	11 (46)	44 (30)
Lymphoma present but not FL/MZL	1 (1)	0 (0)	1 (1)
Lymphoma not present	89 (72)	13 (54)	102 (69)
Unknown	1 (1)	0 (0)	1 (1)

Data cutoff date: 14 September 2020.
Abbreviations: ASCT = Autologous stem cell transplantation; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma, FLIPI = follicular lymphoma international prognostic index; GELF = Groupe d' Etude des Lymphomes Folliculaires; iNHL = indolent non-Hodgkin lymphoma; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; N = subjects treated; PI3K = phosphatidylinositol 3-kinase; Q1 = first quartile; Q3 = third quartile.
Note: Percentages are based on the number of subjects in the analysis set.
a Subjects with iNHL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Subjects with iNHL who progressed > 6 months of completion of the most recent prior treatment are defined as relapsed. Subjects with iNHL who progressed within 6 months of completion each of the first 2 lines of prior treatment are defined as double refractory.
b Time to relapse is defined as the time from initiation of the first line anti-CD20-chemotherapy combination therapy to progression. Number of subjects with time to relapse is based on those who had progressed with date of progression. Percentages are based on the number of subjects who ever received anti-CD20-chemotherapy combination therapy.
c Disease burden, as defined by any of GELF criteria (subject meets the criteria for high tumor bulk versus subject does not meet the criteria for high tumor bulk): Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm, Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm, B symptoms, splenomegaly, pleural effusions or peritoneal ascites, cytopenias, or leukemia.
d Bone marrow assessment at baseline for lymphoma presence is based on investigator reported Lugano bone marrow assessment/ bone marrow assessment using aspirate or core biopsy at screening. If these are not available, lymphoma presence is based on diagnosis history of bone marrow involvement.
e Prior anti-CD20 single agent includes rituximab, ofatumumab, or obinutuzumab.
f One subject received prior therapy that was given for DLBCL, not for the primary disease of FL.
Data Source: ADSL, ADBASE Program Name: t_bchar.sas Output Generated: 20210405T14:16

Table SIII.12. Exposure to Axicabtagene Ciloleucel in ZUMA-5

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
Cyclophosphamide			
Total BSA adjusted dose (mg/m^2)[a]			
n	124	24	148
Mean (SD)	1500.0 (0.0)	1500.0 (0.0)	1500.0 (0.0)
Median (Q1, Q3)	1500.0 (1500.0, 1500.0)	1500.0 (1500.0, 1500.0)	1500.0 (1500.0, 1500.0)
Min, Max	1500, 1500	1500, 1500	1500, 1500
Subjects received +/- 10% planned total dose, n (%)	124 (100)	24 (100)	148 (100)
Fludarabine			
Total BSA adjusted dose (mg/m^2)[a]			
n	124	24	148
Mean (SD)	90.0 (0.0)	90.0 (0.0)	90.0 (0.0)
Median (Q1, Q3)	90.0 (90.0, 90.0)	90.0 (90.0, 90.0)	90.0 (90.0, 90.0)
Min, Max	90, 90	90, 90	90, 90
Subjects received +/- 10% planned total dose, n (%)	124 (100)	24 (100)	148 (100)
Axicabtagene ciloleucel			
Weight adjusted dose received (10^6 CAR T cell/kg)			
n	124	24	148
Mean (SD)	1.94 (0.14)	1.96 (0.11)	1.94 (0.14)
Median (Q1, Q3)	2.00 (1.90, 2.00)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)
Min, Max	1.3, 2.1	1.6, 2.0	1.3, 2.1
Total number of CAR T cells (x10^6)			
n	124	24	148
Mean (SD)	167.10 (29.98)	149.08 (29.35)	164.18 (30.52)
Median (Q1, Q3)	170.00 (141.00, 200.00)	145.00 (130.00, 165.00)	165.00 (140.00, 199.50)
Min, Max	100.0, 200.0	104.0, 200.0	100.0, 200.0
Total number of T cells infused (x10^6)			
n	124	24	148
Mean (SD)	300.92 (98.16)	304.27 (106.69)	301.47 (99.22)
Median (Q1, Q3)	283.70 (241.86, 352.94)	274.77 (246.72, 336.31)	279.24 (244.56, 351.91)
Min, Max	123.5, 769.2	136.1, 583.3	123.5, 769.2
Subjects received +/- 10% planned total dose, n (%)	120 (97)	**24 (100)**	**144 (97)**

Data cutoff date: 14 Sep 2020.
Abbreviations: BSA = body surface area; CAR T = chimeric antigen receptor T cells; FL = follicular lymphoma; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; N = subjects treated; Q1 = first quartile; Q3 = third quartile.
Note: Percentages are based on the number of subjects in the analysis set.
a Total BSA adjusted dose of cyclophosphamide/fludarabine received is calculated by (sum of non-missing doses during conditioning chemo period).
Data Source: ADSL, ADEX Program Name: t_ex.sas Output Generated: 20210405T14:18

PART II: MODULE SIV- POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies (ZUMA-1, ZUMA-5, and ZUMA-7) in the Development Program

Table SIV.1. Important Exclusion Criteria in Pivotal Studies (ZUMA-1, ZUMA-5, and ZUMA-7) in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
History of severe immediate hypersensitivity reaction to any of the agents used in this study.	Could have affected safety outcomes.	No **Rationale**: History of hypersensitivity to the product or any of its excipients is a contraindication for use and hence it is not relevant to include as missing information.
Primary immunodeficiency. Live vaccine ≤6 weeks prior to planned start of conditioning regimen. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Known history of infection with HIV or HBV or HCV (if viral load was detectable per qPCR and/or nucleic acid testing for HBV and HCV).	These patients were excluded from participation in the clinical trial as they were at greater infection risk due to: the fact that axicabtagene ciloleucel is associated with B-cell aplasia (which leads to hypogammaglobulinemia); lymphodepletion per study protocol from conditioning chemotherapy which may result in cytopenias and hypogammaglobulinemia; infection associated with administration of live vaccine; possibility of a synergistic effect on the immune system since live vaccines also stimulate the immune system and this may have resulted in difficulties in the interpretation of safety and efficacy data.	No **Rationale**: Cytopenias, especially prolonged cytopenias and infections, especially serious infections, are important identified risks which is described in section 4.4 of the SmPC - Special warnings and precautions for use.
History of malignancy other than non-melanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, and breast) unless disease free for at least 3 years. History of TFL or transformed MZL (applicable to ZUMA-5 study), small lymphocytic lymphoma, histological Grade 3b FL, and lymphoplasmacytic lymphoma. History of Richter's transformation of CLL or PMBCL (applicable to ZUMA-7)	Inclusion of these patients would have affected the safety and efficacy endpoints of the study, e.g., due to relapse or progression of the malignancy can cause misinterpretation of the endpoints.	No **Rationale**: 'Secondary malignancy of T-cell origin' is an important identified risk, described in section 4.4 of the SmPC - Special warnings and precautions for use. 'Secondary hematologic malignancies excluding T-cell malignancies' is considered an important potential risk.

Criterion	Reason for Exclusion	Considered to be Missing Information
Subjects with detectable CSF malignant cells, or brain metastases, or with a history of CNS lymphoma, CSF malignant cells or brain metastases. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement.	Axicabtagene ciloleucel is associated with neurologic effects and inclusion of these patients would have confounded the safety endpoints of the study.	No **Rationale**: Serious neurologic adverse reaction is an important identified risk and is described in section 4.4 of the SmPC - Special warnings and precautions for use.
History of autoimmune disease (e.g., Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years.	These patients were excluded as it was not known whether stimulation of the immune system by axicabtagene ciloleucel would result in reactivation of immune disorders. Expansion of T-cells and potentially self-reactive T cells may also place these patients at a higher risk of reactivation of autoimmune disorders.	Yes
Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of axicabtagene ciloleucel.	No animal data available. Due to the reproductive toxicity issues with the chemotherapy used for conditioning the patients, women of child-bearing potential or who are pregnant, or breast feeding were excluded for safety reasons.	Yes
History of autologous or allo-HSCT (ZUMA-7).	ZUMA-7 was designed to include only patients as a second line of therapy.	No **Rationale**: These patients were studied in ZUMA-1 and per the proposed SmPC the indication was extended to include adult patients with relapsed or refractory DLBCL and HGBL.
Prior CD19 targeted therapy; Prior chimeric antigen receptor therapy or other genetically modified T-cell therapy or prior randomization into ZUMA-7.	To avoid confounding evaluation of efficacy and safety.	No **Rationale**: The safety profile in these patients is not expected to differ from the known safety profile.

Criterion	Reason for Exclusion	Considered to be Missing Information
Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first dose of axicabtagene ciloleucel or standard of care (ZUMA-7).	To avoid confounding evaluation of efficacy and safety. Elevation in the level of pro-inflammatory cytokines is a known phenomenon with CRS and ICANS. Thus, concomitant use with immunostimulatory agents can contribute the severity of CRS and immune effector cell-associated neurotoxicity syndrome.	No **Rationale**: CRS and serious neurologic adverse reactions including cerebral edema and ICANS are considered important identified risks.
Active tuberculosis (ZUMA-7).	To avoid confounding evaluation of safety.	No **Rationale**: 'Infections' is considered an important identified risk.
Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted (ZUMA-7).	To avoid confounding evaluation of safety.	No **Rationale**: The safety profile in these patients is not expected to differ from the known safety profile. Infections is considered an important identified risk.
Subjects with cardiac atrial or cardiac ventricular lymphoma involvement (ZUMA-7).	To avoid confounding evaluation of safety. Lymphoma with cardiac involvement may confound assessment of CRS which can result in cardiac symptoms.	No **Rationale**: CRS is considered an important identified risk.
History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater CHF, or other clinically significant cardiac disease within 12 months of enrolment (ZUMA-7).	To avoid confounding evaluation of safety.	No **Rationale**: Cardiotoxicity is frequently a sequela of CRS. As CRS is considered an important identified risk, physicians will be aware of the risk. Thus, use in this population will not be considered missing information.
Requirement for urgent therapy due to tumour mass effects, such as bowel obstruction or blood vessel compression (ZUMA-7).	To avoid confounding evaluation of safety.	No **Rationale**: The treatment can be postponed until the patient is medically controlled and stabilised.

Criterion	Reason for Exclusion	Considered to be Missing Information
History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed (ZUMA-7).	To avoid confounding evaluation of safety.	No **Rationale**: 'Infections' is considered an important identified risk and physicians are aware of this, so use in this population will not be considered missing information.
History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrolment (ZUMA-7).	To avoid confounding evaluation of safety. CRS is associated with cardiovascular symptoms like deep vein thrombosis or pulmonary embolism.	No **Rationale**: CRS is considered an important identified risk.

Abbreviations: allo-HSCT = allogeneic haematopoietic stem-cell transplant; CD19 = cluster of differentiation 19; CHF = congestive heart failure; CLL = chronic lymphocytic leukaemia; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HBV = hepatitis B virus; HCV = hepatitis C virus; ICANS = immune effector cell-associated neurotoxicity syndrome. IL2 = interleukin 2; IV = intravenous; MZL = marginal zone lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; qPCR = quantitative polymerase chain reaction; SmPC = summary of product characteristics; TFL = transformed follicular lymphoma.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Table SIV.2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	811 patients were exposed over the whole clinical trial programme.	ADRs with a frequency greater than 1 in 270 could be detected if there were no background incidence.
Due to prolonged exposure	Not applicable as this is a one-time treatment.	There is no risk of prolonged exposure.
Due to cumulative effects	Axicabtagene ciloleucel was given as a single dose to 811 subjects with very few undergoing retreatment.	There is no risk of cumulative effects.
Which have a long latency	As of 18 March 2021, the mean follow up time in ZUMA-1 (Phase 1 and Phase 2 Cohorts 1 and 2) was around 30 months; 43 out of the 108 patients that were treated in ZUMA-1 survived and were followed for more than 4 years; 8 of the 43 were followed for more than 5 years.	No ADRs with a long latency have been identified in the clinical trial programme.

Abbreviation: ADRs = adverse drug reactions

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs (ZUMA-1 Phase 1 and Phase 2 [Cohorts 1 and 2], ZUMA-5, and ZUMA-7)

Table SIV.3. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Elderly population	29% of subjects were ≥65 years of age.
Pediatric population	Not included in the clinical development program
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with AST/ALT levels greater than 2.5 times the upper limit of normal were not included in the clinical development program.
Patients with renal impairment	Patients with creatinine clearance (as estimated by Cockcroft Gault) of 60 mL/minute or less were not included in the clinical development program.
Patients with cardiac impairment (defined as ejection fraction of less than 50%)	Patients with cardiac ejection fraction of 50% or less or clinically significant (ECG) findings were not included in the clinical development program. Patients with pericardial effusions were not included in the clinical development program.
Patients with pulmonary impairment (defined as room air oxygen saturation of less than 92%)	Patients with room air oxygen saturations of less than 92% were excluded and were not included in the clinical development program.
Patients with autoimmune disorders	Patients with autoimmune disorder were not included in the clinical development program.
Population with relevant different ethnic origin	82.5% of patients were white, 4% were black, 4.6% were Asian, and 9% were of other races. 18% were Hispanic/Latino.
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1. Post-Authorization Exposure

SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed axicabtagene ciloleucel is estimated from distribution data and information received from business partners (e.g., Fosun-Kite in China). The distribution data are based on the date the final product was shipped to site. It should be noted that the use of distribution data for patient exposure calculations may overestimate patient exposure as not every patient will ultimately receive treatment.

SV.1.2. Exposure

Cumulative patient exposure to axicabtagene ciloleucel since first marketing approval in the US from 18 October 2017 to 22 August 2022 is estimated to be 8531 (Table SV.1).

Table SV.1. Cumulative Patient Exposure to Marketed Axicabtagene Ciloleucel

Geographic Area	Cumulative to 22 August 2022
US[a]	4911
EEA[b]	2382
Great Britain	647
Canada	161
Switzerland	90
Israel	126
Australia[c]	45
China	166
Japan	3
Total	**8531**

Abbreviations: EEA = European Economic Area; US = United States

a 391 of the 4911 patients in the US were administered axicabtagene ciloleucel for the indication of relapsed/refractory follicular lymphoma.

b European Economic Area: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein. Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

c Includes 2 patients from New Zealand treated in Australia.

PART II: MODULE SVI- ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no properties of axicabtagene ciloleucel that would make it attractive for misuse for illegal purposes. Furthermore, its manufacture and supply are patient-specific and the supply chain would not provide any opportunity for misuse for illegal purposes. Thus, this is not a safety concern.

SVI.2. Risks to Patients in Relation to Quality Characteristics, Storage and Distribution of the Product

In instances where the product cannot be manufactured or if the manufactured product is out of specification, the treating physician will be informed as early as possible by the Marketing Authorization Holder in accordance with section 11.5 of the good manufacturing practices so that appropriate measures for the safety of the patient can be taken.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

SVII.1.1. Risk(s) not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Recognizing that axicabtagene ciloleucel is classified as an advanced therapy medicinal product (ATMP), an overview of ATMP-specific considerations, including risks that are not considered important for inclusion in the list of safety concerns, is provided below.

Table SVII.1. Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Reason	List of Risks	Assessment
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Harvesting T cells (Leukapheresis)	Risks include decrease in white blood cells, hypocalcemia, blood loss, discomfort at venous site, local infection at venous site.
	Product quality characteristics and storage and distribution of the product	Retroviral vector lots are tested for sterility, adventitious agents including mycoplasma and infectious virus, RCR and viral potency prior to release for use in the axicabtagene ciloleucel manufacturing process. The product will be released after the completion of a validated sterility test as long as the bag is not compromised, contents should be free of bacterial contaminants. The product needs to be kept cryopreserved and stored in a vapor phase liquid nitrogen freezer. When stored in this condition the product has been shown to be stable for at least 1 year. The product is shipped in a validated liquid nitrogen vapor phase shipper. Product will remain stable throughout shipping duration. The product remains stable for up to 3 hours post-thaw; however, it is recommended that dosing is completed 30 minutes post thaw. All doses are stored and shipped frozen. Thawing occurs immediately prior to infusion for all subject treated to date. The freeze/thaw procedures have been shown to be safe. Autologous product, therefore, the subjects own leukapheresis material is being used to manufacture axicabtagene ciloleucel, therefore the risk of a transmissible disease is low. Manufacturing is conducted using single use components, therefore transmission from one lot to another is unlikely.
	Administrative procedures	Axicabtagene ciloleucel is administered intravenously and no AEs associated with IV administration, such as injection site reactions have been observed.
	Interaction between product and patient (excluding CRS)	The product comprises autologous T cells engineered ex-vivo, hence graft vs host or host vs graft reactions are neither expected nor observed with axicabtagene ciloleucel.

Reason	List of Risks	Assessment
	Persistence of the product in the patient	The retroviral vector construct is an integral part of the transduced T cell genome; however, the transduced T cells do not persist for an extended period within the patient following treatment with axicabtagene ciloleucel. Evidence to date showed that anti-CD19 CAR T cells peaked within14 days after infusion and decreased to near background levels within 3 months of the infusion but in most evaluable subjects (i.e., responders) a low level of anti-CD19 CAR T cells was measurable beyond the 3-month time point.
	Risk to health care professionals, care givers, offspring and other close contacts with the product (retroviral vector) or its components	Anti-CD19 transduced T cells, like natural T cells, are easily inactivated outside the host by inappropriate media, or exposure to low pH, higher temperatures (>50°C), pasteurization (60°C for 10h), and microwave. Cells present in axicabtagene ciloleucel are easily killed by lipid solvents, alcohol and disinfectants. Shedding Retroviral particles that have not entered and transduced the T cells are removed during the manufacturing process and have a short half-life under the cultured conditions {Merten 2004}. Therefore, it is considered that there is a negligible number of cell-free retroviral vector particles infused into the patient. In general, autologous T cells transduced with retroviral particles are not considered true excreta since they do not shed into the environment spontaneously {Schenk-Braat 2007}. The patients' own ex vivo modified T cells are not shed via saliva, urine, or feces into the environment, including wastewater. Any released retroviral vector construct cannot be transmitted by air and is not expected to be infectious. Patient Samples The patient samples such as blood, bone marrow or lymph node biopsy samples cannot contain free viral vector but will contain the patients engineered T cells which are not pathogenic, do not replicate or survive outside the patient. Axicabtagene ciloleucel contains negligibly low levels of free viral vector. Any potential remaining viral vector particles in the product would be inhibited/inactivated by the complement component of human serum after administration to the patient {Chira 2015, Welsh 1975, Welsh 1976}. Theoretically, if anti-CD19 CAR T cell membrane integrity is challenged and any gamma-retroviral vector that has not incorporated into the host chromatin is released into an aqueous environment, such as waste water, abundant with heterotrophic microorganisms and organic particles, it can be assumed that the gamma-retroviral vector PG13-CD19-H3 Vector, if present at all, will be either degraded by microorganisms or adsorbed onto particles quickly {World Health Organization (WHO) 1979}.

Reason	List of Risks	Assessment
		Accidental injection. In the event that the retroviral vector construct is transmitted through accidental injection, the immune system of medical personnel (or other individuals), would eliminate the cells via their immune system and not experience adverse effects beyond a normal immune reaction. Thus, no lasting negative consequences are expected in the event that an accidental injection occurs.
	Abnormal laboratory and metabolic findings	Twelve percent of the subjects in ZUMA-1 shifted to Grade 3 or higher ALT. Ten percent shifted to Grade 3 or higher AST. Two percent shifted to Grade 3 ALP. Seven percent shifted to Grade 3 or higher creatinine. Eight percent shifted to Grade 3 or higher total bilirubin. One percent shifted to Grade 3 sodium. In addition, in ZUMA-1 (Phase 1 and Phase 2 Cohorts 1 and 2), the events of ≥Grade 3 hypophosphatemia and ≥Grade 3 hyponatremia were reported in 20 (19%) and 12 (11%) subjects, respectively. A majority of these events were assessed by the Investigators as not related to axicabtagene ciloleucel. However, a review of the clinical safety data for these subjects, including all AEs reported for each subject, did not suggest any significant clinical outcome resulting from the events of ≥Grade 3 hypophosphatemia and/or ≥Grade 3 hyponatremia. Furthermore, plausible medical reasons were determined for the reported laboratory events of ≥Grade 3 hypophosphatemia and/or hyponatremia.
Other reasons for considering the risks not important	Conditioning chemotherapy	Bone marrow suppression is a recognized effect of conditioning chemotherapy with cyclophosphamide and fludarabine. CNS risks with fludarabine are recognized events as well. However, such effects are well-known to clinicians and risk minimization measures are part of standard clinical practice for these risks. The risks are therefore not classified as important as per the guidance on GVP Module V.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CNS = central nervous system; CRS = cytokine release syndrome; GVP = Good pharmacovigilance practices; IV = intravenous; RCR = replication-competent retrovirus.

SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

Table SVII.2. Important Identified Risks

Important Identified Risks	Risk-Benefit Impact
Serious neurologic adverse reactions including cerebral edema	In ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, 67% of the subjects experienced neurologic events overall. Serious neurologic events were observed in 27% of the subjects and 32% of the subjects experienced Grade 3 or higher neurologic events. The most common neurologic events of any grade were encephalopathy (37%), followed by tremor (31%), confusional state (27%), aphasia (18%), somnolence (17%), agitation (9%), memory impairment (7%), and mental status changes (6%). The most common Grade 3 or higher neurologic events were encephalopathy (23%), confusional state (9%), somnolence (8%), and aphasia (7%). No events of cerebral edema were reported in ZUMA-1 based on a cut-off date of 11 August 2018. However, one patient in the Expansion Safety Cohort of ZUMA-1 (Cohort 3, which enrolled patients after the completion of the pivotal portion ZUMA-1) experienced fatal cerebral edema attributed to axicabtagene ciloleucel. This serious neurologic adverse reaction has been included in the analysis for completeness. Other neurologic reactions have been reported less frequently in clinical trials and included dysphagia (5%), myelitis (0.2%), and quadriplegia (0.2%). Spinal cord edema was reported, in the context of neurologic toxicity in the post-marketing setting. HCPs should monitor patients for signs and symptoms of neurologic adverse reactions and manage the risks as advised in the risk minimization measures. Neurologic adverse reactions are serious and potentially life-threatening, and proper monitoring and treatment is required to minimize the risk and to ensure an acceptable risk-benefit balance.
CRS	In ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, 93% of the subjects experienced CRS. The most common CRS symptom of any grade was pyrexia (83%), followed by hypotension (44%), tachycardia (24%), hypoxia (23%), and chills (20%). Grade 3 or higher CRS occurred in 11% of subjects. HCPs should monitor patients for signs and symptoms of CRS and manage the risk as advised in the risk minimization measures. Proper monitoring and treatment are required to minimize the risk and to ensure an acceptable risk-benefit balance.
Cytopenias including aplastic anemia	In ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, 86%, 68%, and 62% experienced neutropenia, anemia and thrombocytopenia, respectively. Grade 3 or higher neutropenia (including febrile neutropenia), anemia and thrombocytopenia occurred in 80%, 45% and 40% of subjects respectively. Among the 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. There were no reported AEs of aplastic anemia. One SAE of bone marrow failure was reported which was assessed as not related to axicabtagene ciloleucel.

Important Identified Risks	Risk-Benefit Impact
	HCPs should monitor blood counts. Proper monitoring and treatment are required to minimize the risk, especially prolonged cytopenias, to ensure an acceptable risk-benefit balance.
Infections	In ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, 42% had any grade infection, 25% had Grade 3 infection, and 3% had Grade 4 infection. HCPs should monitor patients for signs and symptoms of infection, especially serious infection, before, during and after axicabtagene ciloleucel infusion and treat appropriately. Prophylactic antimicrobials should be administered according to standard institutional guidelines. Infections can be serious and proper monitoring and treatment is required to minimize the risk and to ensure an acceptable risk-benefit balance. In all patients, the pre-conditioning chemotherapy can cause neutropenia, which increases the risk of infections in patients who will later receive axicabtagene ciloleucel therapy. Patients with active infections or inflammatory disease should not be treated with axicabtagene ciloleucel therapy until these conditions have resolved.
Hypogammaglobulinemia	Hypogammaglobulinemia was reported in 15% in ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2. Thirty-three (31%) of 108 subjects received IVIg therapy at the time of the 24-month analysis. HCPs should monitor immunoglobulin levels after treatment with Yescarta and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement for recurrent infections. The safety of immunization with live viral vaccines during or following Yescarta treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Yescarta treatment, and until immune recovery following treatment with Yescarta.

Abbreviations: AE = adverse event; CSR = cytokine release syndrome; HCP = healthcare professional; IVIg = intravenous immunoglobulin; SAE = serious adverse event.

SVII.1.2.2. Important Potential Risks

Table SVII.3. Important Potential Risks

Important Potential Risks	Risk-Benefit Impact
Secondary malignancy	Secondary malignancy is classified as an important potential risk. There is a theoretical probability of insertional mutagenesis and malignant transformation in cases where RCRs are present in axicabtagene ciloleucel and continued viral replication could result in multiple integrations within the host-cell genome. In addition, the transgene could theoretically insert into a chromosomal region that activates an oncogene or disrupts a tumor suppressor gene leading to a transformation event. However, patients with B-cell NHL treated extensively with chemotherapy are known to be at risk for developing a secondary malignancy such as MDS. In the primary analysis of Phase 1 and Phase 2 Cohorts 1 and 2 of ZUMA-1, two subjects had developed MDS (1 each in Phase 1 and Phase 2), but retrospective analysis showed that both subjects had evidence of pre-existing chemotherapy-induced MDS at enrollment and neither AE was considered related to either the conditioning chemotherapy or the cell infusion.

Important Potential Risks	Risk-Benefit Impact
	Since the ZUMA-1 primary analysis of Phase 1 and Phase 2 Cohorts 1 and 2, one additional subject had an event of MDS 20 months after infusion that was determined to be not related to axicabtagene ciloleucel. The subject had previously received cyclophosphamide, doxorubicin, and bendamustine, which are all associated with development of MDS. Of the 3 subjects who developed MDS in ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, one subject had received retreatment of axicabtagene ciloleucel. Overall, no secondary malignancies related to axicabtagene ciloleucel have been reported. On the current evidence, a causal relationship between secondary malignancy and axicabtagene ciloleucel cannot be confirmed and does not impact the risk-benefit balance. This risk will be further evaluated in the post-marketing period.
Immunogenicity	Immunogenicity is classified as an important potential risk as there is a possibility that antibodies against the CAR will be developed. Three subjects (3%) in ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, had a positive result for antibodies to FMC63 (the parental murine antibody used for development of the anti-CD19 scFv region) at baseline. Anti-CD19 CAR T cell expansion and serum cytokine levels for these 3 subjects were comparable to cohort median values, suggesting that pre-existing antibodies against the scFv parental FMC63 murine antibody had no impact on CAR function in vivo. None of these 3 subjects had developed AEs of anaphylaxis, infusion-related reactions, or autoimmune disease. None of these subjects showed elevation of antibody titers post treatment. In addition, no subjects showed de novo induction of antibodies post treatment. On the confirmatory cell-based assay, 1 of 3 subjects tested positive at baseline. All other time points tested were negative. Antibodies can reduce efficacy and can cause safety issues such anaphylaxis, CRS, infusion reactions etc. that could impact the risk-benefit balance. This risk of autoimmunity will be further evaluated. On the current evidence, a causal relationship between autoimmunity and axicabtagene ciloleucel cannot be confirmed and does not impact the risk-benefit balance. This risk will be further evaluated in the other on-going axicabtagene ciloleucel studies as well as in the post-marketing period.

Important Potential Risks	Risk-Benefit Impact
RCR	The murine γ-retroviral vector PG13-CD19-H3 Vector used for transduction of subject-derived autologous T cells is replication-defective and to date, no RCR has been detected in Vector lots or in axicabtagene ciloleucel final product lots. The risk of RCR occurring in subjects treated with axicabtagene ciloleucel is low due to 1) the vector and packaging cell line used, and 2) rigorous testing prior to release of the final product. All Kite Pharma clinical studies of axicabtagene ciloleucel employ a robust monitoring plan to assess both the presence of RCR and the expansion and persistence of anti-CD19 CAR T cells in peripheral blood of treated subjects. Collection of these samples will allow, in the case of an observed transformation event, retrospective analysis to determine whether the transformation event was due to γ-retroviral insertion and whether this transformation resulted in increased proliferative capacity of a particular clone. The protocol-prescribed monitoring plan includes follow up assessments for RCR at months 3, 6, and 12 for all subjects. After the initial 12-month assessment samples are collected yearly for up to 15 years and held for possible analysis. Subjects who have a positive RCR test result at any time point are to be tested for RCR annually after for 15 years. Subjects who experience AEs that could be associated with the presence of RCR are to be tested for RCR as clinically indicated. Further, a qPCR assay will be utilized to monitor for secondary expansion of anti-CD19 CAR T cells at multiple time points during the first month and at Months 3, 6, 9, 12, 15, 18, and 24 after infusion. If secondary expansion is observed, insertional sites will be characterized in detail utilizing methods, such as linear amplification mediated PCR and also NGS to fully characterize the location and nature of the integration site. A total of 92 subjects in Phase 2 Cohorts 1 and 2 and a total of 7 subjects in Phase 1 were tested for RCR for up to 12 months. No subject had a positive RCR. Taken together, these analyses indicate that modern virus packaging cells, such as PG13, which are characterized by independent gag-pol and env components and pseudotyped viral particles, significantly reduce the risk of RCR generation. Based on the minimal expected risk for the occurrence RCR in subjects treated with axicabtagene ciloleucel, testing during the post authorization period will be event driven.
TLS	In ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, there were two cases of TLS previously reported, neither of which was considered related to axicabtagene ciloleucel.
Aggravation of GvHD	Aggravation of GvHD is classified as an important potential risk. There is a theoretical risk of aggravation of GvHD in patients who have previously undergone an allo-HSCT and then received donor derived engineered CAR T cells (from prior allo-HSCT donor) for their relapsed NHL. This theoretical risk is caused by engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host and having histocompatibility differences with the donor, resulting in donor T cell activation against either the recipient MHC antigens or minor histocompatibility antigens {Liu 2017}. Kochenderfer et al reported results from a study using donor derived leukocytes expressing a CD19 CAR to patients with persistent B-cell malignancies following allo-HSCT {Kochenderfer 2013}; updated data presented by {Brudno 2016b}. This

Important Potential Risks	Risk-Benefit Impact
	study demonstrated that of 20 patients with either B-ALL, CLL or NHL, no patients developed acute GvHD and 2 patients developed chronic GvHD after CAR T-cell infusion. Maude et al {Maude 2014}, Lee et al {Lee 2015}, and Park et al {Park 2018} reported on the administration of recipient-derived CAR T cells for patients with relapsed or refractory ALL or NHL and observed no GvHD following CD 19 CAR T infusion {Smith 2018}. It is important to note that patients with a history of allogeneic stem cell transplantation were excluded from the ZUMA-1 study. In ZUMA-1 Phase 1 and Phase 2, Cohorts 1, and 2, no subjects developed aggravation of GvHD or GvHD. Based on the current evidence, a causal relationship between aggravation of GvHD and axicabtagene ciloleucel cannot be confirmed and does not impact the risk-benefit balance.
Transmission of infectious agents via product	Recipient/patient: Axicabtagene ciloleucel is an autologous cell-based product. With the stringent manufacturing processes associated with axicabtagene ciloleucel, the risk for transmission of an infectious agent is negligible and does not impact the risk-benefit balance. HCPs/manufacturing personnel: Axicabtagene ciloleucel can be potentially infectious (e.g. HIV, HBV, HCV). HCPs should take precautionary measures for handling and disposal of the drug product. Gloves and eye protection are required personal protective equipment for the administration of Yescarta. Disposal of unused product, waste material, all material that has been in contact with Yescarta (solid and liquid) and decontamination of surfaces/cleaning spills related to Yescarta should follow local biosafety guidelines. Awareness of patient infectious status (testing is recommended prior to leukapheresis), adopting Good Manufacturing Practices, and following local biosafety guidelines including the use of personal protective equipment (gloves, eyewear) should ensure no impact on the risk-benefit balance.
Decrease in viability of the product due to inappropriate preparation of infusion	In ZUMA-1 there were no case reports suggestive of irregularities in preparation or administration of Yescarta. Awareness of appropriate preparation, handling and administration should minimize impact on the benefit risk balance.

Abbreviations: AEs = adverse events; ALL = acute lymphoblastic leukemia; allo-HSCT = allogeneic stem-cell transplant; B-ALL = B-cell acute lymphoblastic leukemia; CAR = chimeric antigen receptor; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CLL = chronic lymphocytic leukemia; CRS = cytokine release syndrome; GvHD = graft vs host disease; HBV = hepatitis B virus; HCPs = healthcare professionals; HCV = hepatitis C virus; MDS = myelodysplastic syndrome; MHC = major histocompatibility complex; NGS = next generation sequencing; NHL = non-Hodgkin lymphoma; qPCR = quantitative polymerase chain reaction; RCR = replication-competent retrovirus; scFv = single chain variable region fragment; TLS = tumor lysis syndrome.

SVII.1.2.3. Missing Information

Table SVII.4. Missing Information

Missing Information	Risk-Benefit Impact
Use in pregnancy and lactation	Pregnant and lactating women were excluded from enrollment in the clinical development program and thus the risks of use in this population cannot be defined. It is not known if Yescarta has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, Yescarta is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the fetus. Pregnancy after Yescarta therapy should be discussed with the treating physician. The pregnancy status of women of childbearing potential must be verified before starting Yescarta treatment. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Yescarta.
Use in non-Caucasian patient population	Most of the subjects enrolled in the clinical development program were Caucasians (92% in Phase 1 and Phase 2 Cohorts 1 and 2) thus the risks of use in non-Caucasian patient population cannot be defined. The safety profile for this population will be derived from routine and additional pharmacovigilance activities.
New occurrence or exacerbation of an autoimmune disorder	Subjects with autoimmune disorders were excluded from enrollment in the clinical development program and therefore the safety of use of axicabtagene ciloleucel in this population is considered missing information. A new occurrence or exacerbation of preexisting autoimmune disorder is a theoretical risk. Thus, the risks of use in this population cannot be defined. The safety profile for this population will be derived from routine and additional pharmacovigilance activities.
Long-term safety	Long-term safety of axicabtagene ciloleucel is not yet known. The safety profile of long-term effects will be derived from routine and additional pharmacovigilance activities including a PASS (registry).

Abbreviations: PASS = postauthorization safety study.

SVII.2. New Safety Concerns and Reclassification with a Submission of an updated RMP

Not applicable

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

Table SVII.5. Important Identified Risk: Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS

Important Identified Risk:	**Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS**
Potential mechanisms	Increase in the level of inflammatory cytokines (e.g., IL1, IL6 and GM-CSF) after CAR T cell administration may lead to macrophage and endothelial activation and blood-brain barrier disruption {Siegler 2020}.
Evidence source and strength of evidence	Serious neurologic adverse reactions were reported in clinical trials, post-marketing surveillance, and in patient treated with other CAR T therapies.
Characterisation of the risk	**Clinical trials** **ZUMA-1 and ZUMA-7 (as of 18 March 2021)** **Incidence of Serious Treatment-emergent Neurologic Events by PT and Worst Grade (Safety Analysis Set)**

	Standard of Care Therapy		**Axicabtagene Ciloleucel**					
	ZUMA-7 (N = 168)		**ZUMA-7 (N = 170)**		**ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)**		**Overall (N = 278)**	
MedDRA PT, n (%)	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**
Subjects with any serious treatment-emergent neurologic events	1 (1)	0 (0)	34 (20)	26 (15)	27 (25)	25 (23)	61 (22)	51 (18)
Encephalopathy	1 (1)	0 (0)	17 (10)	15 (9)	20 (19)	20 (19)	37 (13)	35 (13)
Aphasia	0 (0)	0 (0)	9 (5)	8 (5)	4 (4)	4 (4)	13 (5)	12 (4)
Confusional state	0 (0)	0 (0)	6 (4)	4 (2)	5 (5)	4 (4)	11 (4)	8 (3)
Somnolence	0 (0)	0 (0)	5 (3)	3 (2)	3 (3)	3 (3)	8 (3)	6 (2)
Agitation	0 (0)	0 (0)	2 (1)	2 (1)	3 (3)	3 (3)	5 (2)	5 (2)
Tremor	0 (0)	0 (0)	5 (3)	1 (1)	0 (0)	0 (0)	5 (2)	1 (0)
Delirium	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)	2 (2)	3 (1)	3 (1)
Depressed level of consciousness	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	2 (1)	1 (0)
Dysarthria	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	2 (1)	0 (0)
Hypoaesthesia	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)	0 (0)	2 (1)	2 (1)
Lethargy	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	2 (1)	0 (0)

Important Identified Risk: **Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS**

Memory impairment	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	2 (1)	1 (0)
Mental status changes	0 (0)	0 (0)	2 (1)	1 (1)	0 (0)	0 (0)	2 (1)	1 (0)
Seizure	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	2 (1)	1 (0)
Ataxia	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Bradyphrenia	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Cognitive disorder	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Leukoencephalopathy	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (0)
Paraesthesia	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	1 (0)	1 (0)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion date or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column .
Preferred terms are sorted in descending order of the number of subjects with Any Grade in Overall column.
Neurologic events are identified using a modified search strategy based on Topp 2015.
Data Source: ADSL, ADAE Programme Name: t_aewg_neur Output Generated: 20210730T16:06

Incidence of Treatment-related Serious Treatment-emergent Neurologic Events by PT and Worst Grade (Safety Analysis Set)

	Standard of Care Therapy		**Axicabtagene Ciloleucel**					
	ZUMA-7 (N = 168)		**ZUMA-7 (N = 170)**		**ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)**		**Overall (N = 278)**	
MedDRA PT, n (%)	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**
Subjects with any treatment -related serious treatment-emergent neurologic events	0 (0)	0 (0)	32 (19)	25 (15)	26 (24)	24 (22)	58 (21)	49 (18)
Encephalopathy	0 (0)	0 (0)	17 (10)	15 (9)	20 (19)	20 (19)	37 (13)	35 (13)
Aphasia	0 (0)	0 (0)	9 (5)	8 (5)	4 (4)	4 (4)	13 (5)	12 (4)
Confusional state	0 (0)	0 (0)	5 (3)	3 (2)	5 (5)	4 (4)	10 (4)	7 (3)
Somnolence	0 (0)	0 (0)	5 (3)	3 (2)	3 (3)	3 (3)	8 (3)	6 (2)
Tremor	0 (0)	0 (0)	5 (3)	1 (1)	0 (0)	0 (0)	5 (2)	1 (0)

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS

Agitation	0 (0)	0 (0)	2 (1)	2 (1)	2 (2)	2 (2)	4 (1)	4 (1)
Delirium	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)	2 (2)	3 (1)	3 (1)
Depressed level of consciousness	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	2 (1)	1 (0)
Hypoaesthesia	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)	0 (0)	2 (1)	2 (1)
Lethargy	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	2 (1)	0 (0)
Memory impairment	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	2 (1)	1 (0)
Mental status changes	0 (0)	0 (0)	2 (1)	1 (1)	0 (0)	0 (0)	2 (1)	1 (0)
Ataxia	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Bradyphrenia	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Cognitive disorder	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Dysarthria	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Leukoencephalopathy	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (0)
Paraesthesia	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	1 (0)	1 (0)
Seizure	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (0)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; ASCT = autologous stem cell transplantation; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion date or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
For subjects treated with axicabtagene ciloleucel, treatment related TEAEs include TEAEs that are related to axicabtagene ciloleucel. For standard of care therapy arm in ZUMA-7, treatment-related TEAEs include TEAEs that are related to salvage chemotherapy, total body irradiation (given as part of conditioning for ASCT), high-dose therapy, and ASCT.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column.
Preferred terms are sorted in descending order of the number of subjects with Any Grade in the Overall column.
Neurologic events are identified using a modified search strategy based on Topp 2015.
Data Source: ADSL, ADAE Programme Name: t_aewg_neur Output Generated: 20210730T16:06

ZUMA-5 (as of 14 September 2020)

In ZUMA-5, 59% of the subjects had neurological events. The most common neurologic events of any grade were tremor (30%), confusional state (24%), encephalopathy (20%), aphasia (14%), somnolence (11%), and agitation (9%). The most common Grade 3 or higher neurologic events were encephalopathy (9%), confusional state (5%), aphasia (4%), somnolence (3%), and delirium (3%). Overall, 19% of subjects had grade 3 or higher neurologic event (17% subjects had Grade 3 events, 2% had Grade 4 events and no subject had Grade 5 event). Among the 87 subjects who experienced neurologic events, the median time to onset of first neurologic events was 7 days (range: 1 to 177 days) after infusion of axicabtagene ciloleucel. Neurologic events reported in ≥5% of subjects are presented below.

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS

Neurologic AEs Occurring in ≥5% of Subjects in ZUMA-5 (Safety Analysis Set; N = 148)

MedDRA Preferred Term Worst CTCAE Grade	FL (N = 124) n (%)	MZL (N = 24) n (%)	Overall (N = 148) n (%)
Subjects with any treatment-emergent neurologic event	**70 (56)**	**17 (71)**	**87 (59)**
Grade 1	30 (24)	1 (4)	31 (21)
Grade 2	21 (17)	7 (29)	28 (19)
Grade 3	17 (14)	8 (33)	25 (17)
Grade 4	2 (2)	1 (4)	3 (2)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	19 (15)	9 (38)	28 (19)
Tremor	**36 (29)**	**9 (38)**	**45 (30)**
Grade 1	31 (25)	6 (25)	37 (25)
Grade 2	4 (3)	3 (13)	7 (5)
Grade 3	1 (1)	0 (0)	1 (1)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	1 (1)	0 (0)	1 (1)
Confusional State	**28 (23)**	**7 (29)**	**35 (24)**
Grade 1	11 (9)	3 (13)	14 (9)
Grade 2	11 (9)	2 (8)	13 (9)
Grade 3	6 (5)	2 (8)	8 (5)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	6 (5)	2 (8)	8 (5)
Encephalopathy	**24 (19)**	**6 (25)**	**30 (20)**
Grade 1	7 (6)	0 (0)	7 (5)
Grade 2	7 (6)	3 (13)	10 (7)
Grade 3	10 (8)	3 (13)	13 (9)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	10 (8)	3 (13)	13 (9)
Aphasia	**16 (13)**	**4 (17)**	**20 (14)**
Grade 1	6 (5)	1 (4)	7 (5)
Grade 2	7 (6)	0 (0)	7 (5)
Grade 3	3 (2)	3 (13)	6 (4)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS			
	Grade ≥3	3 (2)	3 (13)	6 (4)
	Somnolence	**9 (7)**	**7 (29)**	**16 (11)**
	Grade 1	4 (3)	0 (0)	4 (3)
	Grade 2	3 (2)	5 (21)	8 (5)
	Grade 3	2 (2)	2 (8)	4 (3)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	2 (2)	2 (8)	4 (3)
	Agitation	**10 (8)**	**3 (13)**	**13 (9)**
	Grade 1	5 (4)	1 (4)	6 (4)
	Grade 2	3 (2)	1 (4)	4 (3)
	Grade 3	2 (2)	1 (4)	3 (2)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	2 (2)	1 (4)	3 (2)
	Disturbance In Attention	**7 (6)**	**0 (0)**	**7 (5)**
	Grade 1	7 (6)	0 (0)	7 (5)
	Grade 2	0 (0)	0 (0)	0 (0)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	0 (0)
	Dysarthria	**6 (5)**	**1 (4)**	**7 (5)**
	Grade 1	3 (2)	1 (4)	4 (3)
	Grade 2	2 (2)	0 (0)	2 (1)
	Grade 3	1 (1)	0 (0)	1 (1)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	1 (1)	0 (0)	1 (1)
	Paraesthesia	**6 (5)**	**1 (4)**	**7 (5)**
	Grade 1	5 (4)	0 (0)	5 (3)
	Grade 2	1 (1)	1 (4)	2 (1)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	0 (0)
	Data cutoff date: 14 September 2020.			

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS

Abbreviation: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; FL = follicular lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma; N = subjects treated.
Treatment-emergent adverse events include all AEs with onset on or after axicabtagene ciloleucel infusion date.
Multiple incidences of the same AE in one subject are counted once at the worst grade for this subject.
Note 1: Preferred terms are sorted in descending order of frequency count in the overall column.
Note 2: AEs are coded using MedDRA version 23.0 and graded per CTCAE version 4.03.
Note 3: Neurologic events are identified based on modified Topp et al 2015.
Data Source: ADSL, ADAE Program Name: t_teae.sas Output Generated: 20210405T14:22

Serious related neurologic adverse reactions were reported in ZUMA-5. Except for encephalopathy (11 [7%]), and confusional state (7 [5%]), all the remaining serious related neurologic events occurred in ≤ 5% of the subjects. No events of cerebral edema were reported in ZUMA-5 based on a cut-off date of 14 September 2020.

Incidence of Serious Related Neurologic Events in ZUMA-5 (Safety Analysis Set; N = 148)

MedDRA Preferred Term Worst CTCAE Grade	FL (N = 124) n (%)	MZL (N = 24) n (%)	Overall (N = 148) n (%)
Subjects with any serious axicabtagene ciloleucel-related treatment-emergent neurologic event	**19 (15)**	**7 (29)**	**26 (18)**
Grade 1	2 (2)	0 (0)	2 (1)
Grade 2	3 (2)	2 (8)	5 (3)
Grade 3	12 (10)	4 (17)	16 (11)
Grade 4	2 (2)	1 (4)	3 (2)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	14 (11)	5 (21)	19 (13)
Encephalopathy	**8 (6)**	**3 (13)**	**11 (7)**
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	0 (0)	1 (4)	1 (1)
Grade 3	8 (6)	2 (8)	10 (7)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	8 (6)	2 (8)	10 (7)
Confusional State	**7 (6)**	**0 (0)**	**7 (5)**
Grade 1	2 (2)	0 (0)	2 (1)
Grade 2	1 (1)	0 (0)	1 (1)
Grade 3	4 (3)	0 (0)	4 (3)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS			
	Grade ≥3	4 (3)	0 (0)	4 (3)
	Somnolence	**2 (2)**	**3 (13)**	**5 (3)**
	Grade 1	0 (0)	0 (0)	0 (0)
	Grade 2	0 (0)	1 (4)	1 (1)
	Grade 3	2 (2)	2 (8)	4 (3)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	2 (2)	2 (8)	4 (3)
	Aphasia	**2 (2)**	**1 (4)**	**3 (2)**
	Grade 1	0 (0)	0 (0)	0 (0)
	Grade 2	2 (2)	0 (0)	2 (1)
	Grade 3	0 (0)	1 (4)	1 (1)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	1 (4)	1 (1)
	Agitation	**2 (2)**	**0 (0)**	**2 (1)**
	Grade 1	0 (0)	0 (0)	0 (0)
	Grade 2	0 (0)	0 (0)	0 (0)
	Grade 3	2 (2)	0 (0)	2 (1)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	2 (2)	0 (0)	2 (1)
	Immune Effector Cell-Associated Neurotoxicity Syndrome	**2 (2)**	**0 (0)**	**2 (1)**
	Grade 1	0 (0)	0 (0)	0 (0)
	Grade 2	1 (1)	0 (0)	1 (1)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	1 (1)	0 (0)	1 (1)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	1 (1)	0 (0)	1 (1)
	Tremor	**1 (1)**	**1 (4)**	**2 (1)**
	Grade 1	0 (0)	0 (0)	0 (0)
	Grade 2	1 (1)	1 (4)	2 (1)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	0 (0)
	Mental Status Changes	**1 (1)**	**0 (0)**	**1 (1)**

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS		
Grade 1	1 (1)	0 (0)	1 (1)
Grade 2	0 (0)	0 (0)	0 (0)
Grade 3	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	0 (0)	0 (0)	0 (0)
Neurotoxicity	**1 (1)**	**0 (0)**	**1 (1)**
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	0 (0)	0 (0)	0 (0)
Grade 3	0 (0)	0 (0)	0 (0)
Grade 4	1 (1)	0 (0)	1 (1)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	1 (1)	0 (0)	1 (1)
Seizure	**0 (0)**	**1 (4)**	**1 (1)**
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	0 (0)	0 (0)	0 (0)
Grade 3	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	1 (4)	1 (1)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	0 (0)	1 (4)	1 (1)
Speech Disorder	**1 (1)**	**0 (0)**	**1 (1)**
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	1 (1)	0 (0)	1 (1)
Grade 3	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	0 (0)	0 (0)	0 (0)

Data cutoff date: 14 Sep 2020.
Abbreviation: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; FL = follicular lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma; N = subjects treated.
Treatment-emergent adverse events include all AEs with onset on or after axicabtagene ciloleucel infusion date.
Multiple incidences of the same AE in one subject are counted once at the worst grade for this subject.
Note 1: Preferred terms are sorted in descending order of frequency count in the overall column.
Note 2: AEs are coded using MedDRA version 23.0 and graded per CTCAE version 4.03.
Note 3: Neurologic events are identified based on modified Topp et al 2015.
Data Source: ADSL, ADAE Program Name: t_teae.sas Output Generated: 20210405T14:22

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS

KT-EU-471-0117 (PASS) (as of 01 March 2022)

The effectiveness and safety analysis set included 379 patients. Neurotoxicity was observed in 149 patients (40.3% of those with available information); 36 patients (28.3% of those with available information) experienced Grade 1 as their maximum grade; 34 patients (26.8%) had Grade 2 as their maximum grade; 42 (33.1%) patients had Grade 3 as their maximum grade; 13 (10.2%) had Grade 4 as their maximum grade; and two (1.6%) had Grade 5 neurotoxicity. The grade of neurotoxicity was missing for 22 patients. All neurotoxicity events occurred within 100 days of infusion, and the median time to onset was 8 days (with range 2 to 99 days). The most common symptoms reported were an altered mental status and tremors. The 12-month cumulative incidence for neurotoxicity was 40% (95% CI: 35 to 45%), and the incidence rate per person-year was 0.74 (95% CI: 0.63 to 0.86).

Post-marketing

Serious Neurologic Adverse Reactions including Cerebral Oedema Reported in the Post marketing Setting (Cumulative to 22 August 2022)

Category		Value
Total number of cases		1753
Case reporting rate		21% (/1753/8531)
Total number of events		2347
	Serious	1931
	Non-Serious	416
Event outcomes		
	Fatal	100
	Lost to follow-up	0
	Not Resolved	1185
	Resolved	978
	Resolved with Sequelae	18
	Resolving	131
	Unknown	402

Abbreviations: PT = preferred term

The most common adverse events reported were neurotoxicity (n=832), ICANS (n=716), encephalopathy (n=128) and tremor (n=72).

Reversibility

The majority of neurologic adverse reactions resolved.

Impact on quality of life

AEs such as encephalopathy, aphasia, delirium, dysphasia, confusion, somnolence, tremors, seizures, agitation and hallucinations have significant impact on the patient quality of life; they can cause severe distress, impair ability to read, write or communicate intelligibly and, if serious, can be life-threatening requiring urgent intervention and mechanical ventilation. Severe cases, including cerebral edema, may lead to death.

Risk groups or risk factors	**Patient factors** Younger patients (<65) and male patients had a lower incidence of neurologic events. **Dose-related** A higher dose of CAR T cells and/or potency of the cells was associated with a higher rate of neurologic events.

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema and ICANS
Preventability	Yescarta must be administered in a qualified treatment center by a physician with experience in the treatment of hematological malignancies and trained for administration and management of patients treated with the medicinal product. It is recommended that patients are monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS. For the first 7 days the patient can be hospitalized at the physician's discretion. After the first 7 days following the infusion, the patient is to be monitored at the physician's discretion. Patients must 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 neurological adverse reactions occur. Vital signs and organ function 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/ICANS. Non-sedating, anti-seizure medicines are to 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. The possibility of PML should be considered in immunosuppressed patients with new onset or worsening neurological symptoms and appropriate diagnostic evaluations should be performed. 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.
Impact on the benefit-risk balance of the product	Routine and additional pharmacovigilance activities will further characterize the risk of serious neurologic adverse reactions with respect to number of reports, seriousness, outcome, and risk factors and that the data is consistent with the information already known for this risk. The safe use of axicabtagene ciloleucel will be disseminated through routine risk minimization measures and supported by aRMMs such as HCP educational material, PAC, and Controlled distribution program (see Annex 6). The risk will be mitigated by these measures such that the benefit risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: AE = adverse event; aRMMs = additional risk minimization measures; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CRS = cytokine release syndrome; EU = European Union; GM-CSF = granulocyte-macrophage colony-stimulating factor; HCP = healthcare professional; ICANS = immune effector cell-associated neurotoxicity syndrome; IL1 = interleukin 1; IL6 = interleukin 6; PAC = patient alert card; PASS = postauthorization safety study; PML = progressive multifocal leukoencephalopathy; SmPC = summary of product characteristics.

Table SVII.6. Important Identified Risk: CRS

Important Identified Risk:	CRS
Potential mechanisms	The cytokines implicated in CRS may be directly produced by the infused CAR T-cells, as well as other immune cells such as macrophages that might produce large amounts of cytokines in response to cytokines produced by the infused CAR T cells. In contrast to neurologic AEs, Grade 3+ CRS was more robustly associated with a broad array of cytokine that can be produced by activated myeloid and T cells rather than with the CAR T cell levels post-treatment. A wide variety of cytokines and chemokines including IL6, interferon-γ, TNFα, IL2, IL2Rα, IL1Rα, IL8, and IL10 are elevated in the serum of patients experiencing fever, tachycardia, hypotension, and other toxicities after CAR T cell infusions {Brudno 2016a}. The associations of CRS with several of these cytokines and chemokines is likely related to their known functional activities. IL6 and TNFα mediate vascular permeability, hypotension, fever, and tissue damage {Sprague 2009}; chemokines such as IL8 trigger mobilization and redistribution of activated immune cells throughout the body {Griffith 2014}; and IL1Rα and IL2Rα are indicative of macrophage and general immune activation {Ravelli 2012}. Levels of these cytokines decreased by 1 month post CAR T cell infusion, a finding consistent with the timing and reversibility of CRS.
Evidence source and strength of evidence	CRS was reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Characterisation of the risk	**Clinical trials** **ZUMA-1 and ZUMA-7 (as of 18 March 2021)**

Incidence of CRS Treatment-emergent AEs by PT and Worst Grade (Safety Analysis Set)

	Axicabtagene Ciloleucel					
	ZUMA-7 (N = 170)		ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)		Overall (N = 278)	
MedDRA PT, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any treatment-emergent CRS[a], n (%)	157 (92)	11 (6)	100 (93)	12 (11)	257 (92)	23 (8)
The ten most frequent CRS symptom by PT[b], n (%)						
Pyrexia	155 (99)	14 (9)	83 (83)	12 (12)	238 (93)	26 (10)
Hypotension	68 (43)	18 (11)	44 (44)	10 (10)	112 (44)	28 (11)
Chills	38 (24)	0 (0)	20 (20)	0 (0)	58 (23)	0 (0)
Sinus tachycardia	49 (31)	3 (2)	8 (8)	0 (0)	57 (22)	3 (1)
Hypoxia	31 (20)	13 (8)	22 (22)	9 (9)	53 (21)	22 (9)
Tachycardia	15 (10)	1 (1)	24 (24)	1 (1)	39 (15)	2 (1)
Headache	32 (20)	2 (1)	5 (5)	0 (0)	37 (14)	2 (1)
Fatigue	21 (13)	4 (3)	5 (5)	0 (0)	26 (10)	4 (2)
Nausea	17 (11)	2 (1)	1 (1)	0 (0)	18 (7)	2 (1)
Diarrhoea	14 (9)	1 (1)	3 (3)	1 (1)	17 (7)	2 (1)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; CRS = cytokine release syndrome; CTCAE = Common

Important Identified Risk:	CRS

Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = treatment-emergent adverse event.
Notes: A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion. TEAEs that occurred during the retreatment period are excluded. Preferred terms are sorted in descending order of the number of subjects with Any Grade in the Overall column.
a. Overall CRS is graded according to a modified grading system proposed by Lee and colleagues (Lee et al, 2014). Percentages are calculated using the total number of subjects (N) in each column.
b. Individual CRS symptoms are graded per CTCAE 4.03. Percentages are calculated using the total number of subjects with any treatment emergent CRS.
Data Source: ADSL, ADAE Programme Name: t_aewg_crs Output Generated: 20210730T16:05

Incidence of the ten most common serious CRS Treatment-emergent AEs by PT and Worst Grade (Safety Analysis Set)

	Axicabtagene Ciloleucel					
	ZUMA-7 (N = 170)		ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)		Overall (N = 278)	
MedDRA PT, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Pyrexia	20 (12)	0 (0)	1 (1)	0 (0)	21 (8)	0 (0)
Hypotension	15 (9)	7 (4)	1 (1)	1 (1)	16 (6)	8 (3)
Hypoxia	3 (2)	1 (1)	3 (3)	3 (3)	6 (2)	4 (1)
Atrial fibrillation	2 (1)	2 (1)	2 (2)	2 (2)	4 (1)	4 (1)
Acute kidney injury	1 (1)	0 (0)	2 (2)	2 (2)	3 (1)	2 (1)
Atrial flutter	0 (0)	0 (0)	2 (2)	1 (1)	2 (1)	1 (0)
Dyspnoea	2 (1)	2 (1)	0 (0)	0 (0)	2 (1)	2 (1)
Ejection fraction decreased	0 (0)	0 (0)	2 (2)	1 (1)	2 (1)	1 (0)
Headache	2 (1)	1 (1)	0 (0)	0 (0)	2 (1)	1 (0)
Sinus tachycardia	2 (1)	1 (1)	0 (0)	0 (0)	2 (1)	1 (0)

Data cut-off date is 18 Mar 2021.
Abbreviations: AE = adverse event; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion date. TEAEs that occurred during the retreatment period are excluded.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column.
Preferred terms are sorted in descending order of the number of subjects with Any Grade in Overall column.
Data Source: ADSL, ADAE Programme Name: t_aewg_crs Output Generated: 20210730T16:05

ZUMA-5 (as of 14 September 2020)

In ZUMA-5, CRS occurred in 82% of the 148 treated subjects. The most common CRS symptom of any grade were pyrexia (96%), hypotension (42%), and 26% each for chills, hypoxia, and sinus tachycardia. Grade 3 or higher CRS occurred in 7% of subjects. The MZL subset included a higher percentage of subjects with Grade 3 or higher CRS (8%

Important Identified Risk:	CRS

versus 6%) compared to FL. The median time to onset was 4 days (range 1 to 15 days). No subject in ZUMA-5 had new onset of CRS that started >15 days after the axicabtagene ciloleucel infusion.

The Grade 3 or higher cardiac arhythmias included sinus tachycardia, atrial fibrillation, and electrocardiogram QT prolonged. The observed cardiac events were cardiac failure, pulmonary edema, and ejection fraction decreased. All cardiac events resolved. The subject incidence of CRS observed in ≥5% of subjects in ZUMA-5, are presented below.

Subject incidence of CRS in ≥5% of Subjects in ZUMA-5

MedDRA Preferred Term Worst CTCAE Grade	FL (N = 124) n (%)	MZL (N = 24) n (%)	Overall (N = 148) n (%)
Subjects with any treatment-emergent CRS[a]	**97 (78)**	**24 (100)**	**121 (82)**
Grade 1	43 (35)	6 (25)	49 (33)
Grade 2	46 (37)	16 (67)	62 (42)
Grade 3	7 (6)	1 (4)	8 (5)
Grade 4	0 (0)	1 (4)	1 (1)
Grade 5	1 (1)	0 (0)	1 (1)
Grade ≥3	8 (6)	2 (8)	10 (7)
CRS symptoms by preferred term[b]			
Pyrexia	**94 (97)**	**22 (92)**	**116 (96)**
Grade 1	33 (34)	5 (21)	38 (31)
Grade 2	55 (57)	15 (63)	70 (58)
Grade 3	4 (4)	2 (8)	6 (5)
Grade 4	2 (2)	0 (0)	2 (2)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	6 (6)	2 (8)	8 (7)
Hypotension	**39 (40)**	**12 (50)**	**51 (42)**
Grade 1	7 (7)	2 (8)	9 (7)
Grade 2	29 (30)	8 (33)	37 (31)
Grade 3	2 (2)	2 (8)	4 (3)
Grade 4	1 (1)	0 (0)	1 (1)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	3 (3)	2 (8)	5 (4)
Chills	**25 (26)**	**7 (29)**	**32 (26)**
Grade 1	22 (23)	4 (17)	26 (21)
Grade 2	3 (3)	3 (13)	6 (5)
Grade 3	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	0 (0)	0 (0)	0 (0)
Hypoxia	**23 (24)**	**8 (33)**	**31 (26)**
Grade 1	1 (1)	0 (0)	1 (1)
Grade 2	16 (16)	4 (17)	20 (17)
Grade 3	5 (5)	3 (13)	8 (7)
Grade 4	1 (1)	1 (4)	2 (2)

Important Identified Risk:	CRS			
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	6 (6)	4 (17)	10 (8)
	Sinus Tachycardia	**25 (26)**	**6 (25)**	**31 (26)**
	Grade 1	20 (21)	3 (13)	23 (19)
	Grade 2	3 (3)	3 (13)	6 (5)
	Grade 3	2 (2)	0 (0)	2 (2)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	2 (2)	0 (0)	2 (2)
	Headache	**19 (20)**	**1 (4)**	**20 (17)**
	Grade 1	14 (14)	1 (4)	15 (12)
	Grade 2	5 (5)	0 (0)	5 (4)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	0 (0)
	Tachycardia	**9 (9)**	**3 (13)**	**12 (10)**
	Grade 1	7 (7)	2 (8)	9 (7)
	Grade 2	2 (2)	1 (4)	3 (2)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	0 (0)
	Nausea	**7 (7)**	**2 (8)**	**9 (7)**
	Grade 1	2 (2)	2 (8)	4 (3)
	Grade 2	5 (5)	0 (0)	5 (4)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	0 (0)
	Vomiting	**7 (7)**	**2 (8)**	**9 (7)**
	Grade 1	5 (5)	2 (8)	7 (6)
	Grade 2	2 (2)	0 (0)	2 (2)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	0 (0)
	Fatigue	**6 (6)**	**2 (8)**	**8 (7)**
	Grade 1	3 (3)	1 (4)	4 (3)
	Grade 2	3 (3)	1 (4)	4 (3)
	Grade 3	0 (0)	0 (0)	0 (0)
	Grade 4	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	0 (0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	0 (0)

Important Identified Risk: **CRS**

Malaise	**6 (6)**	**1 (4)**	**7 (6)**
Grade 1	6 (6)	0 (0)	6 (5)
Grade 2	0 (0)	1 (4)	1 (1)
Grade 3	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)
Grade ≥3	0 (0)	0 (0)	0 (0)

Data cutoff date: 14 Septempber 2020.
Abbreviation: AE = adverse event; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; FL = follicular lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma.
Treatment-emergent adverse events include all AEs with onset on or after axicabtagene ciloleucel infusion date.
Multiple incidences of the same AE in one subject are counted once at the worst grade.
Note: Preferred terms are sorted in descending order of frequency count in the overall column.
a. CRS events are graded according to a modification of the criteria of Lee and colleagues (Lee et al, 2014). Percentages are calculated using the total number of subjects in the analysis set as the denominator.
b. Individual CRS symptoms are coded using MedDRA version 23.0 and graded per CTCAE version 4.03. Percentages are calculated using the number of subjects with any TE CRS of any grade.Data Source: ADSL, ADAE Program Name: t_teaecrs.sas Output Generated: 20210405T14:23

KT-EU-471-0117 (PASS) (as of 01 March 2022)

CRS was observed in 312 patients (84.8% of those with available information). The median time to onset was 4 days (with range 1 to 32 days). Information on the grade of CRS was available for 308 of the 312 patients in whom CRS was observed. Grade 1 or 2 CRS (majority American Society for Transplantation and Cellular Therapy grading) was reported for 135 + 140 = 275 (43.8% + 45.5% = 89.3% with available information) patients, and Grade 3 CRS was reported for 32 (10.4%) patients. No Grade 4 cases were reported, and one patient (0.3%) had Grade 5 CRS. The 12-month cumulative incidence for CRS was 84% (95% CI: 79 to 87%). The incidence rate per person-year was 5.63 (95% CI: 5.02 to 6.27).

Post-marketing

CRS Reported in the Post marketing Setting (Cumulative to 22 August 2022)

Category		**Value**
Total number of cases		2252
Case reporting rate		26% (2252/8531)
Total number of events		2314
	Serious	2314
	Non-Serious	0
Events grade 3 or higher		271
Event outcomes		
	Fatal	89
	Lost to follow-up	0
	Not Resolved	48
	Resolved	929

Important Identified Risk:	CRS

	Resolved with Sequelae	5
	Resolving	53
	Unknown	370
Time to event onset range (median) days		0-374 (2)

Abbreviation: CRS = cytokine release syndrome.

Reversibility

In ZUMA-1, the majority of CRS events resolved.

In ZUMA-5, as of the data cut-off date (14 September 2020), CRS had resolved in all except in one subject; the subject with unresolved CRS had FL and died on Day 7 due to multiple organ dysfunction syndrome that was secondary to CRS. For subjects whose CRS had resolved, the median duration of CRS was 6 days (range: 1 to 27 days). For the 96 subjects with FL whose CRS had resolved, the median duration of CRS was 6 days (range: 1 to 27 days). Among subjects with MZL, all cases of CRS had resolved, and the median duration of CRS was 5.5 days (range: 2 to 14 days).

Impact on quality of life

AEs, including fever, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, diarrhea, headache, skin rashes, tachypnea, hypoxemia, tachycardia, hypotension, increased or decreased cardiac output, renal impairment, elevated transaminases and bilirubin, and bleeding, can cause severe distress and require medical intervention. In the short-term CRS will impact the patient's quality of life although this is short lived and likely to be confined to the period of hospitalization with limited long-term effects. In severe cases, CRS-related SAEs may be associated with death.

Risk groups or risk factors	**Patient factors**: A higher disease burden and organ dysfunction was associated with a higher rate of CRS. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement or history of cardiovascular disease. **Dose-related**: A higher dose of CAR T cells and/or potency of the cells was associated with a higher rate of CRS. **Synergistic effects**: Treatment with systemic immunostimulatory agents.
Preventability	Yescarta must be administered in a qualified treatment center by a physician with experience in the treatment of hematological malignancies and trained for administration and management of patients treated with the medicinal product. In the event of CRS, at least 1 dose of tocilizumab, and emergency equipment must be available prior to infusion. The qualified treatment center must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion. It is recommended that patients are monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS. For the first 7 days the patient can be hospitalized at the physician's discretion. After the first 7 days following the infusion, the patient is to be monitored at the physician's discretion.

Important Identified Risk:	CRS
	Patients must 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. Vital signs and organ function must be monitored depending on the severity of the reaction. 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. 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. Patients with medically significant cardiac dysfunction must be managed by standards of critical care and measures such as echocardiography are to be considered.
Impact on the benefit-risk balance of the product:	Routine and additional pharmacovigilance activities will further characterize the risk of CRS with respect to number of reports, seriousness, outcome, and risk factors and determine whether the data is consistent with the information already known for this risk. The safe use of axicabtagene ciloleucel will be disseminated through routine risk minimization measures and supported by aRMMs such as HCP educational material, PAC and Controlled distribution plan (see Annex 6). The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: AE = adverse event; aRMMs = additional risk minimization measures; CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CRS = cytokine release syndrome; FL = follicular lymphoma; HCP = healthcare professional; IL1Rα = interleukin 1 receptor α; IL2 = interleukin 2; IL2Rα = interleukin 2 receptor α; IL6 = interleukin 6; IL8 = interleukin 8; IL10 = interleukin 10; MZL = marginal zone lymphoma; PAC = Patient Alert Card; PASS = postauthorization safety study; SAE = serious adverse event; SmPC = summary of product characteristics; TNFα = tumor necrosis factor alpha.

Table SVII.7. Important Identified Risk: Cytopenias including Aplastic Anemia

Important Identified Risk:	Cytopenias including Aplastic Anemia
Potential mechanisms	Cytopenias, especially prolonged cytopenias, is a well-known risk associated with conditioning chemotherapy. However, there is often difficulty in determining the etiology of cytopenias occurring after CAR T-cell infusions, because chemotherapy that causes cytopenias is normally given before CAR T-cell infusions. Prior treatment with chemotherapeutic agents and underlying disease can also contribute to the occurrence of cytopenias. Patients not receiving conditioning chemotherapy have also experienced cytopenias following CAR T-cell infusion, demonstrating that the CAR T cells cause myelosuppression by a cytokine-mediated mechanism or some other mechanism {Brudno 2016a}.
Evidence source and strength of evidence	Cytopenias were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.

Important Identified Risk:	Cytopenias including Aplastic Anemia

Characterisation of the risk

Clinical trials

ZUMA-1 and ZUMA-7 (as of 18 March 2021)

Incidence of Treatment-emergent Cytopenias (Thrombocytopenia, Neutropenia, Anaemia) by PT and Worst Grade (Safety Analysis Set)

	Standard of Care Therapy		Axicabtagene Ciloleucel					
	ZUMA-7 (N = 168)		ZUMA-7 (N = 170)		ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)		Overall (N = 278)	
MedDRA PT, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any treatment-emergent thrombocytopenia, neutropenia or anaemia	135 (80)	126 (75)	136 (80)	128 (75)	98 (91)	89 (82)	234 (84)	217 (78)
Subjects with thrombocytopenia	101 (60)	95 (57)	50 (29)	25 (15)	62 (57)	41 (38)	112 (40)	66 (24)
Platelet count decreased	64 (38)	60 (36)	30 (18)	12 (7)	33 (31)	18 (17)	63 (23)	30 (11)
Thrombocytopenia	41 (24)	37 (22)	22 (13)	14 (8)	32 (30)	23 (21)	54 (19)	37 (13)
Subjects with neutropenia	92 (55)	91 (54)	122 (72)	119 (70)	88 (81)	81 (75)	210 (76)	200 (72)
Neutropenia	29 (17)	28 (17)	75 (44)	73 (43)	41 (38)	36 (33)	116 (42)	109 (39)
Neutrophil count decreased	47 (28)	47 (28)	52 (31)	49 (29)	37 (34)	36 (33)	89 (32)	85 (31)
Febrile neutropenia	46 (27)	46 (27)	4 (2)	4 (2)	37 (34)	34 (31)	41 (15)	38 (14)
Subjects with anaemia	92 (55)	65 (39)	73 (43)	51 (30)	64 (59)	46 (43)	137 (49)	97 (35)
Anaemia	91 (54)	65 (39)	71 (42)	51 (30)	64 (59)	46 (43)	135 (49)	97 (35)
Anaemia macrocytic	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Haematocrit decreased	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Haemoglobin decreased	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA query; PT = Preferred Term; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
Thrombocytopenia is identified using the SMQ for haematopoietic thrombocytopenia (narrow search).
Neutropenia is identified using MedDRA search terms defined by Kite.
Anaemia (including aplastic anaemia) is identified using the SMQ haematopoietic erythropenia (broad search).
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.

Important Identified Risk:	**Cytopenias including Aplastic Anemia**

Percentages are based on the total number of subjects (N) in each column.
Preferred terms are sorted in descending order of the number of subjects with Any Grade in Overall within each blood cell lineage.
Data Source: ADSL, ADAE Programme Name: t_aewg2 Output Generated: 20210730T16:07

Incidence of Serious Treatment-emergent Cytopenias (Thrombocytopenia, Neutropenia, Anaemia) by PT and Worst Grade (Safety Analysis Set)

	Standard of Care Therapy		Axicabtagene Ciloleucel					
	ZUMA-7 (N = 168)		ZUMA-7 (N = 170)		ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)		Overall (N = 278)	
MedDRA PT, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any serious treatment-emergent thrombocytopenia, neutropenia or anaemia	31 (18)	31 (18)	10 (6)	9 (5)	7 (6)	7 (6)	17 (6)	16 (6)
Subjects with serious thrombocytopenia	6 (4)	6 (4)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (0)
Platelet count decreased	5 (3)	5 (3)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (0)
Thrombocytopenia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subjects with serious neutropenia	26 (15)	26 (15)	10 (6)	9 (5)	7 (6)	7 (6)	17 (6)	16 (6)
Febrile neutropenia	22 (13)	22 (13)	4 (2)	4 (2)	5 (5)	5 (5)	9 (3)	9 (3)
Neutropenia	1 (1)	1 (1)	4 (2)	3 (2)	1 (1)	1 (1)	5 (2)	4 (1)
Neutrophil count decreased	3 (2)	3 (2)	3 (2)	3 (2)	1 (1)	1 (1)	4 (1)	4 (1)
Subjects with serious anaemia	3 (2)	3 (2)	1 (1)	1 (1)	0 (0)	0 (0)	1 (0)	1 (0)
Anaemia	3 (2)	3 (2)	1 (1)	1 (1)	0 (0)	0 (0)	1 (0)	1 (0)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; PT = Preferred Term; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
Thrombocytopenia is identified using the SMQ for haematopoietic thrombocytopenia (narrow search).
Neutropenia is identified using MedDRA search terms defined by Kite.
Anaemia (including aplastic anaemia) is identified using the SMQ haematopoietic erythropenia (broad search).
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column.
Preferred terms are sorted in descending order of the number of subjects with Any Grade in Overall within each blood cell lineage.
Data Source: ADSL, ADAE Programme Name: t_aewg2 Output Generated: 20210730T16:07

Important Identified Risk:	Cytopenias including Aplastic Anemia

ZUMA-5 (as of 14 September 2020)

In ZUMA-5, percentages of subjects who experienced neutropenia, anemia and thrombocytopenia were 65%, 38%, and 34%, respectively. Grade 3 or higher neutropenia (including neutropenia, neutrophil count decreased, febrile neutropenia), anemia and thrombocytopenia occurred in 61%, 24% and 23% of subjects respectively. The subject incidence of cytopenias observed in ZUMA-5 is presented below.

Subject Incidence of Treatment Emergent Thrombocytopenia, Neutropenia, and Anemia (N=148)

	FL (N=124)		**MZL (N=24)**		**Overall (N=148)**	
AEs Group MedDRA Preferred Term	Any n (%)	Grade ≥3 n (%)	Any n (%)	Grade ≥3 n (%)	Any n (%)	Grade ≥3 n (%)
Subjects with any cytopenia	**91 (73)**	**86 (69)**	**20 (83)**	**18 (75)**	**111 (75)**	**104 (70)**
Subjects with neutropenia	79 (64)	75 (60)	17 (71)	16 (67)	96 (65)	91 (61)
Neutropenia	47 (38)	44 (35)	6 (25)	5 (21)	53 (36)	49 (33)
Neutrophil Count Decreased	31 (25)	29 (23)	12 (50)	12 (50)	43 (29)	41 (28)
Febrile Neutropenia	2 (2)	2 (2)	2 (8)	2 (8)	4 (3)	4 (3)
Subjects with thrombocytopenia	44 (35)	29 (23)	6 (25)	5 (21)	50 (34)	34 (23)
Thrombocytopenia	26 (21)	20 (16)	3 (13)	2 (8)	29 (20)	22 (15)
Platelet Count Decreased	20 (16)	11 (9)	4 (17)	3 (13)	24 (16)	14 (9)
Subjects with anaemia	44 (35)	29 (23)	12 (50)	7 (29)	56 (38)	36 (24)
Anaemia	44 (35)	29 (23)	12 (50)	7 (29)	56 (38)	36 (24)

Data cutoff date: 14 Sep 2020.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; FL = follicular lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma; SMQ = standard MedDRA query.
Multiple incidences of the same AE in one subject are counted once at the worst grade for this subject.
Preferred terms are sorted in descending order of Any frequency count in the overall column.
AEs are coded using MedDRA version 23.0 and graded per CTCAE version 4.03.
Events (neutropenia, thrombocytopenia or anemia) with onset on or after axicabtagene ciloleucel infusion date are summarized.
Thrombocytopenia is identified using the SMQ for haematopoietic thrombocytopenia (narrow search).
Neutropenia is identified using MedDRA search terms defined by Kite.
Anaemia (including aplastic anemia) is identified using the SMQ haematopoietic erythropenia (broad search).
Data Source: ADSL, ADAE Program Name: t_teae_cp_m2.sas Output Generated: 20210405T14:23

KT-EU-471-0117 (PASS) (as of 01 March 2022)

	Effectiveness and Safety Analysis set n=379 N (%)
Anemia (Grade unknown)	1 (0.3)
Anemia – Grade 1	2 (0.5)
Anemia – Grade 2	2 (0.5)
Anemia – Grade 3	9 (2.4)
Anemia – Grade 4	2 (0.5)
Cytopenia (Grade unknown)	1 (0.3)

Important Identified Risk:	Cytopenias including Aplastic Anemia

Febrile neutropenia (Grade unknown)	2 (0.5)
Neutropenia (Grade unknown)	2 (0.5)
Neutropenia – Grade 1	3 (0.8)
Neutropenia – Grade 2	2 (0.5)
Neutropenia – Grade 3	2 (0.5)
Neutropenia – Grade 4	31 (8.2)
Pancytopenia (Grade unknown)	2 (0.5)
Pancytopenia – Grade 3	1 (0.3)
Pancytopenia – Grade 4	2 (0.5)
Thrombopenia - grade 1	1 (0.3)
Thrombopenia - grade 2	3 (0.8)
Thrombopenia - grade 3	1 (0.3)
Thrombopenia - grade 4	5 (1.3)

Post-marketing

Cytopenia Events Reported in the Post-marketing Setting (Cumulative to 22 August 2022)

Category		Value
Total number of Cases		423
Case reporting rate		5% 423/8531
Total number of Events		588
	Serious	409
	Non-Serious	179
Event Outcomes		
	Fatal	21
	Lost to follow-up	0
	Not Resolved	143
	Resolved	159
	Resolved with Sequelae	0
	Resolving	61
	Unknown	76

Abbreviations: PT = preferred terms

Reversibility

In ZUMA-1, the majority of cytopenias events resolved.

In ZUMA-5, the worst Grade 3 or higher were prolonged (present on or after Day 30) thrombocytopenia occurred in 14 subjects (9%), prolonged neutropenia occurred in 42 subjects (28%), and prolonged anemias in 11 subjects (7%).

Impact on Quality of Life

Patients with significant cytopenias may require prolongation of their hospital stay until resolution. This may require isolation to limit the risk of infection. This may negatively affect quality of life although this is likely to be of limited duration as the cytopenias resolve over time.

Important Identified Risk:	Cytopenias including Aplastic Anemia
Risk groups or risk factors	Prior exposure to chemotherapy or radiation.
Preventability	Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Yescarta infusion and must be managed according to standard guidelines. Patient blood counts must be monitored after Yescarta infusion.
Impact on the benefit-risk balance of the product:	Routine and additional pharmacovigilance activities will further characterize the risk of cytopenias with respect to number of reports, seriousness, outcome, and risk factors and to determine whether the data is consistent with the information already known for this risk. The safe use of axicabtagene ciloleucel will be disseminated through routine risk minimization measures. The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: CAR T = chimeric antigen receptor T cells; PASS = postauthorization safety study.

Table SVII.8. Important Identified Risk: Infections

Important Identified Risk:	Infections
Potential mechanisms	Prolonged B-cell aplasia is an expected toxicity of anti-CD19 CAR T-cells due to their cytotoxic activity towards CD19 expressing B-cells. In addition, infections could be the result of chemotherapy-induced cytopenias and immunosuppression, including depletion of B-cells and T cells and hypogammaglobulinemia, which is often given before CAR T-cell infusions. However, patients not receiving conditioning chemotherapy have also experienced cytopenias following CAR T-cell infusion, demonstrating that the CAR T cells cause myelosuppression by a cytokine-mediated mechanism or some other mechanism {Brudno 2016a}.
Evidence source and strength of evidence	Infections were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Characterisation of the risk	**Clinical trials** **ZUMA-1 and ZUMA-7 (as of 18 March 2021)** **Incidence of Treatment-emergent Infections by PT and Worst Grade (Safety Analysis Set)**

	Standard of Care Therapy		Axicabtagene Ciloleucel					
	ZUMA-7 (N = 168)		ZUMA-7 (N = 170)		ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)		Overall (N = 278)	
MedDRA PT, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any treatment-emergent infections (bacterial, viral,	51 (30)	19 (11)	70 (41)	24 (14)	43 (40)	29 (27)	113 (41)	53 (19)

Important Identified Risk: **Infections**

opportunistic or unspecified)								
Subjects with bacterial infections	15 (9)	7 (4)	16 (9)	7 (4)	17 (16)	10 (9)	33 (12)	17 (6)
Subjects with opportunistic infections	2 (1)	2 (1)	8 (5)	2 (1)	4 (4)	1 (1)	12 (4)	3 (1)
Subjects with viral infections	8 (5)	1 (1)	26 (15)	7 (4)	24 (22)	7 (6)	50 (18)	14 (5)
Subjects with COVID-19 infection	1 (1)	0 (0)	3 (2)	3 (2)	0 (0)	0 (0)	3 (1)	3 (1)
Subjects with unspecified pathogen infections	40 (24)	15 (9)	44 (26)	14 (8)	31 (29)	21 (19)	75 (27)	35 (13)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SMQ = standard MedDRA query; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column.
Preferred terms are sorted in descending order of the number of subjects with Any Grade in the Overall column within each infection category.
COVID-19 AEs are identified using the SMQ (narrow version) of COVID-19.
Data Source: ADSL, ADAE Programme Name: t_aewg2_inf Output Generated: 20210730T16:07

Incidence of Serious Treatment-emergent Infections by PT and Worst Grade (Safety Analysis Set)

	Standard of Care Therapy		**Axicabtagene Ciloleucel**					
	ZUMA-7 (N = 168)		**ZUMA-7 (N = 170)**		**ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)**		**Overall (N = 278)**	
MedDRA PT, n (%)	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**	**Any Grade**	**Worst Grade ≥ 3**
Subjects with any serious treatment-emergent infections (bacterial, viral, opportunistic or unspecified)	16 (10)	15 (9)	20 (12)	17 (10)	23 (21)	23 (21)	43 (15)	40 (14)
Subjects with serious bacterial infections	4 (2)	4 (2)	2 (1)	2 (1)	6 (6)	6 (6)	8 (3)	8 (3)

Important Identified Risk:	Infections							
	Subjects with serious opportunistic infections	2 (1)	2 (1)	3 (2)	2 (1)	1 (1)	1 (1)	4 (1)	3 (1)
	Subjects with serious viral infections	2 (1)	1 (1)	7 (4)	6 (4)	6 (6)	6 (6)	13 (5)	12 (4)
	Subjects with serious COVID-19 infection	0 (0)	0 (0)	3 (2)	3 (2)	0 (0)	0 (0)	3 (1)	3 (1)
	Subjects with serious unspecified pathogen infections	13 (8)	12 (7)	13 (8)	10 (6)	17 (16)	17 (16)	30 (11)	27 (10)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion date or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column.
Preferred terms are sorted in descending order of the number of subjects with Any Grade in the Overall column within each infection category.
COVID-19 AEs are identified using the SMQ (narrow version) of COVID-19.
Data Source: ADSL, ADAE Programme Name: t_aewg2_inf Output Generated: 20210730T16:07

ZUMA-5 (as of 14 September 2020)

In ZUMA-5, 79 subjects (53%) had AEs of any grade infection. Events of infections reported in ≥5% of subjects were influenza (9 subjects, 6%), upper respiratory tract infection (21 subjects, 14%), pneumonia (18 subjects, 12%), sinusitis (12 subjects, 8%), and urinary tract infection (11 subjects, 7%). Twenty-three subjects (16%) had Grade 3 events, one subject (1%) had Grade 4 event and two subjects (1%) had Grade 5 events. The only serious infection with Grade 3 or higher occurring in ≥5% of subjects was pneumonia (6%). Infections by type are presented below.

- Bacterial infections: 9% of subjects had any grade bacterial infections. The most common bacterial infection PTs of any grade was staphylococcal infection (2%) and 1% of these subjects are Grade 3 or higher.
- Viral infections: 16% of subjects had any grade viral infection. The most common viral infection of any grade was influenza (6%), herpes zoster (3%), and rhinovirus infection (3%). All other viral infections occurred in 1 subject (1%). No viral infections of Grade 3 or higher reported in more than 1% of subjects.
- Opportunistic infections: 5% of subjects had an opportunistic infection. It included 1% each for the following infections: coccidioidomycosis, cryptococcosis, cytomegalovirus infection reactivation, cytomegalovirus viremia, mycobacterium kansasii Infection, ophthalmic herpes simplex, and systemic candida. The serious and grade 3 or higher

Important Identified Risk:	Infections
	opportunistic infections were reported in 2% of subjects and included 1% each for coccidioidomycosis, cytomegalovirus infection reactivation, and systemic candida. • Unspecified infections: 45% of subjects had "unspecified" infections. The most common "unspecified" infection of any grade was upper respiratory tract infection (14%), pneumonia (12%), sinusitis (8%), and urinary tract infection (7%). Seventeen subjects (11%) had serious and grade 3 or higher "unspecified" infections, of which 6% had pneumonia and 2% had urinary tract infection. **KT-EU-471-0117 (PASS) (as of 01 March 2022)** Serious infections were observed for 140 (38.1% of those with available information) patients, with a median time to infection of 23 days (with a range of 1 to 444 days). A total of 246 infections were observed: 177 (72%) bacterial, 38 (15.4%) fungal, and 31 (12.6%) viral. No (0%) parasitic infections were recorded. The infection(s) was/were resolved in 119 (95.2%) patients. The 12-month cumulative incidence for infections was 36% (95% CI: 31 to 41%), and the incidence rate per person-year was 0.64 (95% CI: 0.54 to 0.75). **Post-marketing** **Infections Reported in the Post-marketing Setting (Cumulative to 22 August 2022)**

Category		Value
Total number of Cases		342
Case reporting rate		4% (342/8531)
Total number of Events		505
	Serious	432
	Non-Serious	73
Event Outcomes		
	Fatal	118
	Lost to follow-up	0
	Not Resolved	55
	Resolved	72
	Resolved with Sequelae	0
	Resolving	32
	Unknown	82

Abbreviations: PT = preferred terms

Impact on quality of life

Infections can be debilitating for patients and require intensive medical support. Severe or opportunistic infections in immunocompromised patients can be fatal.

Risk groups or risk factors	**Patient factors**: Underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, and psychological stress. **Additive or synergistic factors**: Surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures.
Preventability	Infusion must be delayed if a patient has active infection. 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.

Important Identified Risk:	Infections
	Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Yescarta. The possibility of PML should be considered in immunosuppressed patients with new onset or worsening neurological symptoms and appropriate diagnostic evaluations should be performed.
Impact on the benefit-risk balance of the product	Routine and additional pharmacovigilance activities will further characterize the risk of infections with respect to number of reports, seriousness, outcome, and risk factors and determine if data is consistent with the information already known for this risk. The safe use of axicabtagene ciloleucel will be disseminated through routine risk minimization measures. The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation; HBV = hepatitis B virus; HCV = hepatitis C virus; PASS = postauthorization safety study; PML = progressive multifocal leukoencephalopathy.

Table SVII.9. Important Identified Risk: Hypogammaglobulinemia

Important Identified Risk:	Hypogammaglobulinemia
Potential mechanisms	B-cell aplasia is an expected consequence of treatment with axicabtagene ciloleucel which may lead to hypogammaglobinemia.
Evidence source and strength of evidence	Hypogammaglobinemia was reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Characterisation of the risk	**Clinical trials** **ZUMA-1 and ZUMA-7 (as of 18 March 2021)** **Incidence of Treatment-emergent Hypogammaglobulinemia by PT and Worst Grade (Safety Analysis Set)**

	Standard of Care Therapy		Axicabtagene Ciloleucel					
	ZUMA-7 (N = 168)		ZUMA-7 (N = 170)		ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)		Overall (N = 278)	
MedDRA PT, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any treatment-emergent Hypogammaglobulinaemia	1 (1)	0 (0)	19 (11)	0 (0)	17 (16)	0 (0)	36 (13)	0 (0)
Hypogammaglobulinaemia	1 (1)	0 (0)	19 (11)	0 (0)	16 (15)	0 (0)	35 (13)	0 (0)
Blood immunoglobulin G decreased	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	0 (0)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; MST = MedDRA search terms; PT =

Important Identified Risk:	Hypogammaglobulinemia

Preferred Term; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column.
Preferred terms are sorted in descending order of the number of subjects with Any Grade in the Overall column. Hypogammaglobulinaemia is identified using an MST strategy defined by Kite.
Data Source: ADSL, ADAE Programme Name: t_aewg_hypo Output Generated: 20210730T16:05

None of the hypogammaglobulinemia cases were serious.

ZUMA-5 (as of 14 September 2020)

In ZUMA-5, hypogammaglobulinemia was reported in 20% of the 148 subjects. One subject (1%) with FL had a worst Grade 3 event.

KT-EU-471-0117 (PASS) (as of 01 March 2022)

Hypogammaglobulinemia was observed for 202 patients, representing 59.9% of those with information available. For 42 patients this information was missing, and 135 patients (40.1%) did not have hypogammaglobulinemia. Of these 202 patients with hypogammaglobulinemia, 83 cases were new onset cases and 101 were ongoing cases; the remaining 18 could not be sorted into either category due to missingness of information. Of the 202 patients with hypogammaglobulinemia, 137 had hypogammaglobulinemia present at some point before infusion. A total of 72 patients were treated for hypogammaglobulinemia, and the condition was resolved in 10 patients. No data was available on time to recovery. The 12-month cumulative incidence for hypogammaglobulinemia was 32% (95% CI: 25 to 38%), and the incidence rate per person-year was 0.80 (95% CI: 0.65 to 0.97).

Post-marketing

Hypogammaglobulinemia Reported in the Post marketing Setting (Cumulative to 22 August 2022)

Category		Value
Total number of Cases		56
Case reporting rate		0.7% (56/8531)
Total number of Events		56
	Serious	53
	Non-Serious	3
Event Outcomes		
	Fatal	0
	Lost to follow-up	0
	Not Resolved	15
	Resolved	5
	Resolved with Sequelae	0
	Resolving	6
	Unknown	5

Abbreviations: PT = preferred terms.

Important Identified Risk:	Hypogammaglobulinemia
	Impact on quality of life Hypogammaglobulinemia predisposes patients to have recurrent infections.
Risk groups or risk factors	Prior treatment with rituximab and concomitant use of other drugs (e.g. steroids) that can induce hypogammaglobulinemia.
Preventability	Immunoglobulin levels should be monitored after treatment with Yescarta and managed using infection precautions, antibiotic prophylaxis and immunoglobulin replacement in case of recurrent infections and must be taken according to standard guidelines.
Impact on the benefit-risk balance of the product	Routine and additional pharmacovigilance activities will further characterize the risk of hypogammaglobulinemia with respect to number of reports, seriousness, outcome, and risk factors and determine if data is consistent with the information already known for this risk. The safe use of axicabtagene ciloleucel will be disseminated through routine risk minimization measures. The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the relatively low number of people affected by the indication.

Abbreviations: CAR T = chimeric antigen receptor T cells; FL = follicular lymphoma; PASS = postauthorization safety study.

Table SVII.10. Important Identified Risk: Secondary Malignancy of T-cell Origin

Important Identified Risk:	Secondary Malignancy of T-cell Origin
Potential mechanisms	A possible mechanism is insertional mutagenesis of the viral vector or the development of RCR during manufacturing, which may contribute to malignant transformation. It is possible that the combination of previous multiple lines of treatment with chemoimmunotherapy, radiation or even autologous or allogeneic transplant, along with the immune dysregulation and inflammation, may drive the occurrence of T-cell malignancies as a multi-hit mechanism {Bouziana 2024}.
Evidence source and strength of evidence	Secondary malignancies of T-cell origin have been reported within weeks and up to several years following the administration of CAR T-cell medicines. These findings imply that CAR T-cell therapies may have been involved in developing T-cell malignancy.
Characterisation of the risk	As of 16 February 2024, 17,578 patients had received axicabtagene ciloleucel. Upon review of the Gilead Global Safety Database cumulative to 05 March 2024, there were 13 subsequent malignancies of T-cell origin among patients who received axicabtagene ciloleucel, for an overall reporting rate of 0.07% (n=13/17,578). This rate was consistent with the clinical trial incidence of T-cell malignancies reported after axicabtagene ciloleucel, namely 0.1% (n=1/905). The median time to onset of these subsequent T-cell malignancies was 12.2 months (range: 1.8-58.5 months). Four of the 13 cases of T-cell malignancies had sufficient tumor biopsy and/or blood sample availability for molecular analysis, including the detection of the CAR transgene. None of the cases demonstrated causality, with CAR detected at frequencies near or below the limit of detection in each case {Martin 2024}. Due to the rarity of the cases, not many studies have explored the genetic changes of these secondary malignancies of T-cell origin and whether they result from insertional mutagenesis of the CAR transgene. Harrison et al. reported a case study of a 51-year-old male patient who received cilta-cel and developed T-cell lymphoma five months post-infusion. The T-cell lymphoma cells showed that the CAR was inserted in the 3′ untranslated region of *PBX2*. Molecular analyses revealed the presence of genetic mutations (*TET2*, *NFkB2*, *PTPRB*, and a germline activating mutation of *JAK3*) before CAR-T

Important Identified Risk:	Secondary Malignancy of T-cell Origin
	manufacturing. Thus, it is unclear whether the transgene integration was associated with the development of the TCL {Harrison 2023}. Ozdemirli et al. described a 71-year-old woman who developed indolent T-cell lymphoma five months after she had received cilta-cel. The T-cell lymphoma harbored a CAR-vector integration in the second intron of *SSU72*; however, the viral integration site did not appear to alter the expression level of SSU72 mRNA. Also, no unusual splicing pattern was observed for the *SSU72* gene. Other genetic aberrations were also detected in the tumor sample and could play a role in developing the malignant phenotype {Ozdemirli 2024}. Similarly, Kobbe et al. described a case of a 60-year-old man who received tisagenlecleucel and developed PTCL one month post-infusion. Vector integration site analysis showed that in the CAR^+-PTCL, only 13 integration sites were identified with substantial enrichment of 3 sites: *DPF2*, *RAB11FIP3*, and *NPLOC4*. Because these genes are not classified as cancer genes and are not involved in hematologic cancers, viral integration in these genes does not provide a likely explanation for the onset of the lymphoma. Molecular characterization of the CAR^+-PTCL and apheresis material showed somatic *DNMT3A* and *TET2* mutations in $CD34^+$ stem cells, and their progeny were detected in the PTCL and in the apheresis specimen that was obtained for CAR T-cell production. The PTCL harbored an additional somatic *TET2* mutation, which was already detectable in the CAR T-cell apheresis product and the final CAR T-cell product at very low frequencies, providing evidence that clonal hematopoiesis had contributed to lymphomagenesis {Kobbe 2024}. The mechanism by which transgene integration can cause clonal expansion and tumorigenesis is not completely understood. In 2018, Fraietta and colleagues described a patient with chronic lymphocytic leukemia treated with CTL019, who experienced clonal CAR T expansion (94% T-cell clonality) in which the CAR transgene insertion was in the *TET2* gene {Fraietta 2018}. Shah and colleagues reported a pediatric acute lymphocytic leukemia patient treated with CD22-directed CAR T that showed significant clonal expansion of the CAR T cells due to lentiviral insertion of the CAR in the *CBL-B* locus {Shah 2019}. Although the CAR T cells expanded in an abnormal and clonal pattern in both cases, they still led to disease remission without malignant transformation. Therefore, there is a gap in understanding the relationship between the CAR transgene integration, prior mutations and transcriptome readouts within the malignant cell.
Risk groups or risk factors	Patients with B-cell lymphoma are at an increased risk of developing T-cell lymphoma with approximately 5-fold higher standardized incidence ratio of developing a second primary T-cell lymphoma {Chihara 2021, Dores 2024}.
Preventability	HCPs should monitor patient's life-long for secondary malignancies. In the event that a secondary malignancy of T-cell origin occurs, the MAH is to be contacted to obtain instructions on patient samples to collect for testing.
Impact on the benefit-risk balance of the product:	Malignancy of T-cell origin is a serious condition that can be life-threatening. Routine and additional pharmacovigilance activities will further characterize the risk of secondary malignancy of T-cell origin with respect to the number of reports and molecular profiling of samples from patients that developed secondary malignancy of T-cell origin. The SmPC includes recommendations for contacting the MAH to receive sampling advice. As part of site qualification training, HCPs are made aware of the need to contact the MAH to obtain recommendations for tumor sample collection and testing following the development of a secondary malignancy of T cell origin.
Public health impact	Minimal impact due to the rarity of these events.

Abbreviations: CAR = chimeric antigen receptor; CAR T = chimeric antigen receptor T cells; HCP = healthcare professional; MAH = marketing authorization holder; PTCL = peripheral T-cell lymphoma; RCR = replication-competent retrovirus; SmPC = summary of product characteristics; TCL = T-cell lymphoma.

SVII.3.1.2. Important Potential Risks

Table SVII.11. Important Potential Risk: Secondary Hematologic Malignancies Excluding T-cell Malignancies

Important Potential Risk:	Secondary Hematologic Malignancies Excluding T-cell Malignancies
Potential mechanisms	The etiology of secondary hematologic malignancy excluding T-cell malignancies after DLBCL is multifactorial and has been suggested to be caused by a combination of exposure to chemotherapy, radiation, rituximab and associated immunosuppression, chronic infections, lifestyle practices, demographics, and genetic susceptibility {Major 2020}. A recent factor that is possibly being implicated in the etiology of secondary hematologic malignancy, excluding T-cell malignancies, is CHIP, which was shown to be associated with an increase in t-MN. Saini et al. showed that the cumulative incidence of t-MN at 24 months appeared significantly higher for patients with preexisting CHIP as compared to CAR-T cell recipients without prior CHIP (19% vs. 4.2%) {Saini 2022}. Yeoh et al. showed that the incidental CHIP variants involving the DNA damage repair pathway were a frequent finding prior to CAR-T infusion (49%) and that the cumulative incidence of myeloid neoplasia following CAR T infusion was 2% at 1 year, 3% at 2 years and 11% at 3 years {Yeoh 2024}. Patients with preexisting CHIP may acquire new mutations or expand their previous variant allele frequency following CAR T therapy. However, it is difficult to consider CAR T therapy as causative of this process {Galli 2024}. There is a theoretical risk that CAR-mediated inflammation could drive the expansion of these CHIP clones to contribute to t-MN. Additionally, perpetual inflammation, possibly from persistent CAR T cells, could exacerbate these clonal expansions over time. While this hypothesis is certainly possible, there is no clear evidence that CAR-mediated inflammation is associated with developing t-MN. Accorsi Buttini et al. reported a case of high-risk MDS following CAR T-cell therapy in a patient with relapsed DLBCL 8 months after CAR T-cell infusion. The bone marrow biopsy revealed multilineage dysplasia without excess of blasts associated with chromosome 7 deletion and *RUNX1* mutation. Next-generation sequencing analysis, retrospectively performed on stored samples, showed a germline *CSF3R* mutation and *CEBPA* clonal hematopoiesis but no *RUNX1* lesion. As the deletion of chromosome 7 and acquisition of *RUNX1* mutation manifested after CAR T therapy, one cannot exclude the possibility that the impairment of immunosurveillance related to either lymphodepletion or CAR T-cell infusion may play a role in the MDS development {Accorsi Buttini 2023}. Falini et al. reported a case of AML in which *DNMT3A* mutation was already present at the time of lymphoma diagnosis; however, *RUNX1* mutations were detected for the first time in the bone marrow sample taken 2 months after CAR T cells. Thus, it was hypothesized that AML may have developed as a consequence of the immunosuppression related to lymphodepletion pre-CAR T-cell infusion, although it cannot be excluded that it could be related to previous multiple genotoxic treatments (e.g., anthracyclines, radiotherapy or ASCT). Of note, the possibility that the AML could have developed following the unintentional insertion of the CAR transgene into AML-associated genes during manufacturing was excluded by flow cytometry, which showed CAR expression only on T lymphocytes inside all peripheral blood populations, thereby excluding the presence of any possible circulating CAR-positive myeloid cells {Falini 2023}. Galli et al. retrospectively tested the CHRS in 55 patients. Twenty-two patients (40%) were found to harbor a CHIP before CAR-T treatment with four patients showing a double mutation. Among genes involved in CHIP, *DNMT3A* was the most frequently mutated (12 cases), followed by *TP53* (4 cases) and *TET2* (3 cases). Patients with an intermediate-high CHRS had more than a twofold increased risk of developing a t-MN within the first 9

Important Potential Risk:	Secondary Hematologic Malignancies Excluding T-cell Malignancies
	months after CAR-T (odds ratio 2.89, 95%, C.I. 1.98–4.19, p<0.001). In detail, among 34 patients with low CHRS, none developed a t-MN, compared to three cases (14%) among the 21 patients with intermediate or high CHRS. An additional risk factor for developing t-MN was the higher number of prior lines of treatment (p=0.001) {Galli 2025}. In summary, the etiology of secondary hematologic malignancy excluding T-cell malignancies following CAR T therapy is difficult to discern, and additional research is needed to determine whether the acquisition of additional mutations and genetic instability seen after CAR T therapy is the result of the CAR T therapy immune dysregulation or whether these changes represent the evolution of clones regardless of CAR T therapy.
Evidence source and strength of evidence	Secondary hematologic malignancies, excluding T-cell malignancies, were reported in clinical trials, post-marketing surveillance, and patients treated with other CAR T therapies.
Characterisation of the risk	Data from the Yescarta safety review entitled 'Therapy Related Myeloid Neoplasms' submitted in December 2023 with Yescarta PSUR/PBRER #10 showed the following: ▪ **LBCL** In the clinical trials, the t-MN incidence rate was 4.1% for patients without prior malignancy and 3.3% for patients with prior malignancy. In the CIBMTR registry, the t-MN incidence rate was 4.2% for patients without prior malignancy and 6.8% for patients with prior malignancy. ▪ **FL** In the clinical trials, the t-MNs incidence rate was 7.0% for patients without prior malignancy and 4.2% in patients with prior malignancy. In the CIBMTR registry, the t-MNs incidence rate was 2.1% for patients without prior malignancy and 2% in patients with prior malignancy. Note: The median follow-up time for FL patients in the registry was only 12 months, so the MAH considered the clinical trial results, which had a median follow-up time of 54 months, to be more reliable. Of note, the analyses of the above-mentioned safety review used data collected across the following ZUMA trials for LBCL: ZUMA-1, ZUMA-6, ZUMA-7 (axicabtagene ciloleucel arm), ZUMA-9, ZUMA-11, ZUMA-12, ZUMA-14, ZUMA-19 with a data cutoff date of 17 October 2023. **Impact on quality of life** Secondary malignancies are long-term debilitating and life-threatening conditions that may require patients to undergo further treatments. This will have a negative impact on the quality and potentially, the duration of life in patients who have already undergone extensive treatment for NHL.
Risk groups or risk factors	**Patient factors**: Age. **Additive or synergistic factors**: Chemotherapy and immunosuppressive treatments. The MAH comprehensively analysed potential risk factors for t-MNs using available data from the CIBMTR registry post-authorization safety study and company-sponsored interventional clinical trials. The analyses found that increased lines of chemotherapy, advanced age (≥60) and prior malignancy were associated with an increased incidence rate of t-MNs.
Preventability	HCPs should monitor patient's life-long for secondary malignancies.

Important Potential Risk:	Secondary Hematologic Malignancies Excluding T-cell Malignancies
Impact on the benefit-risk balance of the product:	Currently there is no substantive evidence of a causal relationship between axicabtagene ciloleucel and secondary hematologic malignancy, excluding T-cell malignancies, and hence the risk-benefit balance for patients who already have a serious disease is not impacted. Routine pharmacovigilance activities will further characterize the risk of secondary hematologic malignancy, excluding T-cell malignancies, with respect to number of reports, seriousness, outcome, and risk factors.
Public health impact	Minimal impact as causal relationship has not been established.

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; CAR T = chimeric antigen receptor T cell; CHIP = clonal hematopoiesis of indeterminate potential; CHRS = clonal hematopoiesis risk score; CIBMTR = Center for International Blood and Marrow Transplant Research; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HCP = healthcare professional; MAH = marketing authorization holder; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; t-MN = treatment-related myeloid neoplasms.

Table SVII.12. Important Potential Risk: Immunogenicity

Important Potential Risk:	Immunogenicity
Potential mechanisms	Mechanisms consist of humoral and T cell-mediated immuno-reactivity which may include: an immunogenic reaction, including a T-cell-mediated immune response, against neo-epitopes associated with the axicabtagene ciloleucel CAR protein; an immune response to the murine scFv; and Type 1 hypersensitivity immune reactions {Lamers 2011, Song 2015}. In most patients, the occurrence of immunogenicity is unlikely due to effects of axicabtagene ciloleucel, chemotherapy induced lymphodepletion and prior anti-CD20 therapy in most patients all of which reduce/deplete normal B-cells.
Evidence source and strength of evidence	There have been a few reports of immunogenicity in clinical trials and post-marketing.
Characterisation of the risk	**Clinical trials** **ZUMA-1** In ZUMA-1, 3 subjects (3%) tested positive in the screening ELISA before lymphodepleting chemotherapy. Two of these 3 subjects also tested positive in a screening ELISA after axicabtagene ciloleucel infusion. In addition, 5 subjects with a negative result in the screening ELISA before lymphodepleting chemotherapy tested positive in a screening ELISA after axicabtagene ciloleucel infusion. One of the 5 subjects who tested positive in a screening ELISA after axicabtagene ciloleucel infusion (at Month 6 after infusion) also tested positive in the confirmatory cell-based assay (at Month 6 after infusion) without the onset of any clinical immunogenicity. This subject had a Grade 1 TEAE of dizziness that began on Day 12 after infusion when the immunogenicity tests were still negative. It was ongoing until Day 174, after the positive screening and confirmatory tests at Month 6 (Day 159 after infusion). Dizziness is a commonly reported adverse event associated with axicabtagene ciloleucel and no other TEAEs suggestive of a potential immune reaction were reported. The subject is in complete response and never relapsed.

Important Potential Risk: **Immunogenicity**

Anti-Axicabtagene Ciloleucel Antibody Summary in ZUMA-1 (Phase 1 and Phase 2 Cohort 1 and Cohort 2) (Safety Analysis Set, N = 108)

	Phase 1	Phase 2		
	(N = 7)	Cohort 1 (N = 77)	Cohort 2 (N = 24)	Total (N = 101)
Subjects with a result at any time[a]	7	77	24	101
Initial antibody test as positive at any time, n (%)	2 (29)	4 (5)	2 (8)	6 (6)
Confirmatory antibody test as positive at any time, n (%)	0 (0)	0 (0)	1 (4)	1 (1)
Subjects with a result at baseline	7	75	24	99
Initial antibody test as positive at baseline, n (%)	0 (0)	3 (4)	0 (0)	3 (3)
Confirmatory antibody test as positive at baseline, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Subjects with an after-baseline result	6	75	22	97
Initial antibody test as positive after baseline with a positive result at baseline, n (%)	0 (0)	2 (3)	0 (0)	2 (2)
Initial antibody test as positive after baseline with no result at baseline, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Initial antibody test as positive after baseline with a negative result at baseline, n (%)	2 (29)	1 (1)	2 (8)	3 (3)
Transient[b], n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Confirmatory antibody test as positive after baseline with a confirmed positive result at baseline, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Confirmatory antibody test as positive after baseline with no result at baseline, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

Important Potential Risk:	Immunogenicity

Confirmatory antibody test as positive after baseline with an unconfirmed positive or a negative result at baseline, n (%)	0 (0)	0 (0)	1 (4)	1 (1)
Transient[c], n (%)	0 (0)	0 (0)	0 (0)	0 (0)

Data cutoff date = 11AUG2021
a Subject with initial antibody or confirmatory antibody test results at baseline or after baseline.
b Transient is defined as a subject with a negative at baseline, developing a positive result, and then returning back to negative at the last time point tested.
c Subjects included in this summary are for those with negative or unconfirmed positive antibody at baseline who later tested positive in both initial and confirmatory test but returned to negative or unconfirmed positive at the subject last timepoint tested.
Data Source: KTE-C19-101 (ZUMA-1) 60-month analysis, Table 14.3.17.1.2 (DCO: 11AUG2021)

ZUMA-5

In ZUMA-5, 20 subjects (13%) were antibody-positive at baseline, and 21 subjects (14%) had a positive antibody test result at any time point. Samples from all 21 subjects were sent for confirmatory testing via a cell-based flow cytometry assay. Results of the confirmatory assay demonstrated that all 21 subjects were antibody negative at all time points tested.

Anti-Axicabtagene Ciloleucel Antibody Summary in ZUMA-5 (Safety Analysis Set)

	Follicular Lymphoma (N = 124)	Marginal Zone Lymphoma (N = 28)	Overall (N = 152)
Subjects with an on-study result[a], n	123	28	151
Antibody-positive at any time, n (%)	14 (11)	7 (25)	21 (14)
Subjects with a result at baseline, n	121	28	149
Antibody-positive at baseline, n (%)	14 (11)	6 (21)	20 (13)
Subjects with a post-baseline result, n	121	28	149
Antibody-positive at post-baseline with a negative or no result at baseline, n (%)	3 (2)	1 (4)	4 (3)
Antibody-positive at post-baseline with a negative result at baseline, n (%)	3 (2)	1 (4)	4 (3)
Antibody-positive at post-baseline with no result at baseline, n (%)	0 (0)	0 (0)	0 (0)
Transient[b], n (%)	2 (2)	1 (4)	3 (2)

Data cutoff date: 31 Mar 2022.
a Subject is considered on-study on or after enrollment
b Transient is defined as developing positive post-baseline with a negative or no results at baseline but result at the subject's last timepoint tested within the study period was negative.
Data Source: KTE-C19-105 (ZUMA-5) 36-month analysis, Table 14.8.1.1 (DCO: 31MAR2022)

Important Potential Risk:	Immunogenicity

ZUMA-6

In ZUMA-6, 1 subject (5%) was antibody-positive at baseline, and none of the subjects was antibody-positive post-baseline.

Anti-Axicabtagene Ciloleucel Antibody Summary in ZUMA-6 (Safety Analysis Set)

	Phase 1				Phase 2
	Cohort 1 (N = 3)	Cohort 2 (N = 3)	Cohort 3 (N = 6)	Total (N = 12)	Total (N = 22)
Subjects with an on-study[a] result, n	2	3	4	9	5
Antibody positive at any time, n (%)	0 (0)	0 (0)	1 (17)	1 (8)	0 (0)
Subjects with a result at baseline, n	2	3	5	10	9
Antibody positive at baseline, n (%)	0 (0)	0 (0)	1 (17)	1 (8)	0 (0)
Subject with postbaseline results, n	2	3	4	9	0 (0)
Antibody positive post-baseline with a negative or no result at baseline, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Transient[b] n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data cutoff date: 17 Oct 2018.
(a) Subject considered on-study on or after enrollment.
(b) Transient is defined as developing positive post-baseline with a negative or no results at baseline but result at the subjects last timepoint tested within the study period was negative.
Data Source: KTE-C19-106 (ZUMA-6), Table 14.3.14.1.1 and Table 14.3.14.1.2 (DCO: 17OCT2018)

ZUMA-7

In the axicabtagene ciloleucel arm of ZUMA-7, 8 subjects (5%) tested positive in the screening ELISA before lymphodepleting chemotherapy. Seven of these 8 subjects also tested positive in a screening ELISA after axicabtagene ciloleucel infusion. In addition, 1 subject with a negative result in the screening ELISA before lymphodepleting chemotherapy tested positive in a screening ELISA after axicabtagene ciloleucel infusion. None of the subjects who tested positive in the screening ELISA tests either before lymphodepleting chemotherapy or after axicabtagene ciloleucel infusion tested positive in the confirmatory cell-based assays.

Important Potential Risk: **Immunogenicity**

Anti-Axicabtagene Ciloleucel Antibody Summary in ZUMA-7 (Safety Analysis Set)

	Axicabtagene Ciloleucel (N = 170)
Subjects with a result prior to or post the initiation of conditioning chemotherapy, n	170
Antibody positive at any time, n (%)	9 (5)
Confirmed antibody positive at any time, n (%)	0 (0)
Subjects with a result prior to initiation of conditioning chemotherapy, n	170
Antibody positive at baseline, n (%)	8 (5)
Confirmed antibody positive at baseline, n (%)	0 (0)
Subjects with a result post initiation of conditioning chemotherapy, n	161
Antibody positive with positive result prior, n (%)	7 (4)
Antibody positive with no result prior, n (%)	0 (0)
Antibody positive with a negative prior, n (%)	1 (1)
Transient[a], n (%)	0 (0)
Confirmed antibody positive with confirmed positive prior, n (%)	0 (0)
Confirmed antibody positive with no result prior, n (%)	0 (0)
Confirmed antibody positive with unconfirmed positive or a negative prior, n (%)	0 (0)
Transient[b], n (%)	0 (0)

Data cutoff date = 18MAR2021
Abbreviations: CAR, chimeric antigen receptor.
Note: Percentages are based on the number of subjects treated with axicabtagene ciloleucel. Data from the retreatment period are not included.
Note: In order to be confirmed antibody positive, a confirmatory positive result is required.
a. Transient is defined as a subject with a negative at baseline, developing a positive result, and then returning back to negative at the last time point tested.
b. Subjects included in this summary are for those with unconfirmed positive or negative antibody at baseline who later tested positive in both initial and confirmatory testings but returned to negative or unconfirmed positive at the subject's last timepoint.
Data Source: KTE-C19-107 (ZUMA-7) Primary analysis, Table 14.3.3.6.1 (DCO: 18MAR2021)

KT-EU-471-0117 (PASS) (as of 01 February 2021)

Not collected.

Post-marketing (Cumulative to 22 August 2022)

The cumulative immunogenicity case reporting rate was 0.1% (3/4497).

Risk groups or risk factors: Not known.

Preventability: None.

Important Potential Risk:	Immunogenicity
Impact on the benefit-risk balance of the product:	From the current evidence, there is no impact on the risk-benefit of axicabtagene ciloleucel. Routine and additional pharmacovigilance activities will further characterize the risk of immunogenicity with respect to number of reports, seriousness, outcome, and risk factors.
Public health impact	No impact based upon current evidence.

Abbreviations: CAR = chimeric antigen receptor; CD20 = cluster of differentiation 20; CRS = cytokine release syndrome; ELISA = enzyme-linked immunoassay; PASS = postauthorization safety study; scFv = single chain variable region fragment; TEAE = treatment-emergent adverse event.

Table SVII.13. Important Potential Risk: TLS

Important Potential Risk:	TLS
Potential mechanisms	TLS occurs when the cellular components of tumor cells are released into the blood after lysis.
Evidence source and strength of evidence	There have been a few reports of TLS in clinical trials and post-marketing.
Characterisation of the risk	**Clinical trials** **ZUMA-1 and ZUMA-7 (as of 18 March 2021)** **Incidence of Treatment-emergent TLS by PT and Worst Grade (Safety Analysis Set)**

	Standard of Care Therapy		Axicabtagene Ciloleucel					
	ZUMA-7 (N = 168)		ZUMA-7 (N = 170)		ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)		Overall (N = 278)	
MedDRA PT, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any treatment-emergent TLS	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (0)
TLS	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (0)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; PT = Preferred Term; TEAE = treatment-emergent adverse event; TLS = tumor lysis syndrome.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column.

Important Potential Risk:	**TLS**
	Preferred terms are sorted in descending order of the number of subjects with Any Grade in the Overall column. Tumour lysis syndrome are identified using the SMQ (narrow version) of tumour lysis syndrome. Data Source: ADSL, ADAE Programme Name: t_aewg_hypo Output Generated: 20210730T16:05 **ZUMA-5 (as of 14 September 2020)** In ZUMA-5, no cases of TLS were reported. **KT-EU-471-0117 (PASS) (as of 01 February 2021)** There were only 2 patients with TLS. Grade of TLS was unknown for both patients. Time to onset was 1.6 and 5.7 months respectively for the two patients. Median time to onset was 3.6 months (range 1.6 to 5.6 months). **Post-marketing (as of 17 April 2021)** The cumulative TLS case reporting rate was 0.0% (1/4497). **Impact on quality of life** The consequences of TLS include the serious morbidity and high risk of mortality associated with the condition itself. Additionally, TLS may delay or force an alteration in the patient's chemotherapy regimen.
Risk groups or risk factors	**Patient factors**: Tumor size and presence of bulky tumor, wide metastatic dispersal, and organ and/or bone marrow involvement. Patients' health status, including presence of hypotension, dehydration, acidic urine oliguria, pre-cancer nephropathy, and previous experience with nephrotoxic agents. **Additive or synergistic factors**: Medications and other compounds that tend to increase uric acid levels.
Preventability	To minimize the risk of TLS, patients with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to axicabtagene ciloleucel infusion. Signs and symptoms of TLS must be monitored, and events should be managed according to standard guidelines.
Impact on the benefit-risk balance of the product:	Routine and additional pharmacovigilance activities will further characterize the risk of TLS with respect to number of reports, seriousness, outcome, and risk factors and that the data is consistent with the information already known for this risk. The safe use of axicabtagene ciloleucel will be disseminated through routine risk minimization measures. The risk will be mitigated by these measures such that the benefit-risk for the product, considering the seriousness of the indication, is positive.
Public health impact	Minimal due to the rarity of the condition.

Abbreviations: PASS = postauthorization safety study; TLS = tumor lysis syndrome.

Table SVII.14. Important Potential Risk: GvHD

Important Potential Risk:	GvHD
Potential mechanisms	There is a theoretical risk of aggravation of GvHD in patients who have previously undergone an allo-HSCT and then received donor derived engineered CAR T cells (from prior allo-HSCT donor) for their relapsed NHL. The mechanism of aggravation of GvHD is via engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host and having histocompatibility differences with the donor, resulting in donor T cell activation against either the recipient MHC antigens or minor histocompatibility antigens {Liu 2017}.
Evidence source and strength of evidence	There have been a few reports of GvHD in patients treated with axicabtagene ciloleucel.
Characterisation of the risk	**Clinical trials** **ZUMA-1 and ZUMA-7 (as of 18 March 2021)** None reported. **ZUMA-5 (as of 14 September 2020)** None reported. **KT-EU-471-0117 (PASS) (as of 01 February 2021)** There were no patients with acute GvHD (Grades 2-4) in the effectiveness and safety analysis set. Two patients developed chronic GvHD, one of whom underwent next treatment for primary disease (non-graft) prior to developing chronic GvHD. Both patients had allo-HSCTs prior to infusion of axicabtagene ciloleucel. **Post-marketing (as of 17 April 2021)** The cumulative GvHD case reporting rate was 0.1% (4/4497). **Impact on quality of life** From the current evidence from ZUMA-1 and ZUMA-5 studies, there does not appear to be any significant impact on quality of life.
Risk groups or risk factors	Patients who had undergone a prior allo-HSCT and then received donor derived CAR T cells (from prior allo-HSCT donor) appear to be at an increased risk of developing aggravation of GvHD or GvHD.
Preventability	Infusion must be delayed if a patient has active GvHD.
Impact on the benefit-risk balance of the product:	From the current evidence, there is no impact on the risk-benefit of axicabtagene ciloleucel. Routine and additional pharmacovigilance activities will further characterize the risk of GvHD or aggravation of GvHD with respect to number of reports, seriousness, outcome, and risk factors.
Public health impact	No impact based upon current evidence.

Abbreviations: allo-HSCT = allogenic stem cell transplant; CAR T = chimeric antigen receptor T cells; GvHD = graft versus host disease; MHC = major histocompatibility complex; NHL = non-Hodgkin lymphoma; PASS = postauthorization safety study.

SVII.3.2. Presentation of the Missing Information

Table SVII.15. Missing Information

Missing Information:	Evidence source
Use in pregnancy and lactation	Anticipated risk/consequence of the missing information: Pregnant and lactating women were excluded from enrollment in the clinical development program. No data on the use of axicabtagene ciloleucel in pregnant women is available. No reproductive and developmental toxicity animal studies have been conducted. The anticipated risk in this population is toxicity to the fetus induced by the preparative chemotherapy. In addition, there are studies that show evidence of maternal immune cells transfer to the fetus during pregnancy {Loubiere 2006} and therefore there is a possibility that CAR engineered T-cells can be transferred to the fetus. Also, there is a potential for the transfer of RCR to the fetus. The consequences of both possibilities could be harmful to the fetus. The risks of use in pregnancy and lactation cannot be defined based on available data and thus the safety profile in this population will be derived from routine pharmacovigilance activities. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with axicabtagene ciloleucel. Use of axicabtagene ciloleucel is not recommended in female patients who are either pregnant or breastfeeding. **KT-EU-471-0117 (PASS) (as of 01 March 2022)** No pregnancies of patients or their partners have been reported. **Post marketing (as of 22 August 2022)** Cumulatively, up to 22 August 2022, a total of 8 events have been reported in 5 cases: maternal exposure during pregnancy (n=4), maternal exposure before pregnancy (n=1), abortion (n=1), gestational diabetes (n=1), and pre-eclampsia (n=1). Cumulatively no congenital anomalies have been reported.
New occurrence or exacerbation of an autoimmune disorder	Anticipated risk/consequence of the missing information: Among the AEs associated with CRS is acute cytokine release and thus it is anticipated that patients with autoimmune disorder will have a less favorable safety profile. It is conceivable that patients treated in a clinical setting may include those patients with autoimmune disorder as off-label treatment. In the post-marketing setting, it is the responsibility of the prescribing physician to determine the appropriate treatment depending on the benefit-risk assessment of treatment and the condition. Risks of treating patients with an autoimmune disorder are not known and the benefit-risk assessment may be difficult to assess. The safety profile in this population will be derived from routine and additional pharmacovigilance activities.

Missing Information:	Evidence source

Clinical trials

ZUMA-1 and ZUMA-7 (As of 18 March 2021)

Incidence of Treatment-emergent Autoimmune Disorder by PT and Worst Grade (Safety Analysis Set)

	Standard of Care Therapy		Axicabtagene Ciloleucel					
	ZUMA-7 (N = 168)		ZUMA-7 (N = 170)		ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 (N = 108)		Overall (N = 278)	
MedDRA PT, n (%)	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3	Any Grade	Worst Grade ≥ 3
Subjects with any treatment-emergent autoimmune disorder	2 (1)	0 (0)	19 (11)	0 (0)	17 (16)	1 (1)	36 (13)	1 (0)
Hypogammaglobulinaemia	1 (1)	0 (0)	19 (11)	0 (0)	16 (15)	0 (0)	35 (13)	0 (0)
Haemophagocytic lymphohistiocytosis	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (0)
Colitis ulcerative	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data cut-off date is 18 March 2021.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event.
Notes: AEs are coded using MedDRA Version 23.1 and graded per CTCAE 4.03.
A TEAE is defined as an AE occurring on or after the first axicabtagene ciloleucel infusion or the first dose of salvage chemotherapy in the standard of care therapy arm in ZUMA-7. TEAEs that occurred during the retreatment period are excluded.
Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Percentages are based on the total number of subjects (N) in each column .
Preferred terms are sorted in descending order of the number of subjects with Any Grade in Overall column. Autoimmune disorders are identified as AEs using the SMQ (narrow version) of immune-mediated/autoimmune disorders.
Data Source: ADSL, ADAE Programme Name: t_aewg_bmf Output Generated: 20210730T16:04

Post marketing (as of 17 April 2021)

Cumulatively, up to 17 April 2021, 7 potential autoimmune events (7 cases) have been reported in subjects/patients administered axicabtagene ciloleucel. Events included noninfective encephalitis (n=2) and one event each of the following: autoimmune colitis, autoimmune disorder, autoimmune neuropathy, encephalitis autoimmune and psoriasis. All the events were reported as new occurrences except for the event of psoriasis which was reported as an aggravation of psoriasis.

It was determined that the cases were confounded by an infectious process, checkpoint inhibitor known to cause autoimmune events, disease progression, or contained minimal information rendering them not able to be assessed.

Missing Information:	Evidence source
Long term safety	Anticipated risk/consequence of the missing information: Specific safety events such as secondary malignancy of T-cell origin and secondary hematologic malignancies excluding T-cell malignancies may occur outside of the early post-administration period for axicabtagene ciloleucel. The PASS registry study for the long-term follow-up of patients' post-treatment will collect this information. Similarly, studies KT-US-982-5968 and KT-US-982-0910 will provide additional long-term safety data. **KT-EU-471-0117 (PASS) (as of 01 March 2022)** As of 01 March 2022, 456 patients have been enrolled in the EBMT registry of which 100-day safety follow up data was available for 379 (83.1%) patients. Most patients (89.7%) had a duration between first infusion and cutoff date of 12-36 months. The median duration between first infusion and cutoff was 25.0 months (with range 5.1 to 39.1). Secondary malignancies were reported for 7 patients. The 12-month cumulative incidence for secondary malignancy was 2% (95% CI: 1 − 4%). No other long-term safety issues were detected.

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; EBMT = European Society for Blood and Marrow Transplantation; MDS = myelodysplastic syndrome; PASS = postauthorization safety study; RCR = replication-competent retrovirus.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	Serious neurologic adverse reactions including cerebral edema and ICANS
	CRS
	Cytopenias including aplastic anemia
	Infections
	Hypogammaglobulinemia
	Secondary malignancy of T-cell origin
Important Potential Risks	Secondary hematologic malignancies excluding T-cell malignancies
	Immunogenicity
	TLS
	Aggravation of GvHD
Missing Information	Use in pregnancy and lactation
	New occurrence or exacerbation of an autoimmune disorder
	Long term safety

Abbreviations: CRS = cytokine release syndrome; GvHD = graft versus host disease; ICANS = immune effector cell-associated neurotoxicity syndrome; RCR = replication-competent retrovirus; TLS = tumor lysis syndrome.

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

The global safety database for axicabtagene ciloleucel is maintained and operated by Gilead Sciences, Inc. for reporting to regulatory authorities. All newly acquired safety information will continue to be actively monitored in accordance with good pharmacovigilance practices including regular review and evaluation of data, routine systematic review of published literature and case reports and both individual case and aggregate safety reviews and analysis.

Routine Pharmacovigilance Activities Beyond Adverse Drug Reaction Reporting and Signal Detection:

Specific Adverse Reaction/Adverse Event Follow-up Questionnaires

Table Part III.1. Specific Adverse Reaction/Adverse Event Follow-up Questionnaires

Name of Questionnaire	Description
Neurologic events	Targeted follow-up questionnaires for neurologic AEs (including serious neurologic adverse reactions) will be utilized as follow up to AE reports to determine start and stop dates of the event, severity and seriousness, outcome, diagnostic results, whether alternative causes for signs and symptoms were ruled out, treatment provided, relevant medical history, and additional medications.
CRS	Targeted follow-up questionnaires for CRS will be utilized as follow up to an ADR report to determine start and stop dates of the event, severity and seriousness, outcome, diagnostic results, whether alternative causes for signs and symptoms were ruled out, treatment provided, relevant medical history, and additional medications. This questionnaire will also collect information on patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary) who experience CRS.
New Malignancy	Targeted follow-up questionnaires for new malignancy will be utilized as follow up to AE reports to obtain further information regarding start and stop dates of the event, severity and seriousness, diagnostic results, pre-existing factors that may have contributed to the development of the new malignancy, relevant medical history and additional medications.

Abbreviations: ADR = adverse drug reaction; AEs = adverse events; CRS = cytokine release syndrome.

A copy of each follow-up questionnaire is provided in Annex 4.

Other Forms of Routine Pharmacovigilance Activities

None.

III.2. Additional Pharmacovigilance Activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

KT-EU-471-0117 (PASS): Long-term, Non-interventional Study of Recipients of Yescarta for Treatment of Relapsed or Refractory DLBCL, PMBCL and FL	
Rationale and Study Objectives	**Primary objective:** To evaluate the incidence rate and severity of ADRs in patients treated with Yescarta, including secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential. **Secondary objectives:** • To determine the overall survival rate and causes of death after administration of Yescarta. • To determine the time to next treatment after administration of Yescarta. • To determine the time to relapse or progression of primary disease after administration of Yescarta. • To assess the safety and effectiveness profile by gender, age, and in special populations (patients with prior ASCT, high risk comorbidity index, patients treated with OOS product), and additional subgroups may also be explored. • To assess the risk of TLS and aggravation of GvHD, and the detection of RCR in samples of patients with secondary malignancies. **Other exploratory objectives:** To determine the occurrence of loss of target antigen and of functional CAR T persistence in patients relapsing after Yescarta therapy.
Study Design	Prospective, long-term, non-interventional, cohort study.
Study Populations	Patients with relapsed or refractory DLBCL and PMBCL and FL.
Milestones	Final Report Submission: 30 June 2039
KTE-C19-105 (ZUMA-5): A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects with Relapsed/Refractory iNHL	
Rationale and Study Objectives	To evaluate the safety and efficacy of axicabtagene ciloleucel.
Study Design	Phase 2, multicenter, single-arm, open-label study
Study Populations	Adult subjects with relapsed or refractory FL or MZL histological subtypes.
Milestones	Safety updates in the nearest PSUR to the annual anniversary: Annual Final report: 30 April 2036
KT-US-982-5968: Long-term Follow-up Study for Participants of Kite-Sponsored Interventional Studies Treated With Gene-Modified Cells	
Rationale and Study Objectives	To evaluate the long-term safety and efficacy of Kite-sponsored interventional studies treated with gene-modified cells.
Study Design	A prospective, long-term follow-up study.
Study Populations	Subjects with solid or hematological malignancies who received an infusion of gene-modified cells in a completed Kite-sponsored interventional study.
Milestones	Safety updates in the PSUR: Annual Final summary of results[1]: closest PSUR following the last patient last visit

[1] Results will be summarised by cohorts belonging to each relevant parent study.

KT-US-982-0910: Molecular profiling of tissue samples from patients who received a Kite-manufactured gene-modified cell therapy and have developed a secondary malignancy of T-cell origin	
Rationale and Study Objectives	This study aims to assess potential CAR transgene involvement in developing a secondary T-cell malignancy in patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel. **Primary objective** To assess potential CAR transgene involvement by performing molecular profiling of tissue samples obtained, or are about to be obtained during routine clinical practice, from patients who were treated with axicabtagene ciloleucel or brexucabtagene autoleucel and developed a secondary T-cell malignancy. The molecular profiling will include the following, as applicable: ▪ The presence of the CAR transgene in the blood and/or tumor and/or bone marrow biopsy, as well as the CAR level, if the CAR transgene was detected. ▪ Presence of RCR. **Exploratory objectives** ▪ To assess the presence of somatic mutations that are common in hematologic malignancies. ▪ Transgene integration site analysis. ▪ To assess the presence of a malignant clone and/or pre-existing mutations before treatment with axicabtagene ciloleucel and brexucabtagene autoleucel that could have led to the development of secondary malignancy of T-cell by performing comparative molecular profiling with apheresis and/or product material (if available). ▪ Transcriptome/RNA analysis
Study Design	
Study Populations	Patients who have received a Kite-manufactured CAR-T cell therapy (axicabtagene ciloleucel or brexucabtagene autoleucel) and have reported a suspected secondary malignancy of T-cell origin.
Milestones	Start of data collection: Q4-2025 End of data collection: N/A at this stage Study Duration: N/A at this stage Final report of study results: N/A at this stage Interim reporting of cases: PSUR Interim summary reports: every 5 years

Abbreviations: ADR = adverse drug reaction; ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; CAR T = chimeric antigen receptor T cells; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; GvHD = graft versus host disease; iNHL = indolent non-Hodgkin lymphoma; MZL = marginal zone lymphoma; OOS = out of specification; PASS = postauthorization safety study; PMBCL = primary mediastinal B-cell lymphoma; PSUR = periodic safety update report; RCR = replication-competent retrovirus; TLS = tumour lysis syndrome.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.3. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
KT-EU-471-0117 (PASS): Long-term, non-interventional study of recipients of Yescarta for	Additional characterization of the identified risks, further evaluation of potential	Serious neurologic adverse reactions including cerebral edema and ICANS CRS	Final Report Submission	30 June 2039

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
treatment of relapsed or refractory DLBCL, PMBCL and FL Ongoing	risks and missing information.	Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia Secondary malignancy of T-cell origin Secondary hematologic malignancies excluding T-cell malignancies TLS Aggravation of GvHD Use in pregnancy and lactation New occurrence or exacerbation of an autoimmune disorder Long term safety		
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
KTE-C19-105 (ZUMA-5): A Phase 2 multicenter study of axicabtagene ciloleucel in subjects with relapsed/refractory iNHL Ongoing	To assess efficacy and safety of axicabtagene ciloleucel in subjects with relapsed/refractory iNHL	Serious neurologic adverse reactions including cerebral edema and ICANS CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary malignancy of T-cell origin Secondary hematologic malignancies excluding T-cell malignancies Immunogenicity TLS Aggravation of GvHD New occurrence or exacerbation of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary	Annual
			Final report	30 Apr 2036
			PSUR	Annually

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
KT-US-982-5968: Long-term Follow-up Study for Participants of Kite-Sponsored Interventional Studies Treated With Gene-Modified Cells Ongoing	To evaluate the long-term safety and efficacy of Kite-sponsored interventional studies treated with gene-modified cells	Serious neurologic adverse reactions including cerebral edema and ICANS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary malignancy of T-cell origin Secondary hematologic malignancies excluding T-cell malignancies Immunogenicity Use in pregnancy and lactation New occurrence or exacerbation of an autoimmune disorder Long term safety	Final summary of results[2]	Closest PSUR following last patient last visit
KT-US-982-0910: Molecular profiling of tissue samples from patients who received a Kite-manufactured gene-modified cell therapy and have developed a secondary malignancy of T-cell origin Planned	**Primary objective** To assess potential CAR transgene involvement by performing molecular profiling of tissue samples obtained or are about to be obtained during routine clinical practice, from patients who were treated with axicabtagene ciloleucel or brexucabtagene autoleucel and developed a secondary T-cell malignancy. The molecular profiling will include the following, as applicable: ▪ The presence of the CAR transgene in the blood and/or tumor and/or bone marrow biopsy, as well as the CAR level, if the CAR transgene was detected.	Secondary malignancy of T-cell origin Long-term safety	Final report Interim reporting of cases: Interim summary reports	N/A at this stage PSUR Every 5 years

[2] Results will be summarised by cohorts belonging to each relevant parent study (ZUMA-1 or ZUMA-6).

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	▪ Presence of RCR. **Exploratory objectives** ▪ To assess the presence of somatic mutations that are common in hematologic malignancies. ▪ Transgene integration site analysis. ▪ To assess the presence of a malignant clone and/or pre-existing mutations before treatment with axicabtagene ciloleucel and brexucabtagene autoleucel that could have led to the development of secondary malignancy of T-cell by performing comparative molecular profiling with apheresis and/or material (if available). ▪ Transcriptome/RNA analysis			

Abbreviations: CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; GvHD = graft versus host disease; ICANS = immune effector cell-associated neurotoxicity syndrome; iNHL = indolent non-Hodgkin lymphoma; PASS = postauthorization safety study; PMBCL = primary mediastinal B-cell lymphoma; PSUR = periodic safety update report; RCR = replication-competent retrovirus; TLS = tumor lysis syndrome.

PART IV:
PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing post-authorization efficacy studies.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 Routine risk minimization measures

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
Serious neurologic adverse reactions including cerebral edema and ICANS	**Routine risk communication**: SmPC sections: 4.2, 4.4, 4.7, and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring and management of serious neurologic adverse reactions, including treatment algorithms, are included in the SmPC sections 4.2 and 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
CRS	**Routine risk communication**: SmPC sections: 4.2, 4.4 and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring and management of CRS, including treatment algorithms, are included in the SmPC sections 4.2 and 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
Cytopenias including aplastic anemia	**Routine risk communication**: SmPC sections: 4.4 and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for blood count monitoring is included in SmPC sections 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
Infections	**Routine risk communication**: SmPC sections: 4.2, 4.4 and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for monitoring the signs and symptoms of infection before, during and after Yescarta infusion and treatment are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers

Safety concern	Routine risk minimization activities
Hypogammaglobulinemia	**Routine risk communication**: SmPC sections: 4.4 and 4.8 PL section: 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring immunoglobulin levels and management using infection precautions, antibiotic prophylaxis and immunoglobulin replacement are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
Secondary malignancy of T-cell origin	**Routine risk communication**: SmPC sections: 4.4 and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: SmPC section 4.4 recommends lifelong monitoring for secondary malignancies. In addition, in the event of a secondary malignancy of T-cell origin, the company is to be contacted to obtain instructions on collecting patient samples for testing. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
Important Potential Risks	
Secondary hematologic malignancies excluding T-cell malignancies	**Routine risk communication**: SmPC sections: 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for life-long monitoring for secondary malignancies is included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
Immunogenicity	**Routine risk communication**: SmPC sections: 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
TLS	**Routine risk communication**: SmPC section: 4.4 PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations that patients with elevated uric acid or high tumour burden receive treatment prior to infusion, and for monitoring and management of TLS are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers

Safety concern	Routine risk minimization activities
Aggravation of GvHD	**Routine risk communication**: SmPC section 4.4 PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Infusion must be delayed if a patient has active GvHD. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
Missing Information	
Use in pregnancy and lactation	**Routine risk communication**: SmPC sections: 4.6 PL section: 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Requirement for verification of pregnancy status of women of childbearing potential included in SmPC section 4.6. Recommendation to refer to information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy in SmPC section 4.6 and PL section 2. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
New occurrence or exacerbation of an autoimmune disorder	**Routine risk communication**: SmPC section 5.1 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers
Long term safety	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers

Abbreviations: CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CRS = cytokine release syndrome; GvHD = graft versus host disease; ICANS = immune effector cell-associated neurotoxicity syndrome; PL = patient leaflet; RCR = replication-competent retrovirus; SmPC = summary of product characteristics; TLS = tumor lysis syndrome.

V.2 Additional Risk Minimization Measures

Table Part V.2. Additional Risk Minimization Activity: HCP Educational Material

HCP Educational Material	
Objective(s)	To inform HCPs on how to monitor and/or manage symptoms associated with CRS, serious neurologic adverse reactions and secondary malignancy of T-cell origin and provide guidance on reporting these serious adverse reactions associated with Yescarta.

HCP Educational Material	
Rationale for the additional risk minimization activity	The HCP educational material will be provided at launch of the product and at the time of updates in each member state and will highlight the risks of Yescarta and will help ensure that the HCPs using Yescarta are made aware of the risks of CRS, serious neurologic adverse reactions and secondary malignancy of T-cell origin and will be able to monitor for them. The HCP educational material will also help HCPs ensure that they have access to a minimum of 1 dose of tocilizumab prior to Yescarta infusion. The treatment center must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment center must have access to suitable alternative measures instead of tocilizumab to treat CRS. CRS is not commonly observed with most anti-cancer medications. Therefore, HCPs may not be as experienced in managing these adverse reactions. It is anticipated that HCP educational material will enhance early diagnosis and proper evidence-based management of these events, including information on when and how to use tocilizumab and/or steroids. The expected result is improvement in the outcomes of or mitigating severe, life-threatening, and fatal CRS and/or neurologic adverse reactions. Details of the key risk messages are provided in Annex 6.
Target audience and planned distribution path	The HCP educational material targets HCPs who are likely to prescribe Yescarta. The method of delivery of the HCP educational material is determined on a Member State basis to align with local clinical organization.
Plans to evaluate the effectiveness of the interventions and criteria for success	None, Study KT-EU-471-0116 was completed and removed from the RMP.
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable.

Abbreviations: CRS = cytokine release syndrome; HCP = healthcare professional; PAC = patient alert card; SOP = standard operating procedure.

Table Part V.3. Additional Risk Minimization Activity: Patient Alert Card (PAC)

PAC	
Objective(s)	To inform patients of the risks of CRS and serious neurologic adverse reactions, associated with Yescarta. For patients to share the information in the PAC with their HCPs.
Rationale for the additional risk minimization activity	Easy and immediate patients' access to information about the common signs and symptoms of CRS, and serious neurologic adverse reactions will promote early medical attention and treatment that will help mitigating the risks. Details of the key risk messages are provided in Annex 6.
Target audience and planned distribution path	The target audience is patients who will be treated with Yescarta. The PAC will be part of the health care professional kit and will be provided to the patient by the hematologist/heme oncologist or nursing staff.
Plans to evaluate the effectiveness of the interventions and criteria for success	None, Study KT-EU-471-0116 was completed and removed from the RMP.
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable.

Abbreviations: CRS = cytokine release syndrome; HCP = healthcare professional; PAC = patient alert card.

Table Part V.4. Additional Risk Minimization Activity: Controlled Distribution Program

Controlled Distribution Program	
Objective(s)	To ensure that Yescarta is only administered in a qualified clinical setting.
Rationale for the additional risk minimization activity	To minimize the important risks of CRS and neurologic adverse reactions, clinical facilities are required to complete a formal site qualification process prior to ordering Yescarta.
Target audience and planned distribution path	The controlled distribution program targets clinical facilities in which Yescarta is administered. The process of qualification is carried out by the Quality Assurance Site Qualification EU team at Kite Pharma EU BV. The site qualification process includes the following steps: • Introduction to key Yescarta processes • Ensuring HCPs are made aware of the need to contact the MAH to obtain recommendations for tumor sample collection and testing following the development of a secondary malignancy of T cell origin • Quality Audit • Training of HCPs • "Dry-run exercise" • Continued monitoring of compliance
Plans to evaluate the effectiveness of the interventions and criteria for success	The evaluation of the effectiveness of the controlled distribution program includes the following: • A post-marketing registry is assessing the incidence of serious neurologic adverse reactions and CRS and thus provides an outcome measure of the effectiveness of the risk minimization program. As of the data cut-off date of 01 March 2022, neurotoxicity was observed in 40.3% of the cases. The majority of cases (51.1%) experienced grade 1 or 2 neurologic events; 33.1%, 10.2%, and 1.6% experienced Grade 3, Grade 4, and Grade 5 neurologic events, respectively. The most common symptoms of neurotoxicity were altered mental status and tremors. CRS was observed in 84.8% of the cases. The majority of cases (89.3%) experienced grade 1 or 2 CRS. Grade 3 was reported in 10.4%. No Grade 4 CRS was reported, and one patient (0.3%) had Grade 5. In summary, the controlled distribution program shows lower rates of neurologic events and CRS to the reported rate in the clinical development program and thus it is considered effective. • Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification.
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable.

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; EU = European Union; HCP = healthcare professional.

V.3 Summary of risk minimization measures

Table Part V.5. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
Serious neurologic adverse reactions including cerebral edema and ICANS	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, 4.7, and 4.8 PL sections 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** • HCP educational material • PAC • Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event follow-up questionnaire **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit
CRS	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 PL sections 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** • HCP educational material • PAC • Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event follow-up questionnaire **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036
Cytopenias including aplastic anemia	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Infections	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit
Hypogammaglobulinemia	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PL section: 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit
Secondary malignancy of T-cell origin	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PL section: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** • HCP educational material • Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event follow-up questionnaire **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit KT-US-982-0910: N/A at this stage
Important potential risk(s)		
Secondary hematologic malignancies excluding T-cell malignancies	**Routine risk minimization measures:** SmPC sections 4.4 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Event follow-up questionnaire **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	None	KT-US-982-5968: closest PSUR following last patient last visit
Immunogenicity	**Routine risk minimization measures:** SmPC sections 4.8 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit
TLS	**Routine risk minimization measures:** SmPC sections 4.4 PL section 2 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036
Aggravation of GvHD	**Routine risk minimization measures:** SmPC section 4.4 PL section 2 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036
Missing information		
Use in pregnancy and lactation	**Routine risk minimization measures:** SmPC sections 4.6 PL section 2 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 KT-US-982-5968: closest PSUR following last patient last visit

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
New occurrence or exacerbation of an autoimmune disorder	**Routine risk minimization measures:** SmPC section 5.1 Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit
Long term safety	**Routine risk minimization measures:** Use restricted to physicians experienced in the treatment of hematological cancers. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit KT-US-982-0910: N/A at this stage

Abbreviations: CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CRS = cytokine release syndrome; GvHD = graft versus host disease; HCP = healthcare professional; ICANS = immune effector cell-associated neurotoxicity syndrome; PAC = patient alert card; PL = patient leaflet; RCR = replication-competent retrovirus; SmPC = summary of product characteristics; TLS = tumor lysis syndrome.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLANERROR! NO DOCUMENT VARIABLE SUPPLIED.

SUMMARY OF RISK MANAGEMENT PLAN FOR YESCARTA (AXICABTAGENE CILOLEUCEL)

This is a summary of the risk management plan (RMP) for Yescarta (axicabtagene ciloleucel). The RMP details important risks of Yescarta, how these risks can be minimized, and how more information will be obtained about Yescarta's risks and uncertainties (missing information).

Yescarta's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Yescarta should be used.

This summary of the RMP for Yescarta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Yescarta's RMP.

I. The Medicine and What is it Used for

Yescarta is authorized 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. In addition, Yescarta is authorized for the treatment of adult patients with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy; and adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy (see SmPC for the full indication). It contains axicabtagene ciloleucel as the active substance and it is a single infusion product for autologous and intravenous use only.

Further information about the evaluation of Yescarta's benefits can be found in Yescarta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/human_med_002292.jsp&mid=WC0b01ac058001d124.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Yescarta, together with measures to minimize such risks and the proposed studies for learning more about Yescarta's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimizes its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Yescarta, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed (e.g., via the periodic safety update report [PSUR]) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Yescarta is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Yescarta are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Yescarta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	Serious neurologic adverse reactions including cerebral oedema and ICANS
	Cytokine release syndrome (CRS)
	Cytopenias including aplastic anemia
	Infections
	Hypogammaglobulinemia
	Secondary malignancy of T-cell origin
Important Potential Risks	Secondary hematologic malignancies excluding T-cell malignancies
	Immunogenicity
	Tumor lysis syndrome (TLS)
	Aggravation of graft versus host disease (GvHD)
Missing Information	Use in pregnancy and lactation
	New occurrence or exacerbation of an autoimmune disease
	Long term safety

II.B. Summary of Important Risks

Yescarta has been assigned the legal status of a medicine subject to medical prescription in the EU, whereby therapy should be initiated by a doctor experienced in the management of haematological cancers (as described in Section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**Serious Neurologic Adverse Reactions including Cerebral Oedema and ICANS**
Evidence for linking the risk to the medicine	Serious neurologic adverse reactions were reported in clinical trials, post-marketing surveillance, and in patient treated with other CAR T therapies.
Risk factors and risk groups	**Patient factors**: Younger patients (<65) and male patients had a lower incidence of neurologic events. **Dose-related**: A higher dose of CAR T cells and/or potency of the cells was associated with a higher rate of neurologic events.
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC sections 4.2, 4.4, 4.7, and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: Healthcare professional (HCP) educational material Patient alert card (PAC) Controlled distribution program
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit See Section VI.2 of this summary for an overview of the post-authorisation development plan.
Important Identified Risk	**CRS**
Evidence for linking the risk to the medicine	CRS was reported in clinical trials, post-marketing surveillance, and in patient treated with other CAR T therapies.
Risk factors and risk groups	**Patient factors**: A higher disease burden and organ dysfunction was associated with a higher rate of CRS. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement or history of cardiovascular disease. **Dose-related**: A higher dose of CAR T cells and/or potency of the cells was associated with a higher rate of CRS. **Synergistic effects**: Treatment with systemic immunostimulatory agents.
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC sections 4.2, 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: HCP educational material PAC Controlled distribution program
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 See Section VI.2 of this summary for an overview of the postauthorisation development plan.

Important Identified Risk	Cytopenias including Aplastic Anaemia
Evidence for linking the risk to the medicine	Cytopenias were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Risk factors and risk groups	Prior exposure to chemotherapy or radiation.
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC sections 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit See Section VI.2 of this summary for an overview of the postauthorization development plan.
Important Identified Risk	**Infections**
Evidence for linking the risk to the medicine	Infections were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Risk factors and risk groups	**Patient factors**: Underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, and psychological stress. **Additive or synergistic factors**: Surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures.
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC sections 4.2, 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit See Section VI.2 of this summary for an overview of the postauthorization development plan
Important Identified Risk	**Hypogammaglobulinemia**
Evidence for linking the risk to the medicine	Hypogammaglobinaemia was reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
Risk factors and risk groups	Prior treatment with rituximab and concomitant use of other drugs (e.g. steroids) that can induce hypogammaglobulinemia.
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC sections 4.4 and 4.8 PL section: 4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit See Section VI.2 of this summary for an overview of the postauthorization development plan.

Important Identified Risk	Secondary Malignancy of T-cell Origin
Evidence for linking the risk to the medicine	Secondary malignancies of T-cell origin have been reported within weeks and up to several years following the administration of CAR T-cell medicines. These findings implied that CAR T-cell therapies may have been involved in developing T-cell malignancy.
Risk factors and risk groups	
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC sections 4.4 and 4.8 PL section: 2, 4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: HCP educational material Controlled distribution program
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit KT-US-982-0910: N/A at this stage See Section VI.2 of this summary for an overview of the postauthorization development plan.
Important potential risk	**Secondary Hematologic Malignancies excluding T-cell malignancies**
Evidence for linking the risk to the medicine	Secondary hematologic malignancies, excluding T-cell malignancies, were reported in clinical trials, post-marketing surveillance, or patients treated with other CAR T therapies.
Risk factors and risk groups	**Patient factors**: Age. **Additive or synergistic factors**: Chemotherapy and immunosuppressive treatments.
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC sections 4.4 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit See Section VI.2 of this summary for an overview of the postauthorization development plan.
Important potential risk	**Immunogenicity**
Evidence for linking the risk to the medicine	There have been a few reports of immunogenicity in clinical trials and post-marketing.
Risk factors and risk groups	Not known
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC section 4.8 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit See Section VI.2 of this summary for an overview of the postauthorization development plan.

Important potential risk	TLS
Evidence for linking the risk to the medicine	There have been a few reports of TLS in clinical trials and post-marketing.
Risk factors and risk groups	**Patient factors** Tumour size and presence of bulky tumour, wide metastatic dispersal, and organ and/or bone marrow involvement. Patients' health status, including presence of hypotension, dehydration, acidic urine, oliguria, pre-cancer nephropathy, and previous experience with nephrotoxic agents. **Additive or synergistic factors**: Medications and other compounds that tend to increase uric acid levels
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC sections 4.4 PL section 2 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 See Section VI.2 of this summary for an overview of the postauthorization development plan.
Important potential risk	**Aggravation of GvHD**
Evidence for linking the risk to the medicine	There have been a few reports of GvHD in patients treated with axicabtagene ciloleucel.
Risk factors and risk groups	Patients who had undergone a prior allogeneic haematopoietic stem-cell transplant (allo-HSCT) and then received donor derived CAR T cells (from prior allo-HSCT donor) appear to be at an increased risk of developing aggravation of GvHD or GvHD.
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC section 4.4 PL section 2 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 See Section VI.2 of this summary for an overview of the post-authorization development plan.
Missing information	**Use in pregnancy and lactation**
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC section 4.6 PL section: 2 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 KT-US-982-5968: closest PSUR following last patient last visit See Section VI.2 of this summary for an overview of the postauthorisation development plan.

Missing information	New Occurrence or Exacerbation of an Autoimmune Disorder
Risk minimization measure(s)	**Routine risk minimization measures**: SmPC section 5.1 Use restricted to physicians experienced in the treatment of haematological cancers. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit See Section VI.2 of this summary for an overview of the postauthorisation development plan.
Missing information	**Long Term Safety**
Risk minimization measure(s)	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of haematological cancers. **ditional risk minimization measures**: None
Additional pharmacovigilance activities	KT-EU-471-0117: 30 Jun 2039 ZUMA-5: 30 Apr 2036 KT-US-982-5968: closest PSUR following last patient last visit KT-US-982-0910: N/A at this stage See Section VI.2 of this summary for an overview of the postauthorisation development plan.

VI.2. Post-authorization Development Plan

II.A.1. Studies which are Conditions of the Marketing Authorization

Table Part VI.3. Studies as Condition of the Marketing Authorization

Study Short Name	Purpose of the Study
KT-EU-471-0117	**Primary objective**: To evaluate the incidence rate and severity of adverse drug reactions (ADRs) in patients treated with Yescarta, including secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinaemia, and pregnancy outcomes in female patients of childbearing potential. **Secondary objectives**: To determine the overall survival rate and causes of death after administration of Yescarta. To determine the time to next treatment after administration of Yescarta. To determine the time to relapse or progression of primary disease after administration of Yescarta. To assess the safety and effectiveness profile by gender, age, and in special populations (patients with prior autologous stem cell transplant, high risk comorbidity index, patients treated with out-of-specification product), and additional subgroups may also be explored. To assess the risk of TLS and aggravation of GvHD, and the detection of RCR in samples of patients with secondary malignancies. **Other exploratory objectives**: To determine the occurrence of loss of target antigen and of functional CAR T persistence in patients relapsing after Yescarta therapy.

II.A.2. Other Studies in Post-Authorization Development Plan

Table Part VI.4. Other Studies in Post-Authorization Development Plan

Study Short Name	Purpose of the Study
KTE-C19-105 (ZUMA-5)	To evaluate the safety and efficacy of axicabtagene ciloleucel.
KT-US-982-5968	To evaluate the long-term safety and efficacy of Kite-sponsored interventional studies treated with gene-modified cells.
KT-US-982-0910	To assess potential CAR transgene involvement in developing a secondary T-cell malignancy in patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel.

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Planned and On-going Studies

Completed Studies

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Non-Interventional Post Authorisation Safety Study (PASS) (KT-EU-471-0117)

KTE-C19-105 (ZUMA-5)

KT-US-982-5968

KT-US-982-0910

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Event follow-up questionnaire – Neurologic events

Event follow-up questionnaire – Cytokine release syndrome (CRS)

Event follow-up questionnaire – New Malignancy

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None.

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

Approved key risk messages for the additional risk minimization measures

Annex 7. Other Supporting Data (Including Referenced Material)

REFERENCES

Annex 8. Summary of Changes to the Risk Management Plan over Time

List of Significant Changes to the RMP Over Time

1. REFERENCES

Accorsi Buttini E, Farina M, Lorenzi L, Polverelli N, Radici V, Morello E, et al. High risk-myelodysplastic syndrome following CAR T-cell therapy in a patient with relapsed diffuse large B cell lymphoma: A case report and literature review. Front Oncol 2023;13:1036455.

ALIQOPA, Bayer HealthCare Pharmaceuticals Inc. ALIQOPA™ (copanlisib) for injection, for intravenous use. U. S. Prescribing Information. Whippany, NJ. Revised: September. 2017:

Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1998;16 (8):2780-95.

Bear AS, Morgan RA, Cornetta K, June CH, Binder-Scholl G, Dudley ME, et al. Replication-Competent Retroviruses in Gene-Modified T Cells Used in Clinical Trials: Is It Time to Revise the Testing Requirements? Molecular therapy : the journal of the American Society of Gene Therapy 2012;20 (2):246-9.

Bhatt VR, Mourya R, Shrestha R, Armitage JO. Primary Mediastinal Large B-Cell Lymphoma. Cancer treatment reviews 2015;41 (6):476-85.

Biasco L, Ambrosi A, Pellin D, Bartholomae C, Brigida I, Roncarolo MG, et al. Integration profile of retroviral vector in gene therapy treated patients is cell-specific according to gene expression and chromatin conformation of target cell. Embo Mol Med 2011;3 (2):89-101.

Bouziana S, Bouzianas D. The Current Landscape of Secondary Malignancies after CAR T-Cell Therapies: How Could Malignancies Be Prevented? Int J Mol Sci 2024;25 (17).

Brentjens RJ, Davila ML, Riviere I, Park J, Wang X, Cowell LG, et al. CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia. Science translational medicine 2013;5 (177):177ra38.

Breyanzi, Bristol-Myers Squibb Company. BREYANZI® (lisocabtagene maraleucel) suspension for intravenous infusion. 2021.

Brudno JN, Kochenderfer JN. Toxicities of Chimeric Antigen Receptor T Cells: Recognition and Management. Blood 2016a;127 (26):3321-30.

Brudno JN, Somerville RP, Shi V, Rose JJ, Halverson DC, Fowler DH, et al. Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016b;34 (10):1112-21.

CancerMPact. Kantar. Available at: www.cancermpact.com. 2021:

Cappell KM, Sherry RM, Yang JC, Goff SL, Vanasse DA, McIntyre L, et al. Long-Term Follow-Up of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy. J Clin Oncol 2020;38 (32):3805-15.

Casulo C. How I manage patients with follicular lymphoma. Br J Haematol 2019;186 (4):513-23.

Casulo C, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33 (23):2516-22.

Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K, et al. Guidelines for the management of diffuse large B-cell lymphoma. British journal of haematology 2016;174 (1):43-56.

Chang EC, Liu H, West JA, Zhou X, Dakhova O, Wheeler DA, et al. Clonal Dynamics In Vivo of Virus Integration Sites of T Cells Expressing a Safety Switch. Molecular Therapy 2016;24 (4):736-45.

Chihara D, Dores GM, Flowers CR, Morton LM. The bidirectional increased risk of B-cell lymphoma and T-cell lymphoma. Blood 2021;138 (9):785-9.

Chihara D, Nastoupil LJ, Williams JN, Lee P, Koff JL, Flowers CR. New insights into the epidemiology of non-Hodgkin lymphoma and implications for therapy [Author Manuscript]. Expert Rev Anticancer Ther 2015;15 (5):531-44.

Chira S, Jackson CS, Oprea I, Ozturk F, Pepper MS, Diaconu I, et al. Progresses towards safe and efficient gene therapy vectors. Oncotarget 2015;6 (31):30675-703.

Cultrera JL, Dalia SM. Diffuse large B-cell lymphoma: current strategies and future directions. Cancer Control: Journal of the Moffitt Cancer Center 2012;19 (3):204-13.

Dabrowska-Iwanicka A, Walewski JA. Primary mediastinal large B-cell lymphoma. Curr Hematol Malig Rep 2014;9 (3):273-83.

Dores GM, Morton LM. T-Cell Neoplasms after B-Cell Neoplasms - The Pre-CAR T-Cell Era. The New England journal of medicine 2024;391 (7):662-4.

Dreyling M, Santoro A, Mollica L, Leppa S, Follows GA, Lenz G, et al. Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol 2017;35 (35):3898-905.

European Medicines Agency. Committee for Medicinal Product for Human Use (CHMP) Guideline on Human Cell-Based Medicinal Products. 21 May, 2008a.

European Medicines Agency. ICH Topic S 9 Nonclinical Evaluation for Anticancer Pharmaceuticals - Step 3 - Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008). December, 2008b.

Evrard SM, Péricart S, Grand D, Amara N, Escudié F, Gilhodes J, et al. Targeted next generation sequencing reveals high mutation frequency of CREBBP, BCL2 and KMT2D in high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. Haematologica 2019;104 (4):e154-e7.

Falini L, Venanzi A, Tini V, Innocente A, Ballanti S, Saldi S, et al. Acute myeloid leukemia development soon after anti-CD19 chimeric antigen receptor T-cell infusion in a patient with refractory diffuse large B-cell lymphoma and pre-existing clonal hematopoiesis. Haematologica 2023;108 (1):290-4.

Finney HM, Lawson AD, Bebbington CR, Weir AN. Chimeric Receptors Providing Both Primary and Costimulatory Signaling in T Cells from a Single Gene Product. J Immunol 1998;161 (6):2791-7.

Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. CA: a cancer journal for clinicians 2010;60 (6):393-408.

Fraietta JA, Nobles CL, Sammons MA, Lundh S, Carty SA, Reich TJ, et al. Disruption of TET2 Promotes the Therapeutic Efficacy of CD19-Targeted T Cells. Nature 2018;558:307-12.

Galli E, Rossi M, Pansini I, Viscovo M, Malara T, Colangelo M, et al. Predicting therapy-related myeloid neoplasms after CAR-T with the Clonal Haematopoiesis Risk Score (CHRS). British journal of haematology 2025;206 (1):372-4.

Global Health Data Exchange (GHDx). GBD Results Tool. Available at: http://ghdx.healthdata.org/gbd-results-tool. Accessed: 31 May 2021. 2019:

Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370 (11):1008-18.

Griffith JW, Sokol CL, Luster AD. Chemokines and chemokine receptors: positioning cells for host defense and immunity. Annual review of immunology 2014;32:659-702.

Harrison SJ, Nguyen T, Rahman M, Er J, Li J, Li K, et al. CAR+ T-Cell Lymphoma Post Ciltacabtagene Autoleucel Therapy for Relapsed Refractory Multiple Myeloma. Blood 2023;142:6939.

Hester L, Park SI, Lund JL. Patterns of comorbidity among older U.S. patients with non-Hodgkin lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017.

Howlader N, Noone A, Krapcho M, Miller D, Bishop K, Altekruse S, et al. SEER Cancer Statistics Review, 1975-2013. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. 2015.

Jacobson C, Locke FL, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-Term Survival and Gradual Recovery of B Cells in Patients With Refractory Large B Cell Lymphoma Treated With Axicabtagene Ciloleucel [Presentation 1187]. American Society of Hematology (ASH) Annual Meeting and Exposition Virtual; 2020 05-08 December.

Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE, Houterman S, Verheij KD, Coebergh JW. A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. British journal of haematology 2005;129 (5):597-606.

Johnson NA, Savage KJ, Ludkovski O, Ben-Neriah S, Woods R, Steidl C, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009;114 (11):2273-9.

Kobbe G, Brüggemann M, Baermann B-N, Wiegand L, Trautmann H, Yousefian S, et al. Aggressive Lymphoma after CD19 CAR T-Cell Therapy. New England Journal of Medicine 2024;391 (13):1217-26.

Kochenderfer JN, Dudley ME, Carpenter RO, Kassim SH, Rose JJ, Telford WG, et al. Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation. Blood 2013;122 (25):4129-39.

Kochenderfer JN, Somerville RPT, Lu T, Shi V, Bot A, Rossi J, et al. Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017a;35 (16):1803-13.

Kochenderfer JN, Somerville RPT, Lu T, Yang JC, Sherry RM, Feldman SA, et al. Long-Duration Complete Remissions of Diffuse Large B Cell Lymphoma after Anti-CD19 Chimeric Antigen Receptor T Cell Therapy. Mol Ther 2017b;25 (10):2245-53.

Kochenderfer JN, Yu Z, Frasheri D, Restifo NP, Rosenberg SA. Adoptive transfer of syngeneic T cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells. Blood 2010;116 (19):3875-86.

Kymriah, Novartis Europharm Limited. Kymriah 1.2 x 10^6 – 6 x 10^8 Cells Dispersion for Infusion. Summary of Product Characteristics. Dublin, Ireland. 2020:

Lamers CH, Willemsen R, van Elzakker P, van Steenbergen-Langeveld S, Broertjes M, Oosterwijk-Wakka J, et al. Immune responses to transgene and retroviral vector in patients treated with ex vivo-engineered T cells. Blood 2011;117 (1):72-82.

Le Gouill S, Talmant P, Touzeau C, Moreau A, Garand R, Juge-Morineau N, et al. The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. Haematologica 2007;92 (10):1335-42.

Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385 (9967):517-28.

Li S, Saksena A, Desai P, Xu J, Zuo Z, Lin P, et al. Prognostic impact of history of follicular lymphoma, induction regimen and stem cell transplant in patients with MYC/BCL2 double hit lymphoma. Oncotarget 2016;7 (25):38122-32.

Liu J, Zhong JF, Zhang X, Zhang C. Allogeneic CD19-CAR-T cell infusion after allogeneic hematopoietic stem cell transplantation in B cell malignancies. J Hematol Oncol 2017;10 (1):35.

Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-Term Safety and Activity of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (ZUMA-1): A Single-Arm, Multicentre, Phase 1-2 Trial. Lancet Oncol 2019;20:31-42.

Loubiere LS, Lambert NC, Flinn LJ, Erickson TD, Yan Z, Guthrie KA, et al. Maternal microchimerism in healthy adults in lymphocytes, monocyte/macrophages and NK cells. Lab Invest 2006;86 (11):1185-92.

Major A, Smith DE, Ghosh D, Rabinovitch R, Kamdar M. Risk and subtypes of secondary primary malignancies in diffuse large B-cell lymphoma survivors change over time based on stage at diagnosis. Cancer 2020;126 (1):189-201.

Martin LJ, Whitmore JB, Shen RR, Neumann F. T-Cell Malignancies With Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy. Blood Adv 2024.

Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England journal of medicine 2014;371 (16):1507-17.

McPhail ED, Maurer MJ, Macon WR, Feldman AL, Kurtin PJ, Ketterling RP, et al. Inferior survival in high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements is not associated with MYC/IG gene rearrangements. Haematologica 2018;103 (11):1899-907.

Merten OW. State-of-the-art of the production of retroviral vectors. J Gene Med 2004;6 (Suppl 1):S105-24.

MONJUVI, MorphoSys US Inc. MONJUVI® (tafasitamab-cxix) for injection, for intravenous use. U.S. Prescribing Information. Boston, MA. Revised July. 2020:

Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107 (1):265-76.

Niitsu N, Okamoto M, Miura I, Hirano M. Clinical features and prognosis of de novo diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC translocations. Leukemia 2009;23 (4):777-83.

Oki Y, Noorani M, Lin P, Davis RE, Neelapu SS, Ma L, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. British journal of haematology 2014;166 (6):891-901.

Ozdemirli M, Loughney TM, Deniz E, Chahine JJ, Albitar M, Pittaluga S, et al. Indolent CD4+ CAR T-Cell Lymphoma after Cilta-cel CAR T-Cell Therapy. The New England journal of medicine 2024;390 (22):2074-82.

Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. The New England journal of medicine 2018;378 (5):449-59.

Petrich AM, Gandhi M, Jovanovic B, Castillo JJ, Rajguru S, Yang DT, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood 2014;124 (15):2354-61.

Pixuvri, CTI Life Sciences Limited. Pixuvri 29 mg powder for concentrate for solution for infusion. Summary of Product Characteristics (SmPC). Last updated 23 March 2018. 2012:

Polivy, Roche Pharma AG. Polivy 140 mg Powder for Concentrate for Solution for Infusion. Summary of Product Characteristics. Grenzach-Wyhlen, Germany. January. 2020:

Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes and immunity 2012;13 (4):289-98.

Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nature reviews. Immunology 2012;12 (4):269-81.

Robbins PF, Kassim SH, Tran TL, Crystal JS, Morgan RA, Feldman SA, et al. A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1-Reactive T-cell Receptor: Long-term Follow-up and Correlates with Response. Clin Cancer Res 2015;21 (5):1019-27.

Rosenwald A, Bens S, Advani R, Barrans S, Copie-Bergman C, Elsensohn MH, et al. Prognostic Significance of MYC Rearrangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol 2019;37 (35):3359-68.

Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010;116 (19):3724-34.

Savage KJ. Primary Mediastinal Large B-Cell Lymphoma. Oncologist 2006;11 (5):488-95.

Schenk-Braat EA, van Mierlo MM, Wagemaker G, Bangma CH, Kaptein LC. An inventory of shedding data from clinical gene therapy trials. J Gene Med 2007;9 (10):910-21.

Scholler J, Brady TL, Binder-Scholl G, Hwang WT, Plesa G, Hege KM, et al. Decade-Long Safety and Function of Retroviral-Modified Chimeric Antigen Receptor T Cells. Sci Transl Med 2012;4 (132):132ra53.

Sehn LH, Antin JH, Shulman LN, Mauch P, Elias A, Kadin ME, et al. Primary diffuse large B-cell lymphoma of the mediastinum: outcome following high-dose chemotherapy and autologous hematopoietic cell transplantation. Blood 1998;91 (2):717-23.

Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood 2015;125 (1):22-32.

Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. N Engl J Med 2021;384 (9):842-58.

Shah NN, Qin H, Yates B, Su L, Shalabi H, Raffeld M, et al. Clonal Expansion of CAR T Cells Harboring Lentivector Integration in the CBL Gene Following Anti-CD22 CAR T-Cell Therapy. Blood Adv 2019;3 (15):2317-22.

Siegler EL, Kenderian SS. Neurotoxicity and Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy: Insights Into Mechanisms and Novel Therapies. Frontiers in immunology 2020;11:1973.

Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, et al. Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network. British journal of cancer 2015;112 (9):1575-84.

Smith M, Zakrzewski J, James S, Sadelain M. Posttransplant chimeric antigen receptor therapy. Blood 2018;131 (10):1045-52.

Snuderl M, Kolman OK, Chen YB, Hsu JJ, Ackerman AM, Dal Cin P, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. The American journal of surgical pathology 2010;34 (3):327-40.

Song DG, Ye Q, Poussin M, Liu L, Figini M, Powell DJ, Jr. A fully human chimeric antigen receptor with potent activity against cancer cells but reduced risk for off-tumor toxicity. Oncotarget 2015;6 (25):21533-46.

Sprague AH, Khalil RA. Inflammatory cytokines in vascular dysfunction and vascular disease. Biochem Pharmacol 2009;78 (6):539-52.

Sun H, Savage KJ, Karsan A, Slack GW, Gascoyne RD, Toze CL, et al. Outcome of Patients With Non-Hodgkin Lymphomas With Concurrent MYC and BCL2 Rearrangements Treated With CODOX-M/IVAC With Rituximab Followed by Hematopoietic Stem Cell Transplantation. Clinical lymphoma, myeloma & leukemia 2015;15 (6):341-8.

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127 (20):2375-90.

Theron A, Alonso-Saladrigues A, Dapena JL, López-Duarte M, Diaz de Heredia C, Verdú-Amorós J, et al. Secondary haematological dysplasia after CAR-T-cell therapy for acute lymphoblastic leukaemia in children. British journal of haematology 2025;206 (1):186-94.

Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology 2015;26 Suppl 5:v116-25.

Tomita N, Tokunaka M, Nakamura N, Takeuchi K, Koike J, Motomura S, et al. Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations. Haematologica 2009;94 (7):935-43.

U.S. Department of Health & Human Services, Food and Drug Administration, Center for Biologic Evaluation and Research (CBER). Guidance for Industry Preclinical Assessment of Investigational Cellular and Gene Therapy Products. November, 2013.

Vainstein V, Avni B, Grisariu S, Kfir-Erenfeld S, Asherie N, Nachmias B, et al. Clonal Myeloid Dysplasia Following CAR T-Cell Therapy: Chicken or the Egg? Cancers (Basel) 2023;15 (13).

Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. The New England journal of medicine 2020;382 (14):1331-42.

Welsh RM, Jr., Cooper NR, Jensen FC, Oldstone MB. Human serum lyses RNA tumour viruses. Nature 1975;257 (5527):612-4.

Welsh RM, Jr., Jensen FC, Cooper NR, Oldstone MB. Inactivation of Lysis of Oncornaviruses by Human Serum. Virology 1976;74 (2):432-40.

Willenbacher E, Willenbacher W, Weger R, Dominik W, Manzl C, Brunner A. Patients with double/triple copy number gains on C-MYC, BCL2, and/or BCL6 treated with standard chemotherapy have a similarly poor prognosis than those with high-grade B cell lymphoma with C-MYC and BCL2 and/or BCL6 rearrangements: a single-center experience on a consecutive cohort of large B cell lymphomas. Annals of hematology 2020;99 (9):2125-32.

World Health Organization (WHO). Human viruses in water, wastewater and soil. Technical Report Series 639. 1979:

World Health Organization (WHO). Cancer today: Data Visualization tools for exploring the global cancer burden in 2020. Available at: https://gco.iarc.fr/today/home. Accessed: 31 May 2021. 2020:

Yeoh ZH, Tiong IS, Dowling MR, Scott HW, O'Leary N, van der Linde S, et al. DNA Damage Repair Pathway Variants Are Frequent in Patients Undergoing CAR-T Cell Therapy for Lymphoma and Associated with Increased Risk of Myeloid Neoplasia Post Cytotoxic Therapy. Blood 2024;144 (Supplement 1):653-.

Zydelig, Gilead Sciences Ltd. Zydelig 100 mg Film-coated Tablets. Summary of Product Characteristics. London, United Kingdom. Revised January. 2021:

Kite A GILEAD Company	**Tecartus/Yescarta Neurologic Events**	**Version 3 Global**

Instructions:
Print or type information for any blank fields, as applicable (some information may be pre-populated). If more space is needed for

Safety_FC@gilead.com or Fax: 1-650-522-5477

Manufacturer Control Number:

Section 1: Please respond to the questions below.

Section 2: Patient and Product Information					
Initials:	**DOB:**	**Sex:**	**Gilead Product:**	**Date dose:**	**Indication:**
Please provide the lot and batch number for the Gilead Product(s):					

Section 3: Neurologic Adverse Event(s) – enter a diagnosis or signs/symptoms if a diagnosis is not available.

Neurologic Adverse Events(s)	**Event Dates**	**CTCAE Grade**	**Serious Criteria**	**Outcome**
	Start Date **Stop Date**	☐ Grade 1 (mild) ☐ Grade 2 (moderate) ☐ Grade 3 (severe) ☐ Grade 4 (life-threatening) ☐ Grade 5 (fatal)	☐ Death ☐ Life-threatening ☐ Hospitalization /prolonged hospitalization ☐ Significant disability ☐ Medically significant ☐ Not applicable (non-serious)	☐ Recovered / resolved ☐ Recovering / resolving ☐ Not recovered / not resolved ☐ Recovered / Resolved with sequelae ☐ Fatal ☐ Unknown
	Start Date **Stop Date**	☐ Grade 1 (mild) ☐ Grade 2 (moderate) ☐ Grade 3 (severe) ☐ Grade 4 (life-threatening) ☐ Grade 5 (fatal)	☐ Death ☐ Life-threatening ☐ Hospitalization /prolonged hospitalization ☐ Significant disability ☐ Medically significant ☐ Not applicable (non-serious)	☐ Recovered / resolved ☐ Recovering / resolving ☐ Not recovered / not resolved ☐ Recovered / Resolved with sequelae ☐ Fatal ☐ Unknown
	Start Date **Stop Date**	☐ Grade 1 (mild) ☐ Grade 2 (moderate) ☐ Grade 3 (severe) ☐ Grade 4 (life-threatening) ☐ Grade 5 (fatal)	☐ Death ☐ Life-threatening ☐ Hospitalization /prolonged hospitalization ☐ Significant disability ☐ Medically significant ☐ Not applicable (non-serious)	☐ Recovered / resolved ☐ Recovering / resolving ☐ Not recovered / not resolved ☐ Recovered / Resolved with sequelae ☐ Fatal ☐ Unknown

If Patient died, please provide:	**If Patient required hospital admission or prolongation of an existing hospitalization, please**

www.gilead.com/privacy or upon request.

Instructions:
Print or type information for any blank fields, as applicable (some information may be pre-populated). If more space is needed for

Safety_FC@gilead.com or Fax: 1-650-522-5477

	provide:
Date of Death: Cause of Death: Autopsy performed? ☐ Yes (Attach copy) ☐ No	Admission Date: Discharge Date:

Section 4: Relevant Laboratory Data – enter N/A if not performed.

Diagnostic Test Date	Brain Imaging or Other Diagnostic Results	Spinal Fluid Results

Was any cerebral edema identified? ☐ No ☐ Yes, please describe how it was identified:

Was tocilizumab administered? ☐ No ☐ Yes

Dose	Dates of Therapy	Response

Was an anti-epileptic administered? ☐ No ☐ Yes

Name of anti-epileptic	Route	Dose	Therapy Dates	Response

Were corticosteroids (CS) administered? ☐ No ☐ Yes

Name of CS	Route	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ No ☐ Yes

Name of CS	Route	Dose	Therapy Dates	Response

Section 5: Relevant Medical History (list below) or ☐ No medical history

Please specify if any history of seizure disorder or other neurologic disorders, CNS involvement of cancer, previous treatment of CNS involvement of cancer or presence of implants or medical devices in the CNS.

Section 6: Additional Medications (including concurrent medications)
If list is too long, please include a printout of the patient's medications.

Drug Name	Indication	Dose and Frequency	Start Date	Stop Date

Section 7: Additional Information

Instructions:
Print or type information for any blank fields, as applicable (some information may be pre-populated). If more space is needed for

Safety_FC@gilead.com or Fax: 1-650-522-5477

Please provide any additional relevant information below or on a separate page.

Section 8: Reporter Details		
Reporter Name:	**Reporter Signature**	**Date:**

Kite A GILEAD Company	**Tecartus/Yescarta** **Cytokine Release Syndrome (CRS)**	**Version 3** **Global**

Instructions:
Print or type information for any blank fields, as applicable (some information may be pre-populated). If more space is needed for

Safety_FC@gilead.com or Fax: 1-650-522-5477

Manufacturer Control Number:

Section 1: Please respond to the questions below.

Section 2: Patient and Product Information					
Initials:	**DOB**:	**Sex**:	**Gilead Product**:	**Date dose**:	**Indication**:
Please provide the lot and batch number for the Gilead Product(s):					

Section 3: CRS – Adverse Event Information (List all that apply).

1. CRS-associated AE (including Lab AEs)
2. CRS-associated organ specific AEs (hepatic, renal, pulmonary, or cardiac)

Event	Start Date	Stop Date	Outcome
CRS			

Overall CRS Grade per Lee et al, Blood, 2014 – choose one

☐ Grade 1	Symptoms are not life threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)
☐ Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% FiO2 or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
☐ Grade 3	Symptoms require and respond to moderate intervention Oxygen requirement ≥40% FiO_2 or Hypostension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
☐ Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
☐ Grade 5	Death

Serious Criteria (check all that apply):

☐ Death Date of death: Cause of death: Was autopsy performed? ☐ No ☐ Yes - Please provide report	☐ Required or ☐ Prolonged hospitalization Admission date: Discharge date: ☐ Congenital anomaly/Birth defect
☐ Life-threatening	☐ Medically important
☐ Persistent or significant disability/incapacity	☐ Non-serious

In your opinion, what is the causal relationship between CRS and the Kite therapy?
☐ Related ☐ Not Related – What was the cause of the CRS?

Were alternate causes for the signs and symptoms ruled out?
☐ No ☐ Yes – Describe how these were ruled out:

Was tocilizumab administered? ☐ No ☐ Yes

Dose	Dates of therapy	Response

Were corticosteroids (CS) administered? ☐ No ☐ Yes

Name of CS	Route	Dose	Therapy Dates	Response

Instructions:
Print or type information for any blank fields, as applicable (some information may be pre-populated). If more space is needed for

Safety_FC@gilead.com or Fax: 1-650-522-5477

Were anti-hypotension medications administered (pressors)? ☐ No ☐ Yes

Name of pressor	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ No ☐ Yes

Name of treatment	Route	Dose	Therapy Dates	Response

Section 4: Relevant Medical History (list below) or ☐ No medical history

Please specify any infection history, including treatment for infection. Please specify any history (including severity and previous treatment) of hepatic, renal, pulmonary, or cardiac disease or impairment.

Section 5: Additional Medications (including concurrent medications) If list is too long, please include a printout of the patient's medications.

Drug Name	Indication	Dose and Frequency	Start Date	Stop Date

Section 6: Additional Information

Please provide any additional relevant information below or on a separate page.

Section 7: Reporter Details

Reporter Name:	Reporter Signature	Date:

GILEAD	Tecartus/Yescarta New Malignancy	Version 3 Global

Instructions:
Print or type information for any blank fields, as applicable (some information may be pre-populated). If more space is needed for any fields, please append additional information. Enter all dates as DD/MMM/YYYY. Report safety information within 24 hours of awareness. Send completed responses to: Safety_FC@gilead.com or Fax: 1-650-522-5477

For new malignancy events after CAR T infusion, please provide the relevant information requested below and contact Kite to obtain instructions on patient samples to collect for testing, if appropriate.

United States: 1-844-454-KITE (5483)
Europe/Rest of World: Please call the company at the contact number in your regional label.
OR
Please contact Kite Medical Information for your requests at: https://kitemedinfo.com/submit-questions/

Manufacturer Control Number:

Section 1: Please respond to the questions below.

Section 2: Patient and Product Information			
Initials:	**Sex (Male or Female):**	**DOB:**	**Study ID (if applicable):**
Gilead Product:	**Date of Administration:**	**Dose:**	**Indication:**
Please provide the lot and batch number for the Gilead Product(s):			

For suspected/potential T cell malignancies, please fill out Section 3.
For suspected/potential non-T cell malignancies, please fill out Section 4.

Section 3: For T cell malignancies ONLY – If not previously reported, please provide the information below

Primary Malignancy Information

Primary Malignancy Type:	**Date of Diagnosis:**

Was mutational analysis done prior to CAR T-cell therapy? If yes, please specify the specimen types tested and results.
☐ No ☐ N/A ☐ Yes, please specify:

How many prior lines of therapy (include autologous and allogenic transplants) were given for the primary malignancy? List them below (if necessary, please provide additional information on separate page).

Therapy	**Therapy Dates**

Secondary Malignancy Information - T cell Malignancy

T cell Tumor Type (e.g., per WHO Edition 5)	**Age at Diagnosis of T cell Malignancy**	**CTCAE Grade**	**Seriousness Criteria**	**Outcome**
		☐ Grade 1 (mild) ☐ Grade 2 (moderate) ☐ Grade 3 (severe) ☐ Grade 4 (life-threatening) ☐ Grade 5 (fatal)	☐ Death ☐ Life-threatening ☐ Hospitalization/prolonged hospitalization ☐ Significant disability ☐ Medically significant ☐ Not applicable (non-serious)	☐ Recovered / resolved ☐ Recovering / resolving ☐ Not recovered / not resolved ☐ Recovered / resolved with sequelae ☐ Fatal ☐ Unknown

Did the T cell malignancy result in death? ☐ Yes ☐ No
Date of Death: **Cause of Death:**

Was autopsy performed?
☐ Yes, provide report ☐ No

Other Relevant Medical History (include start and stop dates):	**Other Relevant Concomitant Medications (include start and stop dates):**

In your opinion, what is the causal relationship between the T cell malignancy and Kite therapy?

☐ **Related -** If related, were alternate causes for the new malignancy ruled out and if so, how were they ruled out?

☐ **Not Related -** If not related, what was the cause of the new malignancy?

Initial Presenting Symptom(s) of T cell Malignancy:	**Start Date of Initial Symptom(s) of T cell Malignancy:**	**Date of Confirmed T cell Malignancy Diagnosis:**

Instructions:
Print or type information for any blank fields, as applicable (some information may be pre-populated). If more space is needed for any fields, please append additional information. Enter all dates as DD/MMM/YYYY. Report safety information within 24 hours of awareness. Send completed responses to: Safety_FC@gilead.com or Fax: 1-650-522-5477

Time of First Clinical Symptom of T cell Malignancy Relative to CAR T Infusion (e.g., weeks, months):

Time of First Biopsy Confirmation Relative to CAR T Infusion (e.g., weeks, months):

Biopsy Result(s)

Location of Biopsy (e.g., node, marrow, skin)	Results of Biopsy

CAR Assay Result(s)

CAR Assay Type (e.g., PCR, IHC)/Tumor Specimen Assayed (e.g., left axillary node)	Diagnostic Tumor CAR Assay Result

Replication Competent Retrovirus/Lentivirus (RCR/RCL) Results (include date):

Other Molecular Analysis Results on Tumor Sample:

Are samples (e.g., lymph node, bone marrow) confirming the diagnosis of secondary T-cell malignancy available to assess for the presence of the CAR (e.g., transgene cassette) in the tumor cells? ☐ Yes ☐ No
If yes, please see the contact information listed on the first page to request a Sampling Kit to send samples.

Provide all original (deidentified) pathology reports (tumor, bone marrow, lymph node) including flow cytometry, IHC/ISHs, and all molecular analyses reports, T-cell receptor gene rearrangement analysis with this questionnaire.

Secondary T cell Malignancy Treatments

Treatment	Date of Treatment

Infections Temporally Associated with T cell Malignancy Diagnosis

Infection	Date	Treatment(s)

To prevent duplicate cases in our database, has this case been reported to any health agencies (i.e.. FDA, EMA, etc.) or included in a publication? ☐ No ☐ Yes, please provide details:

Section 4: Non-T cell Malignancies - If not previously reported, please provide the information below.

New Malignancy	Event Dates	CTCAE Grade	Serious Criteria	Outcome
	Start Date **Stop Date**	☐ Grade 1 (mild) ☐ Grade 2 (moderate) ☐ Grade 3 (severe) ☐ Grade 4 (life-threatening) ☐ Grade 5 (Fatal)	☐ Death ☐ Life-threatening ☐ Hospitalization/prolonged hospitalization ☐ Significant disability ☐ Medically significant ☐ Not applicable (non-serious)	☐ Recovered / resolved ☐ Recovering / resolving ☐ Not recovered / not resolved ☐ Recovered / resolved with sequelae ☐ Fatal ☐ Unknown

Did the T cell malignancy result in death? ☐ Yes ☐ No	Date of Death:	Cause of Death:	Was autopsy performed? ☐ No ☐ Yes, provide report

Diagnostic Results – enter N/A if not performed.

Diagnostic Test Date	Pathology: specify tissue type (including any additional analysis, molecular markers, etc.)	Imaging or Other Diagnostic Results

Instructions:
Print or type information for any blank fields, as applicable (some information may be pre-populated). If more space is needed for any fields, please append additional information. Enter all dates as DD/MMM/YYYY. Report safety information within 24 hours of awareness. Send completed responses to: Safety_FC@gilead.com or Fax: 1-650-522-5477

Additional Event Information

Pre-existing factors that may have contributed to the development of a new malignancy:

In your opinion, what is the causal relationship between the new malignancy and Kite therapy?

☐ **Related -** If related, were alternate causes for the new malignancy ruled out and if so, how were they ruled out?

☐ **Not Related -** If not related, what was the cause of the new malignancy?

Were any treatments administered for the new malignancy? ☐ Yes ☐ No	**Name of treatment:**	**Therapy Date:**	**Response:**

Relevant Medical History ☐ Yes, please describe below. ☐ No medical history or unknown.

Cancer treatment received prior to Kite therapy:	**Please include the dates of diagnosis and stage of disease, start and stop dates, and specific agents of all cytotoxic chemotherapy/targeted therapy regimens as well as therapeutic radiation exposure.**		
Diagnosis and stage	Treatment regimen	Therapy Date	Response

Cancer treatment received after Kite therapy, but prior to new cancer diagnosis:		**Please include the dates of diagnosis and stage of disease, start and stop dates, and specific agents of all cytotoxic chemotherapy/targeted therapy regimens as well as therapeutic radiation exposure.**	
Diagnosis and stage	Treatment regimen	Therapy Date	Response

History of tobacco use?	☐ Yes ☐ No	If yes, please provide the pack year history:
History of environmental exposure (e.g. asbestos, radiation)?	☐ Yes ☐ No	If yes, please describe:
History of hereditary cancer syndromes?	☐ Yes ☐ No	If yes, please describe:
Family history of cancer	☐ Yes ☐ No	If yes, please describe:

Additional Medications (including concurrent medications). If list is too long, please include a printout of the patient's medications.

Drug Name	**Indication**	**Dose and Frequency**	**Start Date**	**Stop Date**

Section 5: Additional Information

Please provide any additional relevant information below or on a separate page.

Section 6: Reporter Details

Reporter Name:	**Reporter Signature**	**Date:**

Annex 6. Details of proposed additional risk minimization activities

Approved key messages of the additional risk minimization measures:

Site qualification and availability of tocilizumab

The Marketing Authorization Holder (MAH) will ensure that hospitals and their associated centers that dispense Yescarta are qualified in accordance with the agreed controlled distribution program by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Yescarta infusion. The treatment center must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat cytokine release syndrome (CRS) instead of tocilizumab are available on-site.

- ensuring healthcare professionals (HCP) involved in the treatment of a patient have completed the educational program.

- As part of site qualification training, ensuring HCPs are made aware of the need to contact the MAH to obtain recommendations for tumor sample collection and testing following the development of a secondary malignancy of T cell origin.

HCP educational program

Prior to the launch of Yescarta in each Member State the MAH must agree with the content and format of the HCP educational materials with the National Competent Authority.

The MAH shall ensure that in each Member State where Yescarta is marketed, all HCPs who are expected to prescribe, dispense, and/or administer Yescarta shall be provided with guidance per their role to:

- facilitate identification of CRS and serious neurologic adverse reactions/ICANS.

- facilitate management of the CRS and serious neurologic adverse reactions/ICANS.

- ensure adequate monitoring of CRS and serious neurologic adverse reactions/ICANS.

- facilitate provision of all relevant information to patients.

- ensure that adverse reactions are adequately and appropriately reported.

- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicine Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site.

- inform on the risk of secondary malignancy of T-cell origin.

Patient educational program

A patient alert card to inform and explain to patients:

- the risks of CRS and serious neurologic adverse reactions, associated with Yescarta.
- the need to report the symptoms to their treating doctor immediately.
- the need to remain in the proximity of the location where Yescarta was received for at least 4 weeks following Yescarta infusion.
- the need to carry the patient alert card at all times.

Of note, the additional risk minimization measures for Yescarta are combined with Tecartus.