EU Risk Management Plan for YESCARTA® (axicabtagene ciloleucel)

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RMP version to be assessed as part of this submission:

Version number:	Data lock point for this RMP:	Date of final sign off:
10.0	**Clinical**: ZUMA-1: 18 March 2021 ZUMA-5: 14 September 2020 ZUMA-7: 18 March 2021 **Post-marketing**: 22 August 2022	Refer to Electronic Signatures

Abbreviations: RMP = risk management plan

Rationale for submitting an updated RMP: Response to request for information.

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		Not applicable
Part IV Plan for Post-authorization Efficacy Studies		Not applicable
Part V Risk Minimization Measures		Not applicable

Part	Module/Annex	Significant Changes to RMP
Part VI Summary of the Risk Management Plan		The evaluation of the effectiveness of the controlled distribution program include: • Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification.
Part VII Annexes		Not applicable

Abbreviations: CRS = cytokine release syndrome; EU = European Union; HCP = healthcare professional; RMP = risk management plan; SmPC = summary of product characteristics.

Other RMP versions under evaluation:

Version Number	Submitted on	Procedure number
9.2	05 Apr 2024	TBD

Details of the currently approved RMP:

Version Number	Approved with Procedure	Date of Approval (Opinion Date)
10.0	EEMEA/H/C/004480/WS2632/0072	25 April 2024

Abbreviations: RMP = risk management plan.

QPPV name:	Anne-Ruth van Troostenburg de Bruyn
QPPV signature:	Refer to Electronic Signatures

Abbreviations: QPPV = qualified person of pharmacovigilance.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

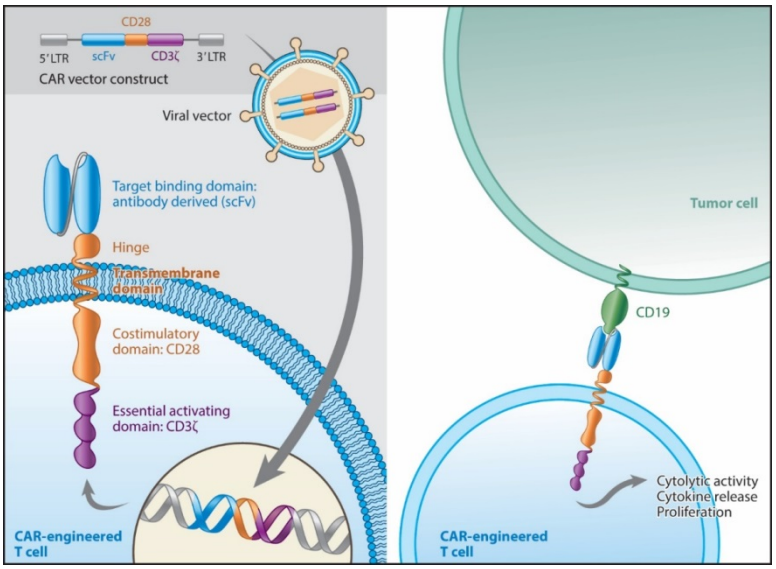
ADR	Adverse drug reactions
allo-HSCT	Allogeneic haematopoietic stem-cell transplant
ASIR	Age-standardized incidence rate
ATMP	Advanced therapy medicinal product
CAR	Chimeric antigen receptor
CAR T	Chimeric antigen receptor T cells
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
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
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):	L01XX70
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; IL2 = interleukin 2; 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

	Crude Prevalence Rates per 100,000 population		
	Overall	**Male**	**Female**
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 yet unsubstantiated possibility, secondary hematologic malignancy (including due to RCR) is considered an important potential 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)
Race, n (%)				
American Indian or Alaska Native	1 (1)	0 (0)	0 (0)	0 (0)
Asian	8 (5)	11 (6)	3 (3)	14 (5)

Characteristic	Standard of care	Axicabtagene Ciloleucel		
	ZUMA-7 (N = 168)	**ZUMA-7 (N = 170)**	**ZUMA-1 (N = 108[b])**	**Overall (N = 278)**
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	-	-

Duration of follow-up	Standard of Care Therapy			Axicabtagene Ciloleucel					
	ZUMA-7 (N=168)			ZUMA-7 (N=170)			ZUMA-1 (N=108[a])		
	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									
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)
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)	-
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)	-	-

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
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
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 (%)			

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
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[e] n (%)			
Yes	39 (31)	10 (42)	49 (33)
No	85 (69)	14 (58)	99 (67)
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)

	FL (N = 124)	MZL (N = 24)	Overall (N = 148)
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	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 hematologic malignancy is considered an important potential risk which is described in section 4.4 of the SmPC - Special warnings and precautions for use.

Criterion	Reason for Exclusion	Considered to be Missing Information
lymphoma, histological Grade 3b FL, and lymphoplasmacytic lymphoma. History of Richter's transformation of CLL or PMBCL (applicable to ZUMA-7)		
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

Criterion	Reason for Exclusion	Considered to be Missing Information
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.
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 immune effector cell-associated neurotoxicity syndrome. 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 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.

Criterion	Reason for Exclusion	Considered to be Missing Information
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.
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; 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.

Type of Special Population	Exposure
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.

Reason	List of Risks	Assessment
	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.
	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

Reason	List of Risks	Assessment
		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}. 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

Important Identified Risks	Risk-Benefit Impact
	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. 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.

Important Potential Risks	Risk-Benefit Impact
	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. 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

Important Identified Risk:	**Serious Neurologic Adverse Reactions including Cerebral Edema**
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)
Memory impairment	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	2 (1)	1 (0)

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

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)
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)

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

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.

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)

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema			
	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)
	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)

Important Identified Risk:	Serious Neurologic Adverse Reactions including Cerebral Edema			
	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.
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)
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)**
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

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.
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% versus 6%) compared to FL. The median time to onset was 4 days (range 1 to 15 days). No

Important Identified Risk:	CRS

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)
Grade 5	0 (0)	0 (0)	0 (0)

Important Identified Risk:	CRS			
	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)
	Malaise	**6 (6)**	**1 (4)**	**7 (6)**

Important Identified Risk:	CRS

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
	Resolved with Sequelae	5

Important Identified Risk:	CRS

	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.

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

Important Identified Risk:	CRS
	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.
Characterisation of the risk	**Clinical trials**

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

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.
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

Important Identified Risk:	Cytopenias including Aplastic Anemia

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

ZUMA-5 (as of 14 September 2020)

Important Identified Risk:	Cytopenias including Aplastic Anemia

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

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

Important Identified Risk: **Infections**

	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, opportunistic or unspecified)	51 (30)	19 (11)	70 (41)	24 (14)	43 (40)	29 (27)	113 (41)	53 (19)
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)

Important Identified Risk: **Infections**

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)
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.

Important Identified Risk:	Infections

- 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 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

Important Identified Risk:	Infections
	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. 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)**

Important Identified Risk:	**Hypogammaglobulinemia**

	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 = 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)

Important Identified Risk:	**Hypogammaglobulinemia**

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.

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.

SVII.3.1.2. Important Potential Risks

Table SVII.10. Important Potential Risk: Secondary Hematologic Malignancy (including due to RCR)

Important Potential Risk:	Secondary Hematologic Malignancy (including due to RCR)
Potential mechanisms	The increased incidence of other malignant neoplasms is attributed to disease- and/or therapy related immunosuppression and possibly genotoxicity, including the administration of conditioning therapy prior to the administration of axicabtagene ciloleucel {Tsimberidou 2009}. Another possible mechanism is insertional mutagenesis of the viral vector, or RCR, which may be created by a recombination between endogenous retroviral element and the viral vector, will integrate into genomic regions that will interfere with or augment the transcription of certain genes and this genotoxicity will result in secondary malignancy.
Evidence source and strength of evidence	Secondary malignancies and RCR were not reported in clinical trials.
Characterisation of the risk	**Clinical trials** **ZUMA-1 and ZUMA-7 (as of 18 March 2021)** Per definition, a new malignancy is an adverse event that occurs after the administration of gene-modified cell therapy and is identified in the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) and in cases of death. A secondary malignancy is the development of a new malignancy suspected to be possibly related to gene-modified cell therapy (i.e., temporally associated with gene-modified cell therapy and without compelling alternate aetiologies). Consistent with the definition above, there were no cases of secondary malignancies. **ZUMA-5 (as of 14 September 2020)** In ZUMA-5, the clinical database was reviewed for the potential AEs of secondary malignancy by searching the SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps). Of 9 AEs that were identified by the above search strategy, 3 were not considered to be secondary malignancies (tumor pain, FL, and benign neoplasm of skin [1 subject each]; the first two AE terms were related to the primary malignancy and the third term did not meet the secondary malignancy criteria). Secondary malignancies identified by the above search strategy were myelodysplastic syndrome (MDS, 1 subject), squamous cell carcinoma (2 subjects), and basal cell carcinoma, prostate cancer and breast cancer (1 subject each). Two additional subjects with secondary malignancies were identified: 1 subject with AML and 1 subject with MDS. Thus, 8 subjects were identified. None of the secondary malignancies were assessed as being related to axicabtagene ciloleucel. **KT-EU-471-0117 (PASS) (as of 01 March 2022)** Secondary malignancies were observed for 7 patients (1.8%). The median time to secondary malignancy was 6.0 months (with range 1.4 to 16.6 months). The 12-month cumulative incidence for secondary malignancies was 2% (95% CI: 1 to 4%). The follow-up adjusted incidence rate per person-year was 0.02 (95% CI: 0.01 to 0.04). No data was available on the causal relationship between these secondary malignancies and Yescarta. **Post-marketing (up to 22 August 2022)**

Important Potential Risk:	Secondary Hematologic Malignancy (including due to RCR)
	The cumulative new malignancy case reporting rate, and MDS/AML case reporting rate was 1.45% (135/9342) and 0.7% (72/9342), respectively. RCR data is not collected by EBMT. **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.
Preventability	HCPs should monitor patient's life-long for secondary 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 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 with respect to number of reports, seriousness, outcome, and risk factors. 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 as causal relationship has not been established.

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; FL = follicular lymphoma; HCP = healthcare professional; MAH = marketing authorization holder; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; PASS = postauthorization safety study; RCR = replication-competent retrovirus; SmPC = summary of product characteristics; SOC = system organ class.

Table SVII.11. 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**

Important Potential Risk:	Immunogenicity

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.

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	2 (29)	1 (1)	2 (8)	3 (3)

Important Potential Risk:	Immunogenicity			
baseline with a negative result at baseline, n (%)				
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)
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)

Important Potential Risk: **Immunogenicity**

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)

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.

Important Potential Risk:	Immunogenicity

(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.

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 re turning 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)

Important Potential Risk:	Immunogenicity
	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.
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.12. 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.

Important Potential Risk:	TLS
	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. 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.13. 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.14. 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. **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	Overall (N = 278)

Missing Information:	Evidence source

					Cohorts 1 and 2 (N = 108)			
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.

Long term safety

Anticipated risk/consequence of the missing information:

Specific safety events such as RCR and secondary malignancy 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.

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
	CRS
	Cytopenias including aplastic anemia
	Infections
	Hypogammaglobulinemia
Important Potential Risks	Secondary hematologic malignancy (including due to RCR)
	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; 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-C19-101 (ZUMA-1): A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive NHL	
Rationale and Study Objectives	To evaluate the safety and efficacy of axicabtagene ciloleucel.
Study Design	Phase 1/2 multicenter, open-label study
Study Populations	Patients with relapsed or refractory DLBCL, PMBCL, TFL, and HGBCL after two or more lines of systemic therapy.
Milestones	Safety updates in the nearest PSUR to the annual anniversary: Annual Final report Cohort 1 and 2: 31 August 2031 Final report Cohort 3: 31 October 2032
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
KTE-C19-106 (ZUMA-6): A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Combination with Atezolizumab in Subjects with Refractory DLBCL	
Rationale and Study Objectives	To evaluate the safety and efficacy of axicabtagene ciloleucel.
Study Design	Phase 1/2, multicenter, open-label study
Study Populations	Patients with relapsed or refractory DLBCL subjects
Milestones	Safety updates in the nearest PSUR to the annual anniversary: Annual Final report: 31 August 2033

Abbreviations: ADR = adverse drug reaction; ASCT = autologous stem cell transplant; 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; HGBCL = high-grade B-cell lymphoma; iNHL = indolent non-Hodgkin lymphoma; MZL = marginal zone lymphoma; NHL = non- Hodgkin lymphoma; OOS = out of specification; PASS = postauthorization safety study; PMBCL = primary mediastinal B-cell lymphoma; PSUR = periodic safety update report; RCR = replication-competent retrovirus; TFL = transformed follicular lymphoma; 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 treatment of relapsed or refractory DLBCL, PMBCL and FL Ongoing	Additional characterization of the identified risks, further evaluation of potential risks and missing information.	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia Secondary hematologic malignancy TLS Aggravation of GvHD Use in pregnancy and lactation New occurrence or exacerbation of an autoimmune disorder Long term safety	Final Report Submission	30 June 2039
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				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
None				
Category 3 - Required additional pharmacovigilance activities				
KTE-C19-101 (ZUMA-1) A Phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive NHL Ongoing	To assess safety and efficacy of axicabtagene ciloleucel in refractory aggressive NHL	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary hematologic malignancy (including due to RCR) 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 Cohort 1 and 2	31 Aug 2031
			Final report Cohort 3	31 Oct 2032
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 CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary hematologic malignancy (including due to RCR) 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
KTE-C19-106 (ZUMA-6): A Phase 1-2 multi-center study evaluating the safety and efficacy of KTE C19 in combination with	To assess efficacy and safety of axicabtagene ciloleucel in combination with atezolizumab in	Serious neurologic adverse reactions including cerebral edema CRS	Safety updates in the nearest PSUR to the annual anniversary	Annual

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Atezolizumab in subjects with refractory DLBCL Ongoing	refractory DLBCL subjects	Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary hematologic malignancy (including due to RCR) Immunogenicity TLS Aggravation of GvHD New occurrence or exacerbation of an autoimmune disorder Long term safety	Final report	31 Aug 2033

Abbreviations: CAR T = chimeric antigen receptor T cells; CD19 = cluster of differentiation 19; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; GvHD = graft versus host disease; iNHL = indolent non-Hodgkin lymphoma; NHL = 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
Serious neurologic adverse reactions including cerebral edema	**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.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers
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 hematologic malignancy (including due to RCR)	**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
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.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers
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; 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 manage symptoms associated with CRS and serious neurologic adverse reactions and provide guidance on reporting these serious adverse reactions associated with Yescarta.
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 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

HCP Educational Material	
	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	**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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
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**:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 30 Jun 2039 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	None	ZUMA-6: 31 Aug 2033
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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Important potential risk(s)		
Secondary hematologic malignancy (including due to RCR)	**Routine risk minimization measures**: SmPC sections 4.4 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**: Event follow-up questionnaire **Additional pharmacovigilance activities**: KT-EU-471-0117: 30 Jun 2039 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Immunogenicity	**Routine risk minimization measures**: SmPC sections 4.8 Use restricted to physicians experienced in the treatment of hematological cancers.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-1: 31 Oct 2032

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: None	ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
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
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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**:

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: None	KT-EU-471-0117: 30 Jun 2039 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033

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; 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 PLAN

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
	Cytokine release syndrome (CRS)
	Cytopenias including aplastic anemia
	Infections
	Hypogammaglobulinemia
Important Potential Risks	Secondary hematologic malignancy (including due to RCR)
	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**
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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the postauthorization development plan.
Important potential risk	**Secondary Hematologic Malignancy (including due to RCR)**
Evidence for linking the risk to the medicine	Secondary malignancies were not reported in clinical trials.
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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C 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-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the postauthorisation development plan.

II.C. Post-authorization Development Plan

II.C.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.C.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-C19-101 (ZUMA-1)	To evaluate the safety and efficacy of axicabtagene ciloleucel.
KTE-C19-105 (ZUMA-5)	To evaluate the safety and efficacy of axicabtagene ciloleucel.
KTE-C19-106 (ZUMA-6)	To evaluate the safety and efficacy of axicabtagene ciloleucel.

PART VII: ANNEXES

Table of Contents

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Annex 2. Tabulated summary of planned, ongoing, and completed pharmacovigilance study program

Planned and On-going Studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
KT-EU-471-0117 Category 1	Additional characterization of the identified risks, further evaluation of potential risks and missing information	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary hematologic malignancy TLS Aggravation of GvHD Use in pregnancy and lactation New occurrence or exacerbation of an autoimmune disorder Long term safety	Final report submission: 30 Jun 2039
KTE-C19-101 (ZUMA-1) Category 3	To assess safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary hematologic malignancy (including due to RCR) Immunogenicity TLS Aggravation of GvHD New occurrence of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary Final report Cohort 1 and 2: 31 Aug 2031 Final report Cohort 3: 31 Oct 2032

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
KTE-C19-105 (ZUMA-5) Category 3	To assess efficacy and safety of axicabtagene ciloleucel in subjects with relapsed/ refractory iNHL.	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary hematologic malignancy (including due to RCR) Immunogenicity TLS Aggravation of GvHD New occurrence of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary Final report: 30 Apr 2036
KTE-C19-106 (ZUMA-6) Category 3	To assess efficacy and safety of axicabtagene ciloleucel in combination with atezolizumab in subjects with refractory DLBCL	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary hematologic malignancy (including due to RCR) Immunogenicity TLS Aggravation of GvHD New occurrence of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary Final report: 31 Aug 2033

Completed Studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission
KT-EU-471-0116 (Prescriber survey) Quantitative Testing of Healthcare Provider Knowledge about YESCARTA (axicabtagene ciloleucel) Risk Minimization Measures Category 3	To assess the prescribers' understanding of the risks of Yescarta.	Serious neurologic adverse reactions including cerebral edema CRS Infections Secondary malignancies Decrease in viability of the product due to inappropriate preparation of infusion	24 Jun 2021

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

Protocols for the studies included in Annex 2, Table 1 are provided in this annex.

Table 1. Overview of Included Protocols

Study Number and Title	Protocol Version	Protocol Date	Procedure Number
Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP			
None			
Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP			
None			
Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority			
Approved protocols:			
KT-EU-471-0117*	v2.1 (Amendment 5)	03 August 2022; endorsed by EMA on 01 December 2022	EMEA/H/C/PSA/S/0087.1
Final protocols not reviewed or not approved:			
KTE-C19-101 (ZUMA-1)	Amendment 10	14 June 2022	Not applicable
KTE-C19-105 (ZUMA-5)	Amendment 7.0 (France)	22 Feb 2023	Not applicable
KTE-C19-106 (ZUMA-6)	Amendment 2	04 August 2021	Not applicable

Abbreviations: EMA = European Medicines Agency; RMP = risk management plan
* Protocol v3.0 (amendment 6), dated 29 September 2023, was submitted on 31 Oct 2023 (procedure EMEA/H/C/PSA/S/0102.3)

The following studies included in the pharmacovigilance plan are planned, and protocols are not currently available: None.

Kite Pharma Inc.

NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA, PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA AND FOLLICULAR, LYMPHOMA
Protocol ID	KT-EU-471-0117
Protocol Version/Date:	Original: 07 February 2019 Version 1.1: 03 July 2019 Version 1.2: 09 October 2019 Version 1.3: 06 November 2019 Version 2.0: 01 July 2021 Version 2.1: 03 August 2022
EU PAS Register No	EUPAS32539
Clinical Trials.gov Identifier	Study not registered
Active substance	Axicabtagene ciloleucel
Medicinal Product	YESCARTA®
Product reference	EMEA/H/C/004480
Procedure number	EMEA/H/C/PSP/S/0079
Joint PASS	No
Research Question and Objectives	Primary objective: To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, cytokine release syndrome (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 allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored. To assess the risk of tumor lysis syndrome (TLS) and aggravation of Graft Versus Host Disease (GvHD), and the detection of replication competent retrovirus (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.
Country (-ies) of study	In countries where YESCARTA will be authorized. At a minimum UK, Spain and Germany will be countries of study, further countries might be added.
Kite Study Director / Author / Contact Person:	Name: Meng Wang Telephone: +44 2085872200 Email: Meng.Wang15@gilead.com
Marketing Authorization Holder	Kite Pharma EU B.V.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
aRMMs	additional Risk Minimization Measures
auto-SCT	Autologous stem cell transplant
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CHMP	Committee for Human Medical Products
CI	Confidence interval
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology of Adverse Events
DLBCL	Diffuse large B-cell lymphoma
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
FL	Follicular Lymphoma
GLPS	Global Patient Safety
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GVHD	Graft Versus Host Disease
GVP	European Medicines Agency Guidelines on Good Pharmacovigilance Practices
HCP	Health Care Professional
HCT	Hematopoietic cell transplantation
HDT	High dose chemotherapy
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HMA	Heads of Medicines Agencies
IL	Interleukin
KM	Kaplan-Meier
LBCL	Large B-Cell Lymphoma
mAb	Monoclonal antibody
MAH	Marketing Authorization Holder
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
OOS	Out of specifications
OS	Overall survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PMBCL	Primary Mediastinal B-cell Lymphoma

PVE	Pharmacovigilance & Epidemiology
QPPV	Qualified Person for Pharmacovigilance
RCR	Replication-competent retrovirus
RWE	Real World Evidence
SAE	Serious adverse event
SADR	Serious adverse drug reaction
scFv	Single-chain variable fragment
SCT	Stem cell transplantation
SSR	Special situation report
TCR	T-cell receptor
US, USA	United States, United States of America

1. RESPONSIBLE PARTIES

Table 1. Table of Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Marketing Authorization Holder (MAH) contact person	Joanne Wallace Director Regulatory Affairs Kite Gilead Sciences International Ltd Flowers Building Granta Park, Abington Cambridge CB21 6GT, UK	Phone: +44 1223 824606 Email: Joanne.Wallace@gilead.com
Study Director	Meng Wang Director, Real World Evidence (RWE) 2 Roundwood Avenue Stockley Park Uxbridge, UB11 1AF United Kingdom	Phone: +44 208587 2200 Email: Meng.Wang15@gilead.com
Medical Monitor	David Muramoto Executive Director, Safety and PV Kite, a Gilead Company 2400 Broadway Santa Monica, CA 90404 USA	Phone: +1 650 389 8742 Email: david.muramoto@gilead.com
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2. PROTOCOL SYNOPSIS/ABSTRACT

Kite Pharma Inc.

Study Title:	LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA, PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA, AND FOLLICULAR LYMPHOMA
Rationale and Background:	To capture long-term follow-up data for recipients of YESCARTA to evaluate the safety, specifically incidence rates and severity of ADRs including long term safety, the risk of subsequent neoplasm as well as the known and potential risks associated with this product. This study will make secondary use of data collected within the infrastructure created by the European Society for Blood and Marrow Transplantation (EBMT) (i.e. the EBMT Registry) to systematically capture information at the time of YESCARTA infusion and for 15 years of follow-up.
Research Question and Objectives:	The primary objective of this study is as follows: • To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential. The secondary objectives of this study are as follows: • 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 allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored.

- To assess the risk of tumor lysis syndrome (TLS) and aggravation of Graft Versus Host Disease (GvHD), and the detection of replication competent retrovirus (RCR) in samples of patients with secondary malignancies.

The other exploratory objectives of this study are as follows:

- To determine the occurrence of loss of target antigen and of functional CAR-T persistence in patients relapsing after YESCARTA therapy.

Study Design: This is a long-term, non-interventional study of patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of therapy, or with relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy, who have been treated with YESCARTA.
Patients' data might be entered into the EBMT Registry up to 1 week prior or anytime following YESCARTA infusion and patients will be followed for 15 years in the EBMT registry.

Population: Recipients of YESCARTA for relapsed/refractory diffuse large B-cell lymphomas (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of therapy, or with relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy, at participating centers who consent to have data reported to the European Society for Blood and Marrow Transplantation (EBMT). Patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary, etc.) will be included in the study analyses. There are no restrictions regarding the patients' performance status of any kind, patients with any grade for Sorror score, ECOG and Karnofsky score are allowed.

Patients participating in interventional clinical trials will not be included in the study analyses.

Variables: This non-interventional secondary use of data study makes use of the EBMT Registry and is dependent on all needed variables to be collected in the EBMT Cellular and Gene Therapy Form. Furthermore, certain variables may not be generated as part of routine medical practice or local regulations limit the ability to collect the information.

- Variables utilized for analysis of Primary Objectives
  - — Secondary malignancy (date of diagnosis, type, location and relevant details on biopsy/diagnostic results)
  - — CRS (grade, date of onset, treatment and resolution status)

- Neurologic toxicity (type, grade, management including treatment, date of onset and resolution status of all neurologic toxicities)
- Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 100 days after the administration of YESCARTA. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive days, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. Date of recovery will be collected for ANC and platelets.
- Serious infections (type, organism, treatment and date of onset of infection as well as resolution status)
- Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. Date of onset, treatment, and resolution status will be collected.
- Pregnancy that occurs after administration of YESCARTA and additional information related to the outcome of the pregnancy and the newborn's health

- Variables utilized for analysis of Secondary Objectives
  - Date and main cause of death, and date of last assessment
  - Additional treatment and date of treatment received for primary disease (DLBCL, PMBCL or FL) after YESCARTA administration
  - Date of the first relapse or progression or significant worsening of the primary disease (DLBCL, PMBCL or FL) after the YESCARTA infusion
  - Grade, date of onset and resolution of TLS
  - Type, resolution status, onset date of aggravation of GvHD. For acute GvHD: grade and relationship to cell therapy
  - In case of a secondary malignancy the sampling for RCR testing, the sample date and the test result (not collected in the current EBMT Cellular and Gene Therapy Form)
- Variables utilized for analysis of Other Exploratory Objectives
  - Date of sampling for loss of target antigen and result (not collected in the current EBMT Cellular and Gene Therapy Form)

- Data on B-cell recovery as an indirect measure of functional CAR-T persistence: date, B-cell count per volume in peripheral blood, and detection method (not collected in the current EBMT Cellular and Gene Therapy Form)

- Variables utilized for analysis of exposure to YESCARTA
  - Name and dose level of lymphodepleting chemotherapy received prior to YESCARTA infusion
  - YESCARTA infusion: date, and whether YESCARTA was released at physician's request, because the manufactured product was out of specification
- Demographics and Baseline Characteristics
  - Age, gender, and country
  - Height and weight at the time of YESCARTA infusion
  - Indication for treatment with YESCARTA
  - Disease subtype (eg, NHL histologies)
  - Disease status at time of cellular therapy (eg, sensitive or resistant to chemotherapy or radiation prior to therapy)
  - Prior lines of treatment and response
  - Disease stage at time of cellular therapy
  - Prognostic information: double/triple hit, international prognostic index, cytogenetics (GCB-DLBCL, ABC-DLBCL)
  - Time from diagnosis of the primary disease to cellular therapy
  - Prior hematopoietic cell transplantation: autologous or allogeneic, donor HLA match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-mismatched relative), source of stem cell product (Umbilical cord Blood, Bone Marrow, Peripheral Blood), immunosuppressants (type and duration), prior GVHD
  - Prior cellular therapy (other than autologous or allogeneic SCT)
  - Performance score (ECOG or Karnofsky)
  - Comorbidities index (Sorror score)
  - Active autoimmune, neurologic and hematological disease; infection related complications

Data Sources:

For this specific protocol: patient data as available within the EBMT Registry for this study. For the EBMT Registry: the patient's medical records

Study Size:

All eligible patients who have been treated with YESCARTA and documented in the EBMT Registry within five years from study start for patients with DLBCL and PMBCL, or for all patients with FL treated with Yescarta within five years from time of approval of FL indication and approval of the protocol for this study to include FL patients.

In addition to the further characterisation of the immediate and established toxicities of YESCARTA, the study is designed to detect rare and delayed safety events occurring in patients during 15 person-years of follow up.

For Large B-Cell Lymphoma (LBCL), the available person-years of follow-up are estimated using a piecewise linear survival curve with 50% survival at 2 years and 30% survival long-term. A 10% overall loss to follow-up is assumed. The targeted accrual will provide 95%, or 83%, or 70% likelihood of detecting one event of interest if the true rate is 1 in 100, or 1 in 150, or 1 in 250 over a 15-year period.

For FL, the available person-years of follow-up are estimated using a piecewise linear survival curve with 72% survival at 2 years and 35% survival long-term. A 10% overall loss to follow-up is assumed. The targeted accrual will provide >99%, 98%, 79%, 54%, 41%, 32%, 27% likelihood of detecting one event of interest if the true rate is 1 in 10, or 1 in 20, or 1 in 50, or 1 in 100, or 1 in 150, or 1 in 200, or 1 in 250 over a 15-year period.

Data Analysis:

- Primary Endpoints
  - — Incidence rates, time to onset, type and location of secondary malignancy
  - — Incidence rates, severity, time to onset, management and resolution of CRS
  - — Incidence rates, severity, time to onset, management and resolution, and type of neurologic events
  - — Incidence rates of prolonged cytopenias
  - — Incidence rates, type, organism, resolution, and time to onset of serious infections
  - — Incidence rates, time to onset of hypogammaglobulinemia, and use of replacement immunoglobulin therapy

  - Incidence rates of pregnancy, and pregnancy outcome among women with childbearing potential

- Secondary Endpoints
  - Overall survival
  - Time to next treatment of the primary disease
  - Time to relapse or progression of the primary disease
  - Primary and secondary endpoints on subgroups by gender, age, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored
  - Incidence rate, severity, resolution, and time to onset of TLS
  - Incidence rate, resolution, time to onset of aggravation of GvHD by acute and chronic type; incidence rate, severity and relationship to cell therapy for acute GvHD
  - Frequency of detection of RCR in samples of patients with secondary malignancies
- Other Exploratory Endpoints
  - Occurrence of loss of target antigen in patients relapsing after YESCARTA therapy
  - Occurrence of functional CAR-T persistence in patients relapsing after YESCARTA therapy

Analysis of all endpoints for this study will include all patients satisfying the eligibility criteria who are documented within the EBMT Registry and treated with YESCARTA.

Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition including 95% confidence intervals (CIs). Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

Patient incidence of endpoint events will be provided. Multivariate Poisson regression analyses will be used to estimate cumulative incidence rates adjusted for follow-up period, specified subgroups and other potential confounders (demographics and baseline characteristics, see Section 7.3.5).

Kaplan- Meier curves will be used to illustrate all time-to-event data. Competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, time to relapse or progression and time to next treatment, and the cumulative incidence at specified time points will be provided.
Cox-proportional Hazard models will be used to model multivariate time-to-event data adjusted for subgroups and other potential confounders (demographics and baseline characteristics; see Section 7.3.5).

Milestones:

DLBCL and PMBCL

Start of data collection:	21 August 2020
End of data collection:	22 May 2040
Study duration:	20 years
Annual Reports:	Annually for 5 years, then every 2 years
Final Study report:	14 November 2040

FL

Start of data collection:	01 March 2023
End of data collection:	01 December 2042
Study duration:	20 years
Annual Reports:	Annually for 5 years, then every 2 years
Final report:	01 June 2043

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPP) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

3. AMENDMENTS AND UPDATES

Table 2. Protocol Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1.1	03 July 2019	Various	Update	To address the comments of the PRAC Request for a Revised PASS protocol in the PRAC PASS protocol assessment report and to implement the respective changes
1.2	09 October 2019	Various	Update	To address the comments of the 2nd PRAC Request for a Revised PASS protocol in the PRAC PASS protocol assessment report and to implement the respective changes
1.3	06 November 2019	Various	Update	To address comments of the 3rd PRAC Request for revisions of the PASS protocol and to implement the respective changes
2.0	01 July 2021	Various	Amendment	To add new indication FL
2.1	03 August 2022	Various	Amendment	To address comments of the PRAC Request for revisions of the PASS protocol to update the milestone dates for FL indication and specify that the EBMT quarterly and annual reports will include both DLBCL and FL indications (not prepared separately)

Protocol Modifications

Protocol modifications may only be made by Kite Pharma Inc., a wholly-owned subsidiary of Gilead Sciences, Inc. Any planned amendments will be discussed with the regulatory authority and EBMT prior to implementation.

4. MILESTONES

Table 3. Protocol Milestones

Milestone	Planned Date
PRAC approval of study protocol*	31 October 2019
Protocol registration in the EU PAS Registry	10 December 2019
DLBCL and PMBCL:	
Start of data collection**	21 August 2020
End of data collection***	22 May 2040
Study duration	20 years
Safety Data Reports****	2020 to 2024, frequency thereafter to be re-evaluated
Annual reports	2021 to 2025 annually, then every 2 years
Final report of study results	14 November 2040
FL:	
Start of data collection**	01 March 2023
End of data collection***	01 December 2042
Study duration	20 years
Safety Data Reports****	2023 to 2028, frequency thereafter to be re-evaluated
Annual reports	2024 to 2028 annually, then every 2 years
Final report of study results	01 June 2043

* Date when EMA/PRAC endorsed protocol version 1.2 and acknowledged Kite's commitments for future protocol edits that resulted in protocol version 1.3, dated 06 November 2019. Per EMA recommendation no formal submission of version 1.3 occurred.
** As the data collection in the EBMT Registry is independent of this study (secondary use of data), the start of data collection is the date from which data extraction starts. First data extraction for study KT-EU-471-0117 will take place three months after protocol registration or contract execution with the EBMT, whichever comes last.
*** 20 years after PRAC approval of protocol or contract execution with the EBMT, whichever comes last, no further data will be included in the study analyses.
**** Quarterly reports will be generated on the basis of quarterly data transmission from EBMT. The reports will be appended to the 6 monthly PSURs, unless a quarterly report generates an urgent new safety finding - when it will be submitted stand-alone in between PSUR cycles.

5. RATIONALE AND BACKGROUND

5.1. Rationale for the Current Study

Engineered autologous T-cell immunotherapy, which uses a patient's own immune cells, offers a promising approach to treating many types of cancer. To be effective, such T cells must possess the appropriate specificity for a tumor, be present in sufficient numbers, and be able to overcome any local immunosuppressive factors. Selecting an appropriate target antigen for T-cell therapy is critical to the potency and safety of the therapy. One type of engineered autologous T-cell therapy comprises T cells that have been engineered ex vivo to express a CAR directed toward a tumor surface antigen. These CARs are fusion proteins with antigen-binding, transmembrane, and T-cell activation domains that, when expressed in T cells, can target tumor antigens for T-cell-mediated killing {Kershaw 2013}. CAR T cell therapies have demonstrated promising antitumor activity across numerous B-cell malignancies, including non-Hodgkin lymphoma (NHL) {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a, Kochenderfer 2017b, KYMRIAH 2020, KYMRIAH™ 2018, Locke 2019, Schuster 2019, Turtle 2016, Wang 2020, YESCARTA 2020, YESCARTA 2019} chronic lymphocytic leukemia (CLL) {Kochenderfer 2015, Porter 2015, Porter 2011}, and acute lymphoblastic leukemia (ALL) {Davila 2014, Gupta 2007, Lee 2015, Maude 2014, Maude 2015, Michea 2018, Singh 2016}.

Anti-CD19 Chimeric Antigen Receptor T-cell Product: Axicabtagene Ciloleucel Axicabtagene ciloleucel is an anti CD19 CAR T cell product manufactured by Kite Pharma, Inc. (hereafter referred to as Kite) that is currently approved for the treatment of r/r large B-cell lymphomas {Locke 2019, Neelapu 2017, YESCARTA 2019}. In the US axicabtagene ciloleucel is also approved for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

CD19 is a 95 kD transmembrane protein expressed only in the B-cell lineage. Expression begins at the pro-B-cell stage and continues throughout B-cell differentiation {Anderson 1984, Nadler 1983, Uckun 1990, Uckun 1988}; expression is downregulated in plasma cells {Gupta 2009, Lin 2004}. CD19 expression is maintained in most B-cell malignancies, including all subtypes of B-cell non-Hodgkin lymphoma (NHL, CLL, non-T-cell ALL, and on a subset of multiple myeloma plasma cells) {Anderson 1984, Garfall 2015, Hajek 2013, Johnson 2009, Leonard 2001, Nadler 1983, Olejniczak 2006, Rodriguez 1994, Uckun 1988}.

Axicabtagene ciloleucel is an autologous CAR T-cell product in which a subject's T cells are engineered to express receptors consisting of a single-chain antibody fragment (ScFv) against CD19 linked to CD3ζ and CD28 T cell activating domains that result in elimination of CD19-expressing cells {Jackson 2016}. 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 {Roberts 2018}. The intracellular signaling domain of CD28 provides a costimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including interleukin (IL)-2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct killing of target cells. In addition, activated T cells secrete cytokines, chemokines, and other molecules that can recruit and activate additional antitumor immune cells {Restifo 2012}. A schematic of the anti-CD19 CAR construct is shown in Figure 1.

Figure 1. Axicabtagene Ciloleucel Anti-CD19 CAR Construct

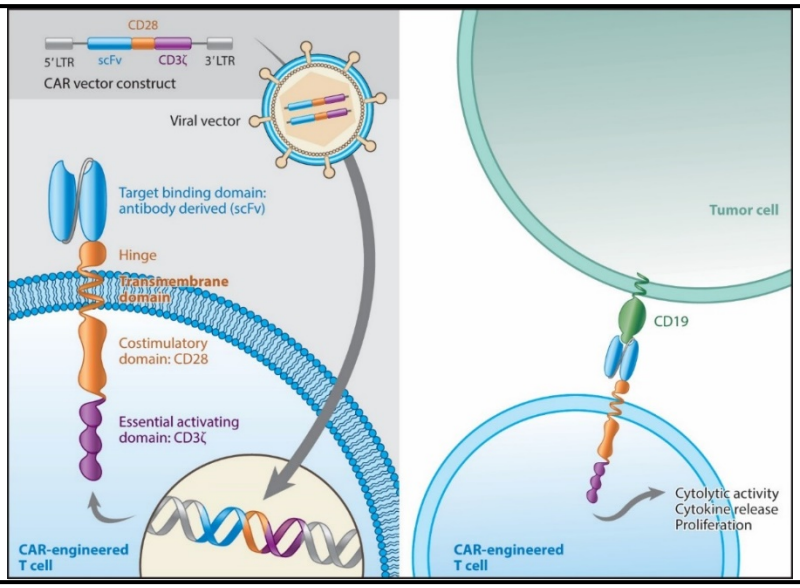

Figure 1: Left panel demonstrates axicabtagene ciloleucel construct with scFv/CD28/CD3ζ, which is inserted in a replication-incompetent gamma-retroviral vector and, upon transfection of T-cells, expresses the chimeric transmembrane protein. The right panel demonstrates the anti-CD19 CAR T-cell binding to its target CD19 on the tumor cell surface.

Treatment of relapsed or refractory large B-cell lymphomas with anti-CD19 CAR T cells results in a high response rate with durable remissions. In the primary analysis based on the modified intent-to-treat (mITT) population (minimum follow up of 6 months) in the pivotal multicenter trial (ZUMA-1) by Kite Pharma, Inc. (hereafter referred to as Kite), the ORR was 72% and complete response (CR) rate was 51%, as determined by an independent review committee. Administration of CAR T cells carries a number of risks independent of target because the immune reaction against tumor cells can elicit a generalized reaction that includes fever, hypotension, respiratory failure, and death {Brudno 2016}. These toxicities are defined as Cytokine Release Syndrome (CRS) and generally occur within the first week from treatment (Table 4). A revised grading system was proposed by Lee and colleagues based on the number of affected organs, severity, and therapeutic approaches needed, ie, vasopressors or ventilatory support {Lee 2014}. Secondly, neurologic events are also observed, which can occur either in the presence or absence of CRS with symptoms ranging from fine tremors to aphasia and seizures (Table 4) {Brudno 2016, Lee 2014, Park 2016}. In the ZUMA-1 pivotal trial, the overall rates of CRS and neurologic events were 93% and 64%, respectively. The rates of Grade 3 or higher CRS and neurologic events were 12% and 31%, respectively. The rate of Grade 5 CRS was 1% (2 subjects). While no Grade 5 neurologic events were reported in the pivotal cohort, Grade 5 events of intracranial hemorrhage (not related to axicabtagene ciloleucel) and cerebral edema (related to axicabtagene ciloleucel) have been reported in the non-pivotal cohorts of ZUMA-1. The median time to onset of first CRS symptoms was 2 days (range: 1 to 12 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median duration of CRS symptoms was 7 days (range: 2 to 29 days, excluding 1 outlying subject with a duration of 58 days). The median time to onset of first neurologic events was 5 days (range: 1 to 17 days). Among the subjects whose neurologic events resolved, the median

duration of neurologic events was 13 days (range: 1 to 191 days, excluding 1 outlying subject with a duration of 451 days).

Table 4. Selected Signs and Symptoms of CRS and Neurologic Events after Infusion of CAR T Cells

Cytokine Release Syndrome Symptoms
Fever
Fatigue
Cardiac failure
Tachycardia
Other cardiac arrhythmias
Dyspnea
Hypoxia
Capillary leak syndrome
Chills
Renal function impairment
Headache
Malaise
Liver function abnormalities
Nausea
Diarrhea
Hypotension
Coagulation impairment
Neurologic Symptoms
Seizures
Somnolence
Headache
Confusion
Agitation
Speech impairment
Tremor
Encephalopathy
Ataxia
Memory impairment
Mental status changes
Hallucinations
Depressed level of consciousness
Delirium
Dysmetria
Brain oedema

Target-specific toxicities are related to direct cytotoxicity against the tumor and normal B cells expressing the antigens. CD19-specific CAR T cells have a direct effect on B cells, which leads to B-cell aplasia and, consequently, hypogammaglobulinemia {Frey 2016, Grupp 2013, Lee 2015, Maude 2014, Maus 2016}.

Patients with lymphoproliferative disorders, such as B-cell lymphomas, have a higher risk of developing other cancers (subsequent neoplasms) compared to the general population (standardized incidence ratio of 1.25 to 1.43) {Bilmon 2014, Chien 2015, Rossi 2015}. This higher risk results primarily from exposure to prior chemotherapy and radiation either as initial or subsequent treatment or as part of an autologous stem cell transplant (auto-SCT). The probability of developing a secondary malignancy 10 years after auto-SCT in patients with lymphoma ranges from 7.9% to 12.9% {Metayer 2003, Seshadri 2009, Smeland 2016}. The types of subsequent neoplasms most commonly observed are acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and melanoma {Bilmon 2014, Metayer 2003, Vaxman 2015}. Cumulative incidence of subsequent neoplasm 10 years after HDT and auto-SCT ranges from 5% to 21% {Bilmon 2014, El-Najjar 2014, Forrest 2005, Pirani 2011, Seshadri 2009, Tarella 2011}.

Axicabtagene ciloleucel manufacturing relies on a replication defective murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T-cell genome, which presents a theoretical risk of oncogenesis via insertional mutagenesis or replication-competent retrovirus (RCR). However, numerous nonclinical {Heinrich 1998 Newrzela 2008} and clinical studies of patients with hematologic malignancies or solid tumors and in patients infected with human immunodeficiency virus (HIV) showed no overt genotoxic effects of γ-retroviral vector-mediated gene transfer of T cells. A review of previous observations of genotoxic events in early clinical trials of γ-retroviral vector-mediated gene transfer into hematopoietic stem cells (HSCs) by Bushman and colleagues indicated that genotoxic events were attributable to activation of oncogenes by retroviral insertion and that the use of HSCs and introduction of cellular growth factors aimed to restore immune competency were facilitating factors {Bushman 2007}.

Among 86 unique patients who exhibited clinical benefit and had follow-up times ranging from 3 months to >5 years across 5 clinical studies of hematologic malignancies and solid tumors, no malignancies secondary to axicabtagene ciloleucel have been reported {Brentjens 2013, Kochenderfer 2016, Kochenderfer 2012, Kochenderfer 2015, Robbins 2015}.

One of these studies has shown no evidence of subsequent neoplasms over a period of up to 23 months in a total of 43 patients with advanced B-cell malignancies treated with retrovirally transduced T cells expressing the same CAR as utilized in axicabtagene ciloleucel {Kochenderfer 2016, Kochenderfer 2012, Kochenderfer 2015}. Long term results from 3 studies to evaluate gamma retroviral vector engineered T-cells for the treatment of HIV showed no treatment-related malignancies among more than 40 patients with HIV who were treated and followed for a period of 1 to 11 years {Scholler 2012}. Notably, Scholler and colleagues have shown that CAR T cells were detected in 98% of samples tested for at least 11 years post-infusion. This analysis represented over 540 patient-years and showed no clinical evidence of viral vector integration-mediated toxicity.

In addition, a retrospective analysis of subjects treated with replication defective γ-retrovirus-transduced T cells across 29 clinical trials spanning from 2001 to 2009, covering 297 individual products and 629 follow-up samples ranging from 1 month to 8 years after infusion, showed no evidence of RCR or insertional mutagenesis {Bear 2012}. In summary, more than a decade of follow-up of patients treated with T cells engineered to express a TCR or CAR encoded by a γ-retroviral vector has not revealed any cases of genotoxicity or RCR that have translated to a subsequent neoplasm.

A theoretical risk remains, however, that genetic modification of T cells with γ-retroviral vectors could result in subsequent neoplasms manifested through insertional mutagenesis introduced during the manufacturing process or by the development of RCR. Although the manufacturing of CAR T cells using vectors similar to the one used in the manufacture of axicabtagene ciloleucel includes provisions to ensure that the virus is replication- defective and the likelihood of insertional mutagenesis in mature polyclonal T cells is low, there is a potential risk of insertional mutagenesis and emergence of RCR after these cell products are more broadly used. Monitoring the presence of γ-retroviral vector sequences and RCR in the development of subsequent neoplasms is an important step to understand the long-term safety profile of this product.

5.1.1. Diffuse Large B-cell Lymphoma (DLBCL)

Treatment of relapsed or refractory DLBCLs with anti-CD19 CAR T cells results in a high response rate with durable remissions. The overall response rate (defined as the sum of complete and partial responses) in the Kite pivotal multicenter trial (ZUMA-1) was 82%, with a complete response rate of 54% {Neelapu 2017}. Due to responses that occurred between the 6- and 12-month data cuts, the overall response rate and the complete response rate (ORR) improved to 83% and 58% respectively in the 12-month analysis {Locke 2019, Neelapu 2017}.

In the ZUMA-1 pivotal trial, the overall rates of CRS and neurologic toxicities were 93% and 64%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 13% and 28%, respectively. The rate of Grade 5 CRS was 1%. While no Grade 5 neurologic toxicities were reported in the pivotal cohort, Grade 5 events of intracranial hemorrhage and cerebral edema have been reported in the non-pivotal cohorts of ZUMA-1. The median time to onset of first CRS symptoms was 2 days (range: 1 to 12 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median time to resolution of CRS symptoms was 8 days. The median time to onset of first neurologic toxicities was 5 days (range: 1 to 17 days). Among the subjects whose neurologic toxicities resolved, the median time to resolution of neurologic toxicities was 17 days.

The rates of CRS and neurologic toxicities in the 24-month analysis were similar to those from the primary analysis. In the 24-month analysis, the overall rates of CRS and neurologic toxicities were 93% and 67%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 11% and 32%, respectively. The rate of Grade 5 CRS was 1%. No new Grade 5 CRS or neurologic events were reported. The median time to onset of first CRS symptoms was 2 days (range: 1 to 12 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median time to resolution of CRS symptoms was 7 days. The median time to onset of first neurologic toxicities was 5 days (range: 1 to 17 days). Among the subjects whose neurologic toxicities resolved, the median time to resolution of neurologic toxicities was 13 days (range: 1 to 191 days) {Locke 2019}.

5.1.2. Follicular Lymphoma (FL)

In the primary analysis of ZUMA-5 with 12 month follow-up, the rates of any grade CRS and neurologic toxicities were 78% and 56%, respectively. The rates of Grade 3 or higher CRS and neurologic toxicities were 6% and 15%, respectively. The rate of Grade 5 CRS was 1%. No Grade 5 neurologic toxicities were observed. The median time to onset of first CRS symptoms was 4 days (range: 1 to 15 days) after infusion of axicabtagene ciloleucel. Among the subjects whose CRS symptoms resolved, the median duration of CRS was 6 days. The median time to onset of first neurologic toxicities was 7 days (range: 1 to 177 days). Among the subjects whose neurologic toxicities resolved, the median duration of neurologic toxicities was 14 days. The rates of CRS and neurologic toxicities, median onset and duration of both CRS and neurologic toxicities in the 18-month analysis were consistent with data observed in the primary analysis.

5.1.3. Purpose of the Current Study

The purpose of this study is to analyze and report on the long-term follow-up data for recipients of axicabtagene ciloleucel captured in the EBMT Registry to address the long-term safety of this product, including secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential. The purpose of the study therefore includes the further characterisation of the immediate and recognised toxicities of YESCARTA, as well as the long-term and delayed onset ADRs.

The EBMT is a non-profit organisation that was established in 1974 to allow scientists and physicians involved in clinical bone marrow transplantation to share their experiences and develop co-operative studies. More recently, the scope of the organisation has broadened to include work in cellular therapy as well. The EBMT has created a specific cell therapy module of its registry and utilizes the infrastructure created for the stem cell transplant registry to systematically capture data on all cell therapies. This study will use the data accrued on YESCARTA in the EBMT Registry to systematically evaluate information on patients receiving YESCARTA and for 15 years of follow-up.

6. RESEARCH QUESTIONS AND OBJECTIVES

This is a long-term safety study of recipients of YESCARTA for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy, or of relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy.

The study will utilize long-term follow-up data for recipients of YESCARTA to evaluate the safety including long term safety, specifically incidence rates and severity of ADRs, the risk of subsequent neoplasm, known and potential risks associated with this product, as well as rare and delayed safety events occurring in patients.

Therefore, the study will make secondary use of the data captured in the EBMT Registry, using the infrastructure EBMT created for the stem cell transplant registry, to systematically capture information at the time of YESCARTA infusion and for 15 years of follow-up.

The primary objective of this study is:

To evaluate the incidence rate and severity of ADRs in patients treated with YESCARTA, including secondary malignancies, cytokine release syndrome (CRS), neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in female patients of childbearing potential.

The secondary objectives of this study are:

- 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 allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored.
- To assess the risk of tumor lysis syndrome (TLS) and aggravation of GvHD, and the detection of RCR in samples of patients with secondary malignancies.

The other exploratory objectives of this study are as follows:

- To determine the occurrence of loss of target antigen and of functional CAR-T persistence in patients relapsing after YESCARTA therapy.

7. RESEARCH METHODS

7.1. Study Design

This study is a long-term, non-interventional study planned to evaluate outcomes of recipients of YESCARTA for treatment of relapsed or refractory DLBCL and PMBCL after two or more lines of systemic therapy, or of relapsed or refractory FL after three or more lines of systemic therapy, in the post-marketing setting, making secondary use of data available in the EBMT Registry. The EBMT centers enter data into the EBMT Registry following the EBMT specific procedures and requirements. The preferred and most common option to enter data into the EBMT Registry is direct electronic data entry by a trained and authorized staff member from the center. This option ensures immediate access of the center's data by the EBMT and authorized users. Alternatively, direct data entry by a national registry on behalf of specific centers that submit paper forms to this national registry is possible. Patients' data may be entered up to 1 week prior or anytime following administration of YESCARTA infusion and patients will be followed for 15 years. Data entry into the EBMT Registry requires signed informed consent by the patient or a legal guardian to allow data to be provided to the EBMT.

7.2. Setting

No treatments, therapy protocols, or procedures are mandated. There is no prescribed visit schedule. Data entered into the EBMT Registry will be obtained from clinical, laboratory, and diagnostic assessments conducted in the course of routine medical practice and available in the patient's medical chart, collected for the primary purpose of patient care. Data will be captured by completion of the EBMT Cellular and Gene Therapy Form for the time points described below (see 7.6), using the most current data available.

Data entry into the EBMT Registry will be done by the EBMT centers irrespective of this study according to EBMT guidance documents in its most current versions (e.g. submitting data to the EBMT (currently dated 21/12/2020)).

The EBMT Cellular and Gene Therapy Form was created in close cooperation with the Committee for Human Medical Products (CHMP) and other relevant Marketing Authorization Holders (MAHs). The aim is not to collect all possible information from the medical charts, but to collect the essential information in the EBMT Registry. For safety data, the forms specifically collect data on events of special interest. There is also an option to add other complications/toxicities in the EBMT Registry. The EBMT therefore collects in their registry a defined data set as specified in the EBMT Cellular and Gene Therapy Form. The EBMT Cellular and Gene Therapy Form is under the control of the EBMT and its content can change throughout the course of the study.

Available data within the EBMT Registry will be analyzed for this study at defined time points. In this registry only predefined data of interest will be collected from the medical charts.

Spontaneous ADR reporting independent from this study is the primary source for detecting new safety concerns/signals. New emerging safety concerns and respective data/variables might also be added throughout the course of the study on the EBMT Cellular and Gene Therapy Form to support structured data collection of such new relevant data during the study, if agreed by the EBMT, who owns this form.

7.2.1. Eligibility

The EBMT Registry collects data on all patients receiving cell therapy. Eligible patient data for this study is from patients treated with YESCARTA for relapsed/refractory diffuse large B-cell lymphomas (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of therapy, or relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy, irrespective of whether the YESCARTA product was within approved product specifications or out of specifications, but released at physician's request. Eligible patient data includes data of patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary, etc.) and with any grade for Sorror score, ECOG and Karnofsky score, i.e. there are no restrictions regarding the patients' performance status of any kind.

Patients participating in interventional clinical trials will not be included in the study analyses.

7.2.2. Study Centers

All centers that are qualified for the use of YESCARTA who provide their data to the EBMT Registry contribute to this study. The centers enter the data directly via the EBMT Cellular and Gene Therapy Form into the EBMT Registry following the EBMT data entry guidance documents (see Section 7.2). The centers will enter initial patient data and any subsequent follow up data.

In a commercial setting, Kite is engaging with sites at time of initial commercial center qualification process to allow the prescribing of YESCARTA and when Kite delivers training on the required additional risk minimization measures (aRMMs). Kite cannot engage in EBMT Registry management related interactions with the centers.

These commercial sites are generally members of EBMT and therefore Kite has non study/registry-related contacts with sites. Nevertheless, because of the responsibilities of Kite to deliver both initial as well as refresher training to qualified prescriber sites, the contact with centers that are contributing to the EBMT Registry can deliver relevant reminders on the importance of spontaneous reporting and that this is not replaceable by reporting into the EBMT Registry.

7.3. Variables

This secondary use of data study makes use of the EBMT Registry and is dependent on all needed variables to be collected in the EBMT Cellular and Gene Therapy Form. Furthermore, certain variables may not be generated as part of routine medical practice or local regulations limit the ability to collect the information.

The EBMT Cellular and Gene Therapy Form specifies the sub-set of data that are transcribed by the centers from the patients' medical charts into the EBMT Registry.

7.3.1. Variables utilized for analysis of Primary Objectives

- Secondary malignancy is defined as the development of any new malignancies, with the exception of relapsed large B-cell lymphomas, occurring after the administration of YESCARTA. The EBMT Registry will collect the date of diagnosis, type, location and, if a biopsy occurred, information whether secondary malignancy was derived from cells that composed or were part of the infused medicinal product or cell/gene therapy product, and this study will utilize this data for analysis.

- CRS is a class effect of CAR T-cell therapies, which may occur at different grades of severity, characterized by fever; rigors; nausea; emesis; headache; hypotension; and pulmonary, hepatic, and renal dysfunction. The EBMT Registry will collect CRS grade, system of grading, date of onset, treatment and resolution status and this study will utilize this data for analysis.

- Neurologic toxicity is a class effect of CAR T-cell therapies and most commonly includes confusion, delirium, aphasia, obtundation, myoclonus, and seizures. The EBMT Registry will collect the type, grade (according to the Common Terminology of Adverse Events [CTCAE] or ICANS score), treatment, date of onset and resolution status of all neurologic toxicities, and this study will utilize this data for analysis.

- Prolonged cytopenias are defined as inability to recover the absolute neutrophil count (ANC) and platelets within 100 days after the administration of YESCARTA. ANC recovery is defined as neutrophil count $\geq 500/mm^3$ for 3 consecutive days, and platelet recovery is defined as platelet count $\geq 50 \times 10^9/L$ without transfusion support within 7 days. The EBMT Registry will collect the date of recovery for ANC and platelets, and this study will utilize this data for analysis.

- Serious infections are defined as viral, bacterial or fungal infections that require intervention or have led to a negative outcome for the patient (including death) as determined by the treating physician and reported to the EBMT Registry. The EBMT Registry will collect the type, organism, treatment and date of onset of infection as well as resolution, and this study will utilize this data for analysis.

- Hypogammaglobulinemia is defined as serum IgG levels below 600 mg/dL. The EBMT Registry will collect for hypogammaglobulinemia the date of onset, treatment, and resolution status, and this study will utilize this data for analysis.

- The EBMT Registry will collect data on any pregnancy that occurs after administration of YESCARTA and additional information related to the outcome of the pregnancy and the newborn's health, and this study will utilize this data for analysis.

Table 5. Grading of CRS

Grade[1]	Sign/Symptom/Intervention
1	Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)
2	Symptoms require and respond to moderate level of intervention: Oxygen requirement < 40% FiO_2, or Hypotension responsive to intravenous fluid infusion or low dose of one vasopressor, or Grade 2 organ toxicity[2]
3	Symptoms require and respond to aggressive intervention: Oxygen requirement > 40% FiO_2, or Hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis
4	Life-threatening symptoms Requirement for mechanical ventilatory support, or Grade 4 organ toxicity (excluding transaminitis)
5	Death

1 CRS grading adapted from Lee, et al {Lee 2014}
2 Organ toxicities are defined according to National Cancer Institute (NCI) Common Terminology of Adverse Events (CTCAE).

7.3.2. Variables utilized for analysis of Secondary Objectives

- Date and main cause of death, and date of last assessment
- Additional treatment and date of treatment received for primary disease (DLBCL, PMBCL or FL) after YESCARTA administration
- Date of the first relapse or progression or significant worsening of the primary disease (DLBCL, PMBCL or FL) after the YESCARTA infusion
- Grade, date of onset and resolution of Tumor lysis syndrome (TLS)
- Type, resolution status, onset date of GvHD. For acute GvHD: grade, and relationship to YESCARTA
- In case of a secondary malignancy the sampling for RCR testing, the sample date and the test result (not collected in the current EBMT Cellular and Gene Therapy Form)

7.3.3. Variables utilized for analysis of Other Exploratory Objectives

- Date of sampling for loss of target antigen and result (not collected in the current EBMT Cellular and Gene Therapy Form)
- Data on B-cell recovery as an indirect measure of functional CAR-T persistence: date, B-cell count per volume in peripheral blood, and detection method (not collected in the current EBMT Cellular and Gene Therapy Form)

7.3.4. Variables for exposure to YESCARTA

- Name and dose level of lymphodepleting chemotherapy received prior to YESCARTA infusion.
- YESCARTA infusion: date, and whether YESCARTA was released at physician's request, because the manufactured product was out of specification.

7.3.5. Variables to Collect for Demographics and Baseline Characteristics

- Age, gender, and country
- Height and weight at the time of YESCARTA infusion
- Indication for treatment with YESCARTA
- Disease subtype (eg, NHL histologies)
- Disease status at time of cellular therapy (eg, sensitive or resistant to chemotherapy or radiation prior to therapy)
- Prior lines of treatment and response
- Disease stage at time of cellular therapy
- Prognostic information: double/triple hit, international prognostic index, cytogenetics (GCB-DLBCL, ABC-DLBCL)
- Time from diagnosis of the primary disease to cellular therapy
- Prior hematopoietic cell transplantation: autologous or allogeneic, donor HLA match type (HLA-identical sibling, syngeneic, HLA-matched other relative, HLA-mismatched relative), source of stem cell product (Umbilical cord Blood, Bone Marrow, Peripheral Blood), immunosuppressants (type and duration), prior GVHD
- Prior cellular therapy (other than autologous or allogeneic SCT)
- Performance score (ECOG or Karnofsky)
- Comorbidities index (Sorror score)
- Active autoimmune, neurologic and hematological disease; infection related complications

7.4. Data Sources

The source data for the EBMT Registry will be the data presented in the patients' medical records. A sub-set of these data from patients' medical records will be transcribed by the centers in the EBMT Registry utilizing the EBMT Cellular and Gene Therapy Form (Appendix 5). The data on patients receiving YESCARTA available in the EBMT Registry will be the data source for this study.

The EBMT maintains a registry which encompasses all haematopoietic stem cell transplant (HSCT) procedures for all indications. It also stores immunosuppressive treatments for bone marrow failure syndromes (i.e. aplastic anaemias), cell therapy treatments other than HSCT and donor information pertaining to collection and donor follow up.

All EBMT centers are asked to submit the minimum essential data as recorded through the MED-A and/or EBMT Cellular and Gene Therapy Form. Centers are instructed to electronically submit the first registration on the day of treatment (Day 0) or within a week of Day 0. An update should be submitted 100 days, and 6 months after the date of transplant or cell therapy infusion for non-transplanted patients, or when the patient dies, whichever comes first. Yearly follow up data should be submitted for all patients from then onwards.

7.5. Study Size

This study plans to evaluate all eligible patients who have been treated with YESCARTA and documented in the EBMT Registry within five years from study start for patients with DLBCL and PMBCL, or for all patients with FL treated with Yescarta within five years from time of approval of FL indication and approval of the protocol for this study to include FL patients and to follow these patients for 15 years. In addition to the further characterisation of the immediate toxicities of YESCARTA, the study is designed to detect rare or late onset safety events occurring in patients. Therefore, the primary analysis will consist of estimation of the rate of endpoint events per 15 person-years of follow up and the cumulative incidence of the event by 15 years, along with 95% confidence intervals (CIs). The events of interest (i.e., those described in Section 7.3.1) are subject to competing risks of death, which decrease the available person-years of follow-up.

For DLBCL and PMBCL, the available person-years of follow-up are estimated using a piecewise linear survival curve with 50% survival at 2 years and 30% survival long-term, indicating an average person-years of follow-up of 6.7 years. A 10% overall loss to follow-up is further assumed, resulting in total person-years of follow-up of approximately 4522. For FL, the available person-years of follow-up are estimated using a piecewise linear survival curve with 72% survival at 2 years and 35% survival long-term, indicating an average person-years of follow-up of 8.7 years. A 10% overall loss to follow-up is further assumed, resulting in total person-years of follow-up of approximately 1171. The assumed person-years of follow-up will provide the likelihood of seeing at least one event of interest as shown in Table 6, if the true event rate per 15 years of follow up is 1:250 through 1:10, respectively.

Table 6. Likelihood of Observing ≥ 1 Event of Interest for Patients with LBCL, FL Followed for Up to 15 Years

	True Event Rate						
Disease Type	**1:10**	**1:20**	**1:50**	**1:100**	**1:150**	**1:200**	**1:250**
LBCL	> 99%	> 99%	> 99%	95%	87%	78%	70%
FL	> 99%	98%	79%	54%	41%	32%	27%

a 2-year survival rate used in the calculation for LBCL and FL are based on the observed 2-year survival rate from ZUMA-1 study primary analysis for LBCL and from ZUMA-5 study primary analysis for FL.

b The likelihood calculation is based on projection that 1500 LBCL and 300 FL patients will be commercially treated in EU, and 50% of them will consent to participate in the study, ie, 750 and 150 commercially treated subjects in EU are assumed to be enrolled into the study. The true number of patients required to be enrolled to the study is depending on the number of patients enrolled according to the 5-year accrual period since the study starts implementing for the corresponding indication.

7.6. Data Management

Data will be entered into the EBMT Registry by the centers utilizing the EBMT Cellular and Gene Therapy Form. EBMT will liaise with individual centers and will provide standard training on how to enter the data and how to use the data management system. Trained personnel will enter data directly into the EBMT Registry database, users will have user accounts with password in order to have access to the EBMT Registry database. EBMT will cooperate with centers to reduce the amount of missing/erroneous data in the registry.

An imperative need for clear understanding of the secondary nature of the data is appreciated, wherein data are transcribed into the EBMT registry from the medical record. To fully ensure the secondary categorization of the data is not disrupted, personnel at the centers will be trained and instructed by the EBMT to enter only information available in the medical record, and to make no inferences outside of this practice.

Data will be collected at the center's standard follow up time points, including at least time points during the first year at Day 100, 6 and 12 months and then annually for 15 years after infusion. Expedited reporting of individual case safety reports to EBMT or by EBMT will not occur. Reporting of adverse events by centers or clinicians will follow the standard spontaneous reporting system per local regulations and time lines as described in Section 9.

The center that administers YESCARTA is responsible for reporting follow-up unless the responsibilities are formally transferred to and accepted by a healthcare provider at another center. Patients who receive a hematopoietic cell transplantation (HCT) or other cellular therapy or any other treatment for the primary disease after YESCARTA will continue to be followed.

EBMT will conduct the study specific analyses and provide overviews to update Kite Inc. regarding the progress of the data entry into the EBMT Registry. Reports will be jointly prepared as described in Section 10.1.

7.6.1. Data Transfer Procedure

EBMT provides raw data outputs in a standard format to Kite. Safety datasets are provided quarterly and full datasets annually.

7.7. Data Analysis

7.7.1. Primary Endpoints

- Incidence rates, time to onset, type and location of secondary malignancy
- Incidence rates, severity, time to onset, management and resolution of CRS
- Incidence rates, severity, time to onset, management and resolution, and type of neurologic events
- Incidence rates of prolonged cytopenias
- Incidence rates, type, organism, resolution, and time to onset of serious infections
- Incidence rates, time to onset of hypogammaglobulinemia, and use of replacement immunoglobulin therapy
- Incidence rates of pregnancy, and pregnancy outcome among women with childbearing potential

Time to onset of event of interest (secondary malignancy, or CRS, or neurologic events, or serious infections, or hypogammaglobulinemia) is defined as the time from YESCARTA infusion to the date of onset of the first event of interest, i.e., the date of the first onset of the event or censoring – the date of the YESCARTA infusion + 1. Deaths before experiencing the event will be taken as a competing risk.

7.7.2. Secondary Endpoints

- Overall survival: overall survival is the time from the date of YESCARTA infusion to the date of death due to any reason.
- Time to next treatment of the primary disease: time from YESCARTA infusion to next treatment of the primary disease (DLBCL, PMBCL or FL) or death due to relapse or progression of the primary disease. Non-primary disease related mortality will be taken as a competing risk.
- Time to relapse or progression of the primary disease: time to relapse or progression is defined as the time from YESCARTA infusion to the first relapse or progression or significant worsening of the primary disease (DLBCL, PMBCL or FL), or death due to relapse or progression of the primary disease. Non-primary disease related mortality will be taken as a competing risk. Relapse of the primary disease is defined as reappearance of the primary tumor among patients who achieved a remission as the best response. Progression of the primary disease is defined by at least a 50% increase in the size of an existent mass or lymph node or increase in the number of lymph nodes or new sites of disease.

- Primary and secondary endpoints on subgroups by gender, age, and in special populations (patients with prior allogeneic SCT, high risk comorbidity index, patients treated with Out of Specifications (OOS) product), and additional subgroups may also be explored.

- Incidence rate, severity, resolution, and time to onset of TLS.

- Incidence rate, resolution, time to onset of aggravation of GvHD by acute and chronic type; incidence rate, severity and relationship to cell therapy for acute GvHD.

- Frequency of detection of RCR in samples of patients with secondary malignancies.

7.7.3. Other Exploratory Endpoints

- Occurrence of loss of target antigen in patients relapsing after YESCARTA therapy.

- Occurrence of functional CAR-T persistence in patients relapsing after YESCARTA therapy.

7.7.4. General Considerations for Data Analysis

The study will make secondary use of the data available in the EBMT Registry. Analysis of all endpoints for this study will include all patients satisfying the eligibility criteria who are documented within the EBMT Registry and treated with YESCARTA. Categorical variables will be summarized descriptively by number and percentage of patients in each categorical definition including 95% confidence intervals (CIs). Continuous variables will be summarized descriptively by mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum.

Incidence rates of endpoint events will be provided, except where indicated. Multivariate Poisson regression analyses will be used to estimate incidence rates, adjusted for follow-up period, specified subgroups and other potential confounders (demographics and baseline characteristics; see Section 7.3.5).

Kaplan-Meier curves will be used to illustrate all time-to-event data. Competing risk analysis method will be used for the analysis of time to onset and duration of endpoint events, time to relapse or progression and time to next treatment, and the cumulative incidence at specified time points will be provided. Cox-proportional Hazard models will be used to model multivariate time-to-event data adjusted for subgroups and other potential confounders (demographics and baseline characteristics; see Section 7.3.5).

The analysis will be firstly based on complete case analysis when the percentage of missing is around 5-10%. However, the potential impact of the missing values on the analysis will be also evaluated and possible patterns of relationship between missing values and both influential characteristics and outcomes will be investigated. Results of the analysis of the type of missing data will be described in the results to support the appropriateness of the statistical analysis performed.

Missing events due to deaths will be adjusted through competing risk analysis method for time-to-event subjects describe above and in Section 7.7.5 and 7.7.6. The extent of missing data in the study will be described and tabulated. When possible the number of missing data will be reduced by retrieving the data or imputing the correct value if it can be derived from other information already collected in this protocol. Imputation methods as sensitivity analyses will be used to account for missing values in the dataset for those variables used in multivariate modeling (demographics, baseline disease assessment, medical history, treatment history) following the current ENCePP guidelines {Pharmocovigilance 2018}, {Rubin 1987}, {Moons 2006}, {Wlelch 2014}. Multiple imputation by chained equations (MICE) as sequential regression multiple imputation will be used handling of missing data {Azur 2011}. Using MICE, missing values are imputed based on the observed values for a given individual and the relationships within the data for other participants. The imputation methods will not be applied when the percentage of missing is significant (>40%), or the assumption of the imputation methods is not hold.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by Preferred Term (PT) and primary System Organ Class (SOC).

7.7.5. Analysis of Primary Endpoint

Secondary malignancy: The overall incidence of secondary malignancies, and secondary malignancy by type and location will be summarized using frequencies and percentages, as well as follow-up adjusted rates. Cumulative incidence curve of time to onset of secondary malignancy shown out to 15 years, treating death prior to secondary malignancy as a competing event. Estimates and 95% CIs for the cumulative incidence of secondary malignancy will be provided at 1, 2, 5, 10, and 15 years.

CRS: The overall incidence and grade of CRS will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of CRS and 95% CI will also be estimated using competing risk analysis method, with death before experiencing CRS treated as a competing event for the onset of CRS up through 30 days after YESCARTA infusion. Management and resolution of CRS will also be described.

Neurologic events: The overall incidence and grade of neurologic events, both overall and by type, will be described using frequencies and percentages, as well as follow-up adjusted rates. The incidence of neurologic events and 95% CI will also be estimated using competing risk analysis method, with death before experiencing neurologic events treated as a competing event for the onset of neurologic event up through 90 days after YESCARTA infusion. Treatment and resolution of neurologic toxicities will be described.

Prolonged cytopenias: The proportion of patients who fail to recover neutrophil and platelet counts, as previously specified, by Day 100 after the administration of YESCARTA will be described along with 95% CI using exact binomial methods.Serious infections: The incidence of serious infections, type and organism will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of serious infections after YESCARTA infusion and 95% CI will be estimated using competing risk analysis method, with death before experiencing serious infections treated as a competing event.

Hypogammaglobulinemia: The incidence of hypogammaglobulinemia will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of hypogammaglobulinemia after YESCARTA infusion and 95% CI will be estimated using competing risk analysis method, with death before experiencing hypogammaglobulinemia treated as a competing event for the onset of hypogammaglobulinemia. Use of replacement therapy will also be described as part of this endpoint.

Pregnancy and pregnancy outcome: Both the proportion of women who become pregnant and the pregnancy outcome and the newborn's health will be described as part of this outcome.

7.7.6. Analysis of Secondary Endpoints

Overall survival: Overall survival (OS) is the time from date of YESCARTA infusion to the date of death due to any reason. All patients will be followed up for survival information regardless of whether they received additional treatment post infusion. Patients who are alive at last contact will be censored at that time, but no censoring will be done for additional treatment. OS will be summarized using the Kaplan-Meier (KM) estimate. The median OS along with 95% CIs will be presented if appropriate. Causes of death will also be reported.

Time to next treatment: The cumulative incidence of time to next treatment and 95% CI will be estimated using competing risk analysis method, with death without relapse or progression considered as a competing risk. Pointwise estimates and 95% CIs at 6, 12, 24, and 36 months will be calculated.

Time to relapse or progression of the primary disease: The cumulative incidence of relapse or disease progression and 95% CI will be estimated using competing risk analysis method, with death without relapse or progression considered as a competing risk. Pointwise estimates and 95% CIs at 6, 12, 24, and 36 months will be calculated.

TLS: The overall incidence and grade of TLS will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of TLS after YESCARTA infusion and 95% CI will be estimated using competing risk analysis.

Aggravation of GvHD: The overall incidence of GvHD, both overall and by type, will be described using frequencies and percentages, as well as follow-up adjusted rates. The cumulative incidence of GvHD after YESCARTA infusion and 95% CI will be estimated using competing risk analysis. The severity and relationship to YESCARTA will also be summarized.

RCR: The detection of RCR in samples of patients with secondary malignancies will be described using frequencies and percentages.

7.7.7. Analysis of Other Exploratory Endpoints

Loss of target antigen: Occurrence of loss of target antigen in patients relapsing after YESCARTA therapy will be described using frequencies and percentages.

Functional CAR-T persistence: Occurrence of functional CAR-T persistence in patients relapsing after YESCARTA therapy will be described using frequencies and percentages.

7.7.8. Interim Analysis

Annual reports will be prepared for the first five years and then every 2 years, in which an analysis of treated patients for the primary and secondary endpoints will be included. The study objective is not associated with formal hypothesis testing and no overall type I error control. These interim analyses are administrative interim analyses for the purpose of monitoring the progress of the study enrollment, safety and effectiveness profile of YESCARTA.

After start of data collection and until the patients at the EBMT centers have signed the revised version of the informed consent for data entry into the EBMT Registry, EBMT will provide data to Kite in anonymized form as aggregated reports. Only the revised informed consent form allows the EBMT to share pseudonymized data with Kite. Once the majority of patients signed this revised informed consent form, EBMT will provide Kite with a quarterly raw data output. Based on the data transferred, Kite performs an aggregate data analysis for YESCARTA within 30 days (45 days for the first report). Two quarterly reports will be submitted as appendices to the PSUR to the PRAC. In case an intervening quarterly report identifies a major new safety finding, the respective report will be submitted promptly as stand-alone document.

Interim analysis and annual reports will include both LBCL and FL indications.

7.8. Quality Control

The data collected will be entered in the EBMT database according to standard operating procedures, work instructions, manuals and guidelines that are in place and maintained by EBMT.

At a registry level EBMT has built in more than 4.000 control triggers, which promote consistency of the data. In addition, EBMT personnel and registry users can run data quality reports, which predominantly focus on missing data. For all studies (both retrospective and prospective) based on registry data additional data cleaning efforts are done, including the analyses of outliers, additional data requests and if needed statistic adjustments for missing data.

Apart from remote monitoring activities, on-site monitoring of data for 10% of the included YESCARTA patients will be performed by the EBMT. Centers will be selected for on-site monitoring based on a risk-based approach using quality indicators as described in the monitoring plan.

Additional quality control measures supported by EBMT include:

- Automatic data validation checks verify the accuracy and internal consistency of entries in the database at the point of entry.
- Data quality control reports can be run by users (or by registry personnel) to check for missing or inconsistent or incorrect data.
- Follow-up requests on missing or incorrect data are issued by the registry/Study Office, this also applies, if yearly follow up data was not submitted for a patient during the 15 year follow-up period.
- Education and training sessions (face to face and on-line) are available for data entry staff.
- Remote manual data quality review in accordance with the study data quality and monitoring documents. In addition, monitors will engage centers with regard to data quality and completeness via telephone calls and may perform onsite visits, as documented in the study monitoring plan.

7.9. Limitations of the Research Methods

The EBMT Registry allows patient data entry any time after YESCARTA infusion; therefore this study has the characteristic disadvantages of retrospective studies, for example, information bias, history bias and recall bias. However, there will be an effort to encourage patient documentation in the EBMT Registry as promptly as possible to capture data continuously going forward.

Information bias can be prevented by using standard measurement instruments, like electronic data collection form and appropriate training of personnel entering the data. Appropriate training of personnel entering data is also important to avoid missing values when checking the patients' medical records.

7.10. Other Aspects

7.10.1. Study Discontinuation

No patient's treatment will be dictated by the protocol of this long-term observational study or by EBMT, or Kite. Consequently, continuing or discontinuing this study will not impact patient care. Therefore, identification of adverse effects of YESCARTA will not constitute sufficient reason to terminate the study. However, early termination of the study will be considered if:

- Sufficient information is accumulated to meet the scientific objectives of the study
- The feasibility of collecting sufficient information reduces to unacceptable levels because of low exposure rates, extremely slow patient accrual, or loss of the ability to follow-up

In the event that such conditions are met, any consideration for termination of the study will be discussed and agreed with the European Medicines Agency (EMA) beforehand.

8. PROTECTION OF HUMAN SUBJECTS

Because this is a non-interventional study with no pre-specified interventions and no interaction with patients, no potential physical or psychological risks to patients exist. This study will make secondary use of data collected within the EBMT Registry to capture information about YESCARTA.

EBMT will use standard processes for ensuring the protection of human subjects for patients whose cellular therapy data are reported to the EBMT Registry. Participating centers are responsible for obtaining informed consent, registering patients, and submitting baseline and follow-up data on participating patients into the EBMT Registry following EBMT's procedures and requirements.

There is no potential benefit to those who agree to have their data entered into the EBMT Registry. All benefits of long-term follow-up data collection will assist in understanding late effects that occur after treatment with CAR T cells, and thus will be benefiting future patients. The only risk to patients is the risk of loss of privacy and confidentiality. This is a well-mitigated risk in relationship to the potential benefit to future recipients from knowledge gained through these research studies.

8.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the European Medicines Agency – Guideline on Good Pharmacovigilance Practices (GVP) Modules VI and VIII – Post-Authorisation Safety Studies, following the requirements for studies making secondary use of data, and including the archiving of essential documents. The study will further be conducted in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), by enclosing the ENCePP Checklist in the submission and registering the study in the EU PAS Registry.

8.2. Informed Consent

No specific informed consent will be obtained to participate in this secondary analysis of existing data. According to established practices of the EBMT and country requirements, at each of the centers an informed consent document will be obtained from each participating patient and maintained at the center. With this informed consent document patients will be consenting to provide their data into the EBMT Registry.

8.3. Confidentiality

All data evaluated for this study will be collected in an EBMT data collection form with a unique identifier for each patient by each participating center. The patient identifiers will be removed and the data will contain no patient identifiable fields when analyzed data is shared with Kite by the EBMT.

9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

The operational model for this post-authorization safety study protocol qualifies as non-interventional research with a design based on secondary use of data (i.e. utilizing data from patients medical records that was previously collected for another purpose and included into the EBMT Registry data set; and where the adverse events have already occurred and will not be reported in expedited manner) as outlined in GVP Module VI. By this guidance, reporting of safety information in the form of individual case safety reports is not required and all adverse event and safety data are only required to be recorded and summarized in the interim safety analysis and in the final study report. All adverse events will be summarized in aggregate during all reporting efforts, including in the interim and final study reports.

Reporting of individual adverse events and adverse reactions will follow the standard spontaneous reporting system per local regulations and timelines. The centers will report any suspected adverse reactions directly to Kite, health authorities or to the EMA. The SmPC and packaging materials provide respective details and contact information. Kite further gives clear guidance to HCPs in the aRMMs of the need and importance to spontaneously report and that this is not substituted by reporting into the EBMT Registry.

9.1. Kite Reporting Requirements to Regulatory Authorities

Kite is responsible for analyzing spontaneous reports of all safety information received independently from this study and reporting to regulatory agencies as determined by country-specific legislation or regulations.

9.2. Definitions

9.2.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Any medical condition or clinically significant laboratory abnormality with an onset date before YESCARTA treatment cycle was initiated. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

9.2.2. Adverse Events of Special Interest

An **Adverse Events of Special Interest** (AESI) for this study is considered to be an event in the focus of the primary objective: secondary malignancies, CRS, neurologic toxicities, prolonged cytopenia, serious infections, and hypogammaglobulinemia. As part of the primary objective, pregnancy outcomes in female patients of childbearing potential are also of special interest.

9.2.3. Adverse Drug Reactions

An **adverse drug reaction** (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

9.2.4. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

9.2.5. Serious Adverse Drug Reaction

A SADR is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

9.2.6. Special Situations Reports

This study has a primary endpoint to investigate pregnancy outcomes in female patients of childbearing potential reported to Kite. Other Special situation reports (SSRs) are not within the objectives of the study, but if reported spontaneously, Kite will accept these reports and handle them as appropriate.

Special situation reports include reports of abuse, drug interactions, counterfeit or falsified medicine, exposure via breastfeeding, lack of effect, medication error, misuse, occupational exposure, off-label use, overdose, pregnancy, product complaints, transmission of infectious agents via the product, and unexpected benefit. Definitions are examples are provided below:

- Abuse: Persistent or sporadic intentional excessive use of a medicinal product by a patient.
- Drug interactions: Any reports of drug/drug, drug/food, or drug/device interactions.
- Counterfeit or falsified medicine: Any medicinal product with a false representation of: a) its identity, b) its source, or c) its history.
- Exposure via breastfeeding: Reports of any exposure to a medicinal product during breastfeeding.
- Lack of effect: A report of a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.
- Medication error: Any unintentional error in the prescribing, dispensing, preparation for administration or administration of a medicinal product while the medication is in the control of a healthcare professional, patient or consumer.
- Misuse: Use of a medicinal product that is intentional and inappropriate not in accordance with its authorized product information.
- Occupational exposure: Exposure to a medicinal product as a result of one's professional or non-professional occupation.
- Off-label use: Where a medicinal product is intentionally used by a Health Care Professional for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population (e.g., the elderly).
- Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose in the product labelling.

- Pregnancy reports (maternal pregnancy and partner pregnancy): Reports of pregnancy following maternal or paternal exposure to the product.
- Product complaint: Complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.
- Unexpected benefits: An unintended therapeutic effect where the results are judged to be desirable and beneficial.
- Transmission of infectious agents via the product: Any suspected transmission of an infected agent through a Kite medicinal product.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Study Report and Publications

Reports listed below will be inclusive of both LBCL and FL patients'data.

10.1.1. Safety Data Reports

After start of data collection and until the patients at the EBMT centers have signed the revised version of the informed consent for data entry into the EBMT Registry, EBMT will provide data to Kite in anonymized form as aggregated reports. Only the revised informed consent form allows the EBMT to share pseudonymized data with Kite. Once the majority of patients signed this revised informed consent form, EBMT will provide Kite with a quarterly raw data output. Based on the data transferred, Kite performs an aggregate data analysis for YESCARTA within 30 days (45 days for the first report). Two quarterly reports will be submitted as appendices to the PSUR to the PRAC. In case an intervening quarterly report identifies a major new safety finding, the respective report will be submitted promptly as stand-alone document. A particular focus are the Adverse Events of Special Interest (AESIs) – which are considered to be the events which are the focus of the primary objective (please see below and in Section 9.2.2) – where information is available for patient level presentation and causality assessment, this will be included.

The safety data reports will contain the following information, as available:

- Patient enrollment in registry
- Baseline characteristics
- Aggregate numbers of reported fatal adverse events
- Aggregate numbers of all reported adverse events
- Review of events considered primary objectives of the PASS study:
  secondary malignancies, CRS, neurologic toxicities, prolonged cytopenia, serious infections, hypogammaglobulinemia
- If reported, review of any unexpected events, which do not fall under the previously recognized risks or ADRs of special interest
- Review of pregnancies and outcomes
- Summary and conclusions

10.1.2. Annual Reports

Annual reports will be prepared for the first five years and then every 2 years, in which an analysis of treated patients for the primary and secondary endpoints will be included. The versions of the EBMT Cellular and Gene Therapy Form utilized in the EBMT Registry during the respective time period will be provided as appendices to these reports. The EBMT Cellular and Gene Therapy Form is under the control of the EBMT and its content can change throughout the course of the study (see 7.2).

Based upon the approved reports, Kite will submit information to regulatory agencies in accordance with any agreements/commitments.

10.1.3. Final Report

Following the final data analysis, Kite and EBMT will cooperate to prepare, review and approve an appropriate final report, which will be submitted to the Regulatory authorities as applicable by Kite as the study sponsor.

10.1.4. Publications, Conference Abstracts, and Manuscripts

All proposed publications and conference presentations arising from the study will be reviewed by Kite and EBMT representatives prior to submission. Both EBMT and Kite will share responsibilities in the development of the statistical analysis plan, data analysis, and abstracts and manuscripts. The EBMT investigators and Kite staff may share authorship. The study contract between EBMT and Kite will outline the requirements for publication.

Kite shall communicate to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript within two weeks after first acceptance for publication.

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12. APPENDICES

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	None		

Appendix 2. ENCePP Checklist for Study Protocols

Study title:
LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND PRIMARY MEDIASTINAL B-CELL LYMPHOMA

EU PAS Register® number: EUPAS32539 **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	4, 9
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.6
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	4, 9

4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	4, 9
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	4, 9
	4.2.5 Duration of follow-up	☒	☐	☐	4, 9
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	4, 9

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4, 8, 9
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4, 9
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	4, 9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	4, 9

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4, 9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4, 9
9.1.3 Covariates and other characteristics?	☒	☐	☐	4, 9
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4, 9
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4, 9
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	4, 9
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	4, 9
10.3 Are descriptive analyses included?	☒	☐	☐	4, 9
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	9
12.1.3 Residual/unmeasured confounding?	☐	☒	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Meng Wang

Date: dd/Month/year

Signature: _____

Appendix 3. Reference Safety Information

Current version of the EU SmPC for YESCARTA®.

Appendix 4. Kite Signature Page

KITE PHARMA INC.

LONG-TERM, NON-INTERVENTIONAL STUDY OF RECIPIENTS OF YESCARTA FOR TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA, PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA AND FOLLICULAR LYMPHOMA

ORIGINAL, 07 FEBRUARY 2019
VERSION 1.1, 03 JULY 2019
VERSION 1.2, 09 OCTOBER 2019
VERSION 1.3, 06 NOVEMBER 2019
VERSION 2.0, 01 JULY 2021
VERSION 2.1, 03 AUGUST 2022

This protocol has been approved by Kite Pharma Inc. The following signatures document this approval.

Meng Wang

Kite Study Director (Printed)
Author

Signature

Date

Dr. Anne-Ruth van Troostenburg de Bruyn

Kite Gilead EU QPPV (Printed)

Signature

Date

Appendix 5. Cellular and Gene Therapy Form

EBMT Cellular and Gene Therapy Form provided for entries in the EBMT Registry at the time point of this protocol version. During the course of the study updated versions of this form will be provided as appendices of annual reports (see Section 10.1.2).

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)
Protocol Number:	KTE-C19-101 (ZUMA-1)
Indication:	Relapsed/Refractory Large B-Cell Lymphoma
Kite Investigational Product	KTE-C19
Kite IND Number:	016278
EudraCT Number:	2015-005007-86
Clinical Trials.gov Identifier:	NCT02348216
Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Contact Information:	The medical monitor name and contact information is provided on the Key Study Team Contact List
Protocol Version/Date:	Original: 26 November 2014 Amendment 10.0: 14 June 2022

SPONSOR AND INVESTIGATOR SIGNATURE PAGE

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGMENT

A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)

Amendment 10.0, 14 June 2022

This protocol has been approved by Kite Pharma, Inc. The following signature documents this approval.

Jenny Kim
Kite Medical Monitor Name (Printed)

DocuSigned by: Jenny Kim
Signed By: Jenny Kim
Signing Reason: I approve this document
Signing Time: 2022-06-22 18:21:37Z (UTC)
GILEAD
O: Gilead Sciences Inc., OU: Gilead Sciences Inc.
L: Foster City, C: US
Issuer: Symantec Individual Document Signing RSA CA
A848F85FCFB4437D8DC26EC07C0B6B47
Signature

June 22, 2022 | 11:21:42 AM PDT
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner, and dependent children)
- Sub-investigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma, Inc.

Principal Investigator Name (Printed) | Signature

Date | Study Site Number

PROTOCOL SYNOPSIS

Title	A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1).
Indication	The indication is for the treatment of adult subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), transformed follicular lymphoma (TFL), and high grade B-cell lymphoma (HGBCL) after two or more lines of systemic therapy.
Study Design	Study KTE-C19-101 is a Phase 1/2 multicenter, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with relapsed or refractory aggressive non-Hodgkin lymphoma (NHL). The trial will be separated into 3 distinct phases designated as the Phase 1 study, Phase 2 pivotal study (Cohort 1 and Cohort 2), and Phase 2 safety management study (Cohort 3, Cohort 4, Cohort 5, and Cohort 6). Phase 1 Study During Phase 1 study, approximately 6 to 24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 pivotal study as depicted in Figure 3 and outlined in Section 9.10. Phase 2 Pivotal Study In the Phase 2 pivotal study, approximately 92 subjects will enroll into 2 separate cohorts designated as Cohort 1 and Cohort 2: • Cohort 1 will enroll approximately 72 adult subjects with refractory DLBCL. • Cohort 2 will enroll approximately 20 adult subjects with refractory PMBCL and TFL. TFL is defined as subjects who received prior therapy for follicular lymphoma. Phase 2 Safety Management Study In the Phase 2 safety management study (SMS), approximately 170 subjects will enroll into 4 separate cohorts designated as Cohort 3, Cohort 4, Cohort 5, and Cohort 6. • Cohort 3 will enroll approximately 40 adult subjects with relapsed or refractory transplant ineligible DLBCL, PMBCL, or TFL.

	• Cohort 4 will enroll and dose approximately 40 adult subjects with relapsed or refractory DLBCL, PMBCL, TFL or HGBCL after **2** or more lines of systemic therapy. • Cohort 5 will enroll and dose approximately 50 adult subjects with relapsed or refractory DLBCL, PMBCL, TFL or HGBCL after 2 or more lines of systemic therapy. • Cohort 6 will enroll and dose approximately 40 adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 or more lines of systemic therapy. NOTE: Cohort 6 is not open for enrollment in Germany Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods: • Screening • Enrollment/Leukapheresis period • Bridging therapy (if applicable; safety management study only) or debulking therapy (if applicable, safety management study, Cohort 5 only) • Conditioning chemotherapy period • Investigational product (IP) treatment period • Post-treatment assessment period • Long-term follow-up period For study requirements assigned to each study period, refer to Section 7 for details. At the end of KTE-C19-101, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in a separate long-term Follow-up (LTFU) study, KT-US-982-5968.
Study Objectives	<u>Phase 1 Study</u> The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel regimens. <u>Phase 2 Pivotal Study</u> The primary objective of the Phase 2 pivotal study is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR) in subjects with DLBCL, PMBCL, and TFL. Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints.

	Phase 2 Safety Management Study The primary objective of the Phase 2 safety management study is to assess the impact of prophylactic regimens, earlier interventions, tumor debulking, and prophylactic steroid use on the rate and severity of cytokine release syndrome (CRS) and neurologic toxicity. Secondary objectives will include assessment of efficacy, levels of anti-CD19 chimeric antigen receptor (CAR) T cells, cytokines in blood/serum, and the change in European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6.
Study Hypothesis and Endpoints	Phase 1 Study Primary Endpoint • Incidence of adverse events defined as dose-limiting toxicities (DLT) Secondary Endpoints • Objective response rate (complete response [CR] + partial response [PR]) per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma • Duration of response (DOR) • Overall survival (OS) • Progression-free survival (PFS) • Incidence of adverse events and clinical significant changes in safety lab values • Incidence of adverse events and clinical significant changes in safety lab values • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines in serum • Incidence of anti-axicabtagene ciloleucel antibodies Exploratory Endpoints • Objective response rate (CR + PR) per revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} and duration of second response among subjects retreated with axicabtagene ciloleucel {Cheson 2007} • Objective response rate and DOR as determined by IWG Response Criteria for Malignant Lymphoma

	• Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product Phase 2 Pivotal Study This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the objective response rate to axicabtagene ciloleucel in Cohort 1 and Cohort 2 is significantly greater than 20%. Primary Endpoint • Objective response rate (CR + PR) per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by study investigators. Secondary Endpoints • Objective response rate per Independent Radiology Review Committee (IRRC) • DOR • PFS • OS • Incidence of adverse events and clinical significant changes in safety lab values • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines in serum Incidence of anti-axicabtagene ciloleucel antibodies Exploratory Endpoint(s) for Phase 2 Pivotal Study • Objective response rate (CR + PR) per revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} and duration of second response among subjects retreated with axicabtagene ciloleucel • Objective response rate and DOR as determined by IWG Response Criteria for Malignant Lymphoma {Cheson 2014} • Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product Phase 2 Safety Management Study

	No hypothesis will be tested in Cohort 3, Cohort 4**,** Cohort 5, and Cohort 6. NOTE: Cohort 6 is not open for enrollment in Germany. Primary Endpoint • Incidence and severity of CRS and neurologic toxicities. Secondary Endpoints • Objective response rate (complete response [CR] + partial response [PR]) per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by study investigators. • DOR • PFS • OS • Incidence of adverse events and clinically significant changes in safety lab values • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines in blood • Incidence of anti-axicabtagene ciloleucel antibodies • Changes over time in the EQ-5D scale score and visual analogue scale (VAS) score (Phase 2 SMS only) Exploratory Endpoints • Biomarkers based on assessment of blood cells, tumor cells, and the proposed actions of the investigational product
Sample Size	Approximately 268 to 286 subjects Phase 1 Study: approximately 6 to 24 subjects Phase 2 Pivotal Study: approximately 92 subjects enrolled into 2 cohorts • Cohort 1: approximately 72 subjects • Cohort 2: approximately 20 subjects Phase 2 Safety Management Study: approximately 170 subjects enrolled and dosed within 4 cohorts • Cohort 3: approximately 40 subjects • Cohort 4: approximately 40 subjects • Cohort 5: approximately 50 subjects

	• Cohort 6: approximately 40 subjects NOTE: Cohort 6 is not open for enrollment in Germany.

Study Eligibility	Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both phases of the study.
Treatment	Investigational Product: • Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells will be administered. Under circumstances where subjects initially respond and subsequently relapse, subjects may be eligible for a second course of conditioning chemotherapy and axicabtagene ciloleucel. Refer to Section 6 for treatment and Section 7.13.10 for retreatment details. Bridging Therapy (Phase 2 Safety Management Study) • At the discretion of the investigator, bridging therapy may be considered for subjects particularly with high disease burden at screening or baseline assessment (eg, bulky disease or rapidly progressing disease). • For subjects receiving bridging therapy, refer to Section 6 for bridging therapy details. Debulking Therapy (Phase 2 Safety Management Study, Cohort 5) • Debulking therapy should be applied to all subjects enrolled in Cohort 5 with the aim of reducing lymphoma burden. Debulking therapy is to be administered after leukapheresis and prior to administration of conditioning chemotherapy or axicabtagene ciloleucel. • Refer to Section 6.2.2 for debulking therapy details Conditioning Chemotherapy • Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details. Additional axicabtagene ciloleucel regimens may be explored in Phase 1 per Section 9.10. <u>Phase 2 Safety Management Study</u> • Subjects assigned to Cohort 3 will receive the same conditioning chemotherapy and axicabtagene ciloleucel regimen as described above and will also receive prophylactic tocilizumab and levetiracetam for toxicity management as outlined in Section 6.3.4 and Section 6.4.

	• Subjects assigned to Cohort 4 will receive the same conditioning chemotherapy and axicabtagene ciloleucel regimen as described above, but toxicity management will intervene at lower grades of CRS and neurologic toxicities as outlined in Section 6.4.1. • Subjects assigned to Cohort 5 will receive the same conditioning chemotherapy and axicabtagene ciloleucel regimen as other safety management cohorts; toxicity management will be completed as outlined in Section 6.4.2. • Subjects assigned to Cohort 6 will receive the same conditioning chemotherapy and axicabtagene ciloleucel regimen as described above and will receive prophylactic steroids; toxicity management will intervene at lower grades of CRS and neurologic toxicities as outlined in Section 6.4.1. NOTE: Cohort 6 is not open for enrollment in Germany.
Procedures	At specific time points as outlined in the schedule of assessments, subjects will undergo the following assessments/procedures: collection of informed consent, general medical history including previous treatments for NHL, physical exam including vital signs and performance status, neurologic assessments, blood draws for complete blood count (CBC), chemistry panels, cytokines, C-reactive protein, lymphocyte subsets, anti-axicabtagene ciloleucel antibodies, replication-competent retrovirus (RCR) and anti-CD19 CAR T cell analysis. Women of childbearing potential will undergo a urine or serum pregnancy test. Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), brain magnetic resonance image (MRI), a positron emission tomography–computed tomography (PET-CT), possible bone marrow aspirate/biopsy and leukapheresis. Subjects assigned to Cohort 3, Cohort 4, Cohort 5, and Cohort 6 will complete the EQ-5D questionnaire at baseline and after axicabtagene ciloleucel (see Section 7.4 and schedule of assessments [SOA]) infusion and will have lumbar punctures performed for the collection of cerebrospinal fluid **(**CSF**)** (see Section 7.9 and SOA) before and after axicabtagene ciloleucel infusion. Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events and will have their disease assessed. NOTE: Cohort 6 is not open for enrollment in Germany.

Safety Review Team and Data Safety Monitoring Board	An SRT, that is internal to the study sponsor and in collaboration with at least one study investigator, will review safety data in Phase 1 of the study. The SRT will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 3 and outlined in Section 9.10. Phase 2 Pivotal Study: An independent Data Safety Monitoring Board (DSMB) will meet when 20 and 50 subjects in the modified intent-to-treat (mITT) set of Cohort 1 have had the opportunity to complete their 3 month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. Phase 2 Safety Management Study: The DSMB will meet to review Cohort 3, Cohort 4, Cohort 5, and Cohort 6 safety data when 20 subjects in each cohort have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days. The DSMB may meet more often as needed. Refer to Section 9.11 and Section 9.12. NOTE: Cohort 6 is not open for enrollment in Germany.
Statistical Considerations	Phase 1 Study The primary endpoint for the Phase 1 study is the incidence of DLT. Phase 2 Pivotal Study The primary endpoint for the Phase 2 pivotal study (Cohort 1 and Cohort 2) of the study is objective response rate per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by the study investigators. This endpoint will be based on a modified intent-to-treat (mITT) population consisting of all subjects enrolled and treated with axicabtagene ciloleucel at a dose of at least 1×10^6 anti-CD19 CAR T cells/kg. This study uses a single-arm design to test for an improvement in response rate in the DLBCL cohort (n = 72) and in Cohorts 1 and 2 combined (n = 92). For the test of efficacy this study has $\geq$ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha level of 0.025.

	The overall 1-sided alpha level of 0.025 will be divided between the inference in Cohort 1 and the inference in Cohorts 1 and 2 combined using the methodology described in Song et al and Wang et al {Moye 2001, Song 2007, Wang 2007}. The objective response for Cohort 1 will be tested at a 1-sided alpha level of 0.0220 and the objective response rate in Cohort 1 and 2 combined will be tested at a 1-sided alpha level of 0.0075. Within Cohort 1, two interim and one primary analyses will be performed. • Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will be for futility only. • Interim analysis 2 will be conducted after 50 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will assess early demonstration of efficacy. • The primary analysis of Cohort 1 will occur after 72 subjects in the mITT set have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion. Accrual to the study will continue during interim analysis 1 and interim analysis 2 of Cohort 1. For Cohort 1 and Cohort 2 combined, 1 primary analysis will be performed when 72 subjects in the mITT set in Cohort 1 and 20 subjects in the mITT set in Cohort 2 have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion. <u>Phase 2 Safety Management Study</u> The primary objective of Cohort 3 is to assess the impact of prophylactic regimens on the rate and severity of CRS and neurologic toxicities. The primary objective of Cohort 4 is to assess the impact of earlier interventions on the incidence and severity of CRS and neurologic toxicities. The primary objective of Cohort 5 is to assess the impact of debulking therapy on the incidence and severity of CRS and neurologic toxicities. The primary objective of Cohort 6 is to assess the impact of prophylactic steroid use and earlier interventions on the incidence and severity of CRS and neurologic toxicities.

	The secondary objectives of Cohort 3, Cohort 4, Cohort 5, and Cohort 6 include assessment of efficacy endpoints (ORR, DOR, PFS, OS) and levels of anti-CD19 CAR T cells and cytokines in the blood. Analyses of the safety and efficacy endpoints of this portion of the study will be entirely descriptive, with no formal statistical testing being performed. NOTE: Cohort 6 is not open for enrollment in Germany.

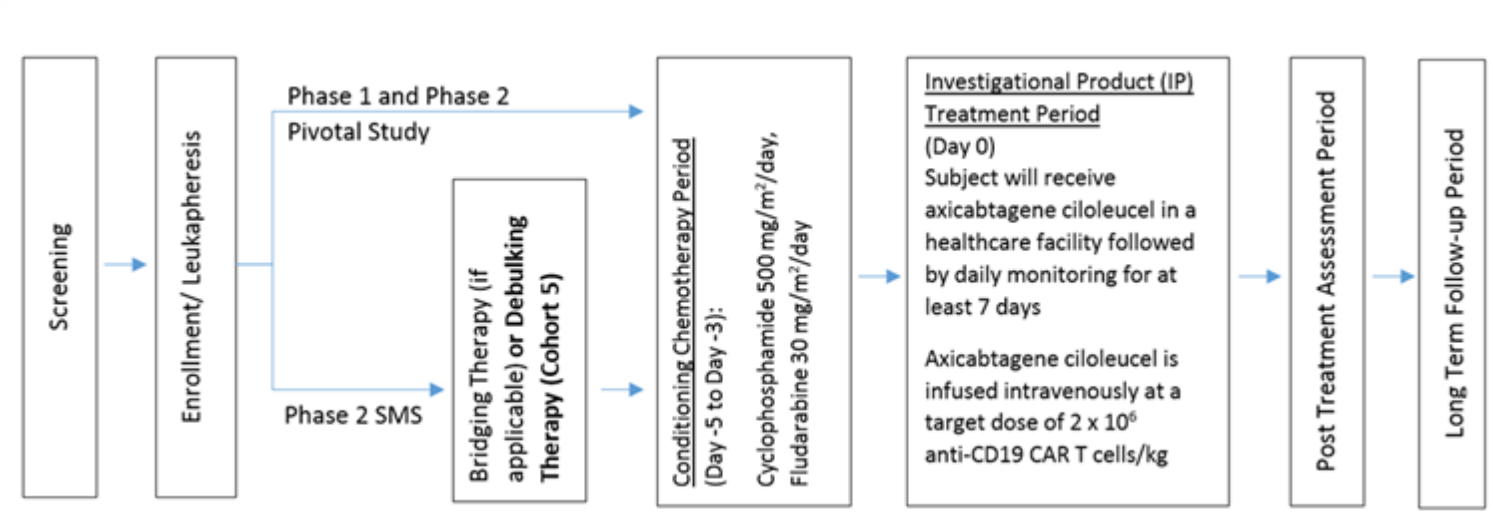
STUDY GLOSSARY

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the curve
BBB	Blood brain barrier
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CPF	Cell processing facility
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
DSMB	Data Safety Monitoring Board
eACT™	Engineered autologous cell therapy
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life-5 Dimensions
FAS	Full analysis set
FL	Follicular lymphoma
GCP	Good Clinical Practice
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
HGBCL	High grade B-cell lymphoma
HIV	Human immunodeficiency virus

Abbreviation or Term	Definition/Explanation
HLH	Hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
ID	Identification
IP	Investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRRC	Independent Radiological Review Committee
IV	Intravenous
IWG	International Working Group
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
mITT	Modified intent-to-treat
MMSE	Mini-Mental Status Exam
MRI	Magnetic resonance imaging
MSGV1	Murine stem cell virus-based vector
NaCl	Sodium chloride
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
RCR	Replication-competent retrovirus
qPCR	Quantitative polymerase chain reaction
SAE	Serious adverse event
scFv	Single-chain variable fragment
SD	Stable disease
SMS	Safety management study
SOA	Schedule of assessment
SPD	Sum of the product of diameters
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation or Term	Definition/Explanation
Study Day 0	Defined as the first day that axicabtagene ciloleucel is administered to the subject
TFL	Transformed follicular lymphoma
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cell

Figure 1. Study Schema (Phase 1 and Phase 2)



Notes: Study KTE-C19-101 is a Phase 1-2 single-arm, open-label, multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory DLBCL, PMBCL and TFL.

During Phase 1, approximately 6-24 subjects with DLBCL, PMBCL or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 3 and outlined in Section 9.10.

Upon SRT recommendation, the pivotal Phase 2 will commence and enroll subjects into 2 separate cohorts designated as Cohort 1 and Cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL.
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL. Refer to entrance criteria for TFL eligibility requirements.

Upon completion of enrollment of the Phase 2 pivotal study, the Phase 2 Safety Management Study will commence and enroll subjects into **4** separate cohorts designated as Cohort 3, Cohort 4, Cohort 5, and Cohort 6.

- Cohort 3 will enroll adult subjects with relapsed or refractory transplant ineligible DLBCL, PMBCL, and TFL.
- Cohort 4 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL and HGBCL after 2 systemic lines of therapy.
- Cohort 5 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.
- Cohort 6 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.

Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will follow through the following study periods: a screening period, an enrollment/leukapheresis period, a conditioning chemotherapy period, an IP treatment period, a post treatment assessment period and a long-term follow-up period.

Cohort 6 is not open for enrollment in Germany.

After the end of KTE-C19-101, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in a separate long-term follow-up study, KT-US-982-5968.

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1. OBJECTIVES

The primary objective of Phase 1 study is to evaluate the safety of axicabtagene ciloleucel regimens.

The primary objective of Phase 2 pivotal study is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR) in subjects with diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints.

The primary objective of the Phase 2 safety management study is to assess the impact of a prophylactic regimen, earlier interventions, debulking therapy**,** or prophylactic steroid use on the rate and severity of cytokine release syndrome (CRS) and neurologic toxicities. The key secondary objectives include assessment of efficacy, levels of anti-CD19 chimeric antigen receptor (CAR) T cells, cytokines in blood/serum, and the change in European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6.

2. DISEASE BACKGROUND AND RATIONALE

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes or natural killer cells. In the United States, B cell lymphomas represent 80-85% of cases reported. In 2013, approximately 69,740 new cases of NHL and over 19,000 deaths related to the disease were estimated to occur. Non-Hodgkin lymphoma is the most prevalent hematological malignancy and is the seventh leading site of new cancers among men and women and account for 4% of all new cancer cases and 3% of deaths related to cancer {Howlader 2017}. Large B-cell lymphomas represent the most common sub-group of NHL {Rodriguez-Abreu 2007}.

2.1. Diffuse Large B-cell Lymphoma

DLBCL is the most common subtype of large B-cell lymphoma, accounting for approximately 30% of NHL cases. There are approximately 22,000 new diagnoses of DLBCL in the United States each year. In the past two decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of CHOP and immunotherapy. The addition of rituximab into combination therapies for DLBCL have greatly improved patient outcomes. However, patients with chemotherapy-refractory DLBCL following treatment under the current standards of care still have a particularly dire prognosis, with no curative treatment options {Flowers 2010}.

The population with the highest unmet need continues to consist of patients who do not respond to first line combination chemotherapy (typically R-CHOP) or who do not respond to their last course of combination chemotherapy, as the disease is mostly insensitive to subsequent combination chemotherapy (typically R-ICE, R-ESHAP) (Table 1). In a review of 64 patients with DLBCL with disease progression during first line chemotherapy or only transient response (≤90 days) after end of induction treatment, the response rate to second line therapy was 15% and the median overall survival (OS) was 6 months, and no patient survived more than 26 months after first diagnosis {Josting 2000}. An analysis of outcome in 1126 patients with DLBCL after first line R-CHOP included 33 patients with primary refractory DLBCL who received second line therapy with curative intent. Only 3 (9%) patients were able to receive autologous stem cell transplantation (ASCT), and only 1 (3%) patient achieved long-term survival {Hitz 2010}. Seshadri et al analyzed 120 patients who did not respond to second line platinum-based chemotherapy regimens (e.g., R-ICE) and showed that only 14% responded to their third line therapy {Seshadri 2008}. Ardeshna et al followed 19 patients with large B-cell lymphoma, and 9 patients with TFL who did not respond to second line chemotherapy. Only 5 of the 28 total patients (18%) responded to third line chemotherapy {Ardeshna 2005}.

Table 1. Historical Responses in Refractory NHL (SD or PD to Last Line of Therapy)

Setting	Outcome to Subsequent Therapy
Refractory to 1st line	
{Philip 1995}	ORR 21%
{Josting 2000}	ORR 15%, median OS 6 mos
{Ardeshna 2005}	ORR 0%
{Hitz 2010}	Proceeded to ASCT 9%, 3% survived > 1 year
{Telio 2012}	ORR 23%, median OS 10 mos
{Matasar 2013}	ORR 10%
Refractory to 2nd line	
{Moskowitz 1999}	Median OS 5 mos
{Ardeshna 2005}	ORR 18%, median OS (large B-cell lympohoma) <6 mos
{Seshadri 2008}	ORR 14%
Relapsed After ASCT	
{Nagle 2013}	Median OS 8 mos

Abbreviations: ASCT, autologous stem cell transplant; mos, months; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; SD, stable disease.

These consistently discouraging results demonstrate that new treatment options are urgently needed for patients whose tumors have demonstrated a lack of response to chemotherapy.

This trial will enroll patients with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

2.2. Primary Mediastinal B-cell Lymphoma and Transformed Follicular Lymphoma

PMBCL has distinct clinical, pathological, and molecular characteristics compared to DLBCL. PMBCL is thought to arise from thymic (medullary) B cells and represents approximately 3% of patients diagnosed with large B-cell lymphoma. PMBCL is typically identified in the younger adult population in the fourth decade of life with a slight female predominance {Savage 2006, Sehn 1998}. Gene expression profiling suggests deregulated pathways in PMBCL overlap with Hodgkin lymphoma. Initial therapy of PMBCL generally includes anthracycline-containing regimens with rituximab with or without involved field radiotherapy. A recent Phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) demonstrated radiotherapy may not be required {Dunleavy 2013}.

Follicular lymphoma (FL), a B cell lymphoma, is the most common indolent (slow-growing) form of NHL, accounting for approximately 20% to 30% of all NHLs. Some patients with FL will transform (TFL) histologically to DLBCL which is more aggressive and associated with a poor outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years with the risk of transformation continuing to drop in subsequent years. The biologic mechanism of histologic transformation is unknown. Initial treatment of TFL is influenced by prior therapies for follicular lymphoma but generally includes anthracycline-containing regimens with rituximab to eliminate the aggressive component of the disease {National Comprehensive Cancer Network 2014}.

Treatment options for relapsed/refractory PMBCL and TFL are similar to those in DLBCL. Given the low prevalence of these diseases, no large prospective randomized studies in these patient populations have been conducted. Patients with chemotherapy refractory disease have a similar or worse prognosis {Kuruvilla 2008} to those with refractory DLBCL.

In addition, the international, multicohort retrospective non-Hodgkin lymphoma research (SCHOLAR-1) study retrospectively evaluated outcomes in patients with chemorefractory DLBCL, PMBCL, and TFL. SCHOLAR-1 integrated data from two Phase 3 studies (LYSARC-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and Mayo Clinic/University of Iowa Specialized Program of Research Excellence). Among 861 patients, 635 were included based on chemorefractory search criteria. Outcomes were consistently poor, regardless of refractory subgroup and across cohorts. The results of SCHOLAR-1 indicated that patients with chemorefractory, aggressive DLBCL represent a homogenous patient population with a response rate of 26% (complete response [CR] rate of 7%) and median overall survival of 6.3 months {Crump 2017}.

2.3. High Grade B-cell Lymphoma

In 2016, the World Health Organization introduced a new category of large B-cell lymphomas called high-grade B-cell lymphoma (HGBCL) {Swerdlow 2016}. This designation includes large B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements that are phenotypically intermediate to DLBCL or B-cell lymphoma, unclassifiable (this latter category has since been eliminated). MYC rearrangements in large B-cell lymphomas are associated with a poor prognosis that is worsened in cases of concomitant BCL2 and/or BCL6 alterations, ie, double- or triple-hit lymphomas. As such, patients with HGBCL are likely to face poor survival outcomes.

In summary, axicabtagene ciloleucel may provide a viable treatment option to relapsed/refractory large B-cell lymphoma patients with no other curative alternatives.

2.4. Study Rationale

As most advanced cancers eventually become refractory to conventional therapies, new treatment modalities are needed. Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and tumor infiltrating lymphocytes have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumor,

be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. Engineered T cells are a promising approach for cancer therapy {Kershaw 2013}.

Engineered **a**utologous **c**ell **t**herapy (eACT™) is a process by which a patient's own T cells are collected and subsequently genetically altered to recognize and target antigens expressed on the cell surface of specific malignancies {Kochenderfer 2013}. The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies and has opened possibilities for the treatment of patients with a wide variety of cancer types including B cell malignancies expressing the CD19 antigen.

2.4.1. CD19 and Expression

CD19 is a 95 kDa transmembrane protein expressed only in the B cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B cell malignancies including all subtypes of B cell NHL, chronic lymphocytic leukemia (CLL), and non-T-cell acute lymphoblastic leukemia (ALL) {Blanc 2011} with the exception of multiple myeloma.

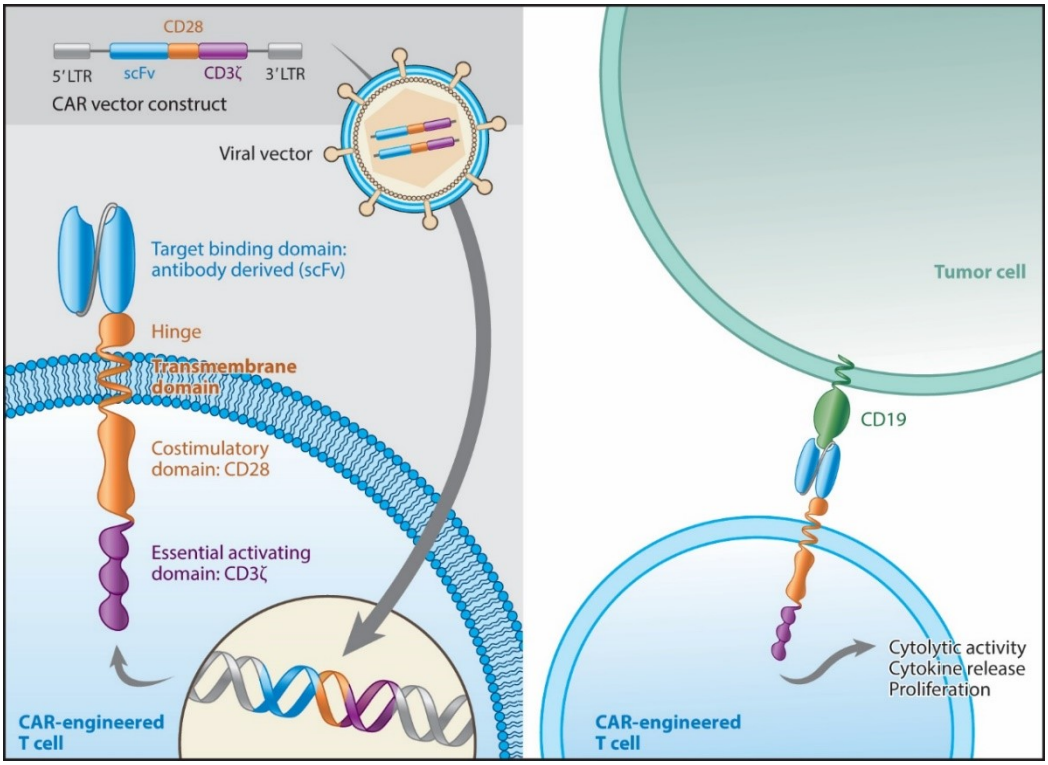
2.4.2. Anti-CD19 CAR T-cell Product

Anti-CD19 CAR T cells are autologous human T cells that have been engineered to express an extracellular single-chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem.

An anti-CD19 CAR vector construct has been designed, optimized and initially tested at the Surgery Branch of the National Cancer Institute (NCI, IND 13871) (Figure 2) {Kochenderfer 2009, Kochenderfer 2010}. The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 {Nicholson 1997}. A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and persistence of anti-CD19 CAR T cells {Kowolik 2006}. The signaling domain of the CD3-zeta chain is essential for T cell activation. These fragments were cloned into the murine stem cell virus-based (MSGV1) vector, utilized to genetically engineer the autologous T cells. Treatment with anti-CD19 CAR T cells is currently being administered to subjects with CD19+ B cell malignancies in ongoing NCI protocol (09-C-0082; IND 13871). The same CAR vector construct will be used in this study.

The CAR construct is inserted into the T cells' genome by retroviral vector transduction. Briefly, peripheral blood mononuclear cells (PBMCs) are obtained by leukapheresis and Ficoll separation. Peripheral blood mononuclear cells are activated by culturing with an anti-CD3 antibody in the presence of recombinant interleukin 2 (IL-2). Stimulated cells are transduced with a retroviral vector containing an anti-CD19 CAR gene and propagated in culture to generate sufficient engineered T cells for administration.

Figure 2. Axicabtagene Ciloleucel



2.4.3. Prior Experience with Axicabtagene Ciloleucel and other Anti-CD19 CAR T Cells

Refer to the current axicabtagene ciloleucel Investigator's Brochure (IB) for the most current anti-CD19 CAR T-cell study results.

2.4.4. Axicabtagene Ciloleucel

Kite Pharma, Inc., (hereafter referred to as Kite Pharma or Kite) is developing an eACT™ (axicabtagene ciloleucel) that targets CD19 expression on B cell malignancies. The CAR vector construct is identical to the one used in NCI protocols (Surgery Branch protocol 09-C-0082; IND 13871; Pediatric Branch protocol 12-C-0112G; IND 14985). Kite Pharma in conjunction with the NCI Surgery Branch has developed a rapid, closed, and bead-less process for the generation of the anti-CD19 CAR T cells. Closing the process retains the characteristics of the T cell product {Better 2014}. See the investigational product manual for more details.

3. STUDY DESIGN

3.1. General Study Design

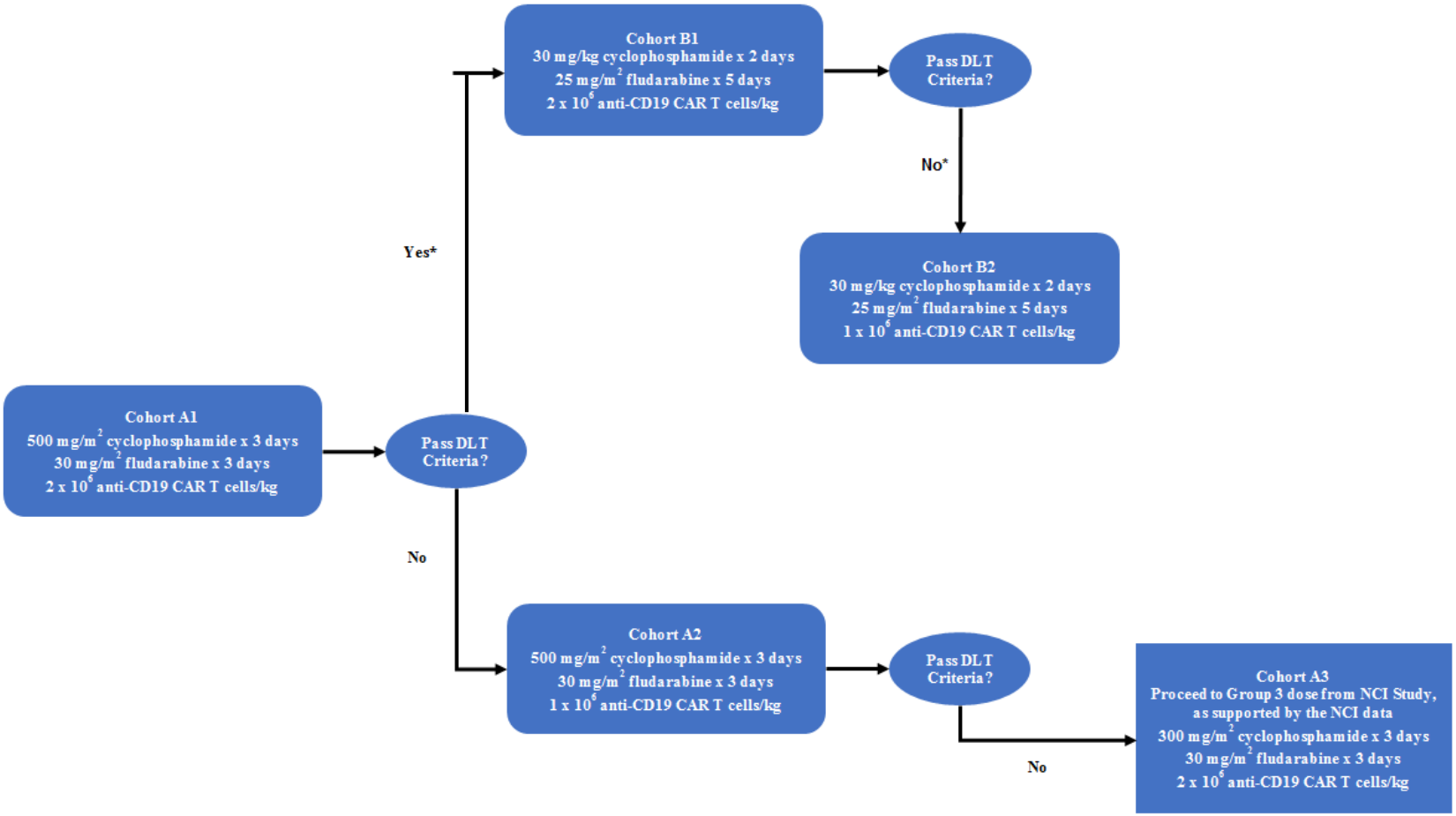
Study KTE-C19-101 is a Phase 1-2 multicenter, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with refractory NHL. Study KTE-C19-101 will be separated into 3 distinct phases designated as Phase 1 study, Phase 2 pivotal study (Cohort 1 and Cohort 2), and Phase 2 safety management study (Cohort 3,Cohort 4, Cohort 5, and Cohort 6).

NOTE: Cohort 6 is not open for enrollment in Germany.

Phase 1 Study

During Phase 1, approximately 6 to 24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens. If the initial regimen is determined to be safe, a higher dose of conditioning chemotherapy may be investigated. If the regimen is determined to not be safe, reduced doses of conditioning chemotherapy and/or axicabtagene ciloleucel may be explored. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 3 and outlined in Section 9.10.

Figure 3. Phase 1 Dosing Cohorts and Regimens



*May be explored: see Section 9.6

Phase 2 Pivotal Study

In Phase 2 pivotal study, subjects will enroll into 2 separate cohorts designated as Cohort 1 and Cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL.
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL.
- TFL is defined as subjects who received prior chemotherapy for follicular lymphoma.

During the Phase 2 pivotal study, an independent data safety monitoring board (DSMB) will meet when 20 and 50 subjects in the modified intent-to-treat (mITT) set of Cohort 1 have had the opportunity to complete the 3 month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit.

Phase 2 Safety Management Study (SMS)

In the Phase 2 safety management study (SMS), subjects will enroll into 4 separate cohorts designated as Cohort 3, Cohort 4, Cohort 5, and Cohort 6.

- Cohort 3 will enroll adult subjects with relapsed or refractory transplant ineligible DLBCL, PMBCL, or TFL.
- Cohort 4 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.
- Cohort 5 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.
- Cohort 6 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.

  NOTE: Cohort 6 is not open for enrollment in Germany.

The DSMB will meet to review safety data when 20 subjects in each Cohort 3, Cohort 4, Cohort 5, and Cohort 6 have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days. The DSMB may meet more often as needed.

Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods:

- Screening period
- Enrollment/Leukapheresis period

- Bridging therapy (if applicable, for Phase 2 SMS) or debulking therapy (if applicable, Phase 2 SMS, Cohort 5)
- Conditioning chemotherapy period
- Investigational product (IP) treatment period
- Post treatment assessment period
- Long-term follow-up period

For study requirements assigned to each study period, please refer to the schedule of assessments (SOA) and Section 7 for details.

A study schema is drawn out and described at the end of the protocol synopsis section.

3.2. Participating Sites

Approximately 35 centers located in North America and Europe will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

3.3. Number of Subjects

Participants in this trial will be referred to as "subjects". It is anticipated that approximately 268 to 286 subjects will be enrolled and dosed in this study as defined below:

Phase 1 study: approximately 6 to 24 subjects

Phase 2 pivotal study: approximately 92 subjects enrolled into 2 cohorts

- Cohort 1: approximately 72 subjects
- Cohort 2: approximately 20 subjects

Phase 2 safety management study: approximately 170 subjects enrolled and dosed within 4 cohorts

- Cohort 3: approximately 40 subjects
- Cohort 4: approximately 40 subjects
- Cohort 5: approximately 50 subjects
- Cohort 6: approximately 40 subjects

It should be noted that Kite Pharma may choose to close enrollment at any time. Please refer to the statistical considerations section of the protocol for sample size estimations.

NOTE: Cohort 6 is not open for enrollment in Germany.

3.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified number of subjects are attained in the dose-limiting toxicity (DLT) evaluable (Phase 1) and mITT sets (Phase 2). Subjects who have not received the target dose of axicabtagene ciloleucel will be retained in the analyses of disposition and safety, where appropriate (Section 10.5).

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary. For a subject who completes the entire protocol from the date of informed consent through the completion of the long-term follow-up period, the duration of the study will take approximately 15 years to complete. However, individual study duration will vary depending on a subject's screening requirements, response to treatment, survival and, if applicable, timing of transition to the separate Long-term Follow-up (LTFU) study, KT-US-982-5968 (discussed in Section 3.5.3).

The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects.

3.5.2. Completion of the Study (Phase 1/Phase 2)

Completion of the study is defined as the time at which the last subject completes at least 24 months of assessments, is lost to follow-up, withdraws consent, or dies. Upon activation of KT-US-982-5968 at the subject's study site, the subject will be offered the opportunity to complete the LTFU assessments under the KT-US-982-5968 protocol.

The primary analyses will be conducted when 72 subjects in the mITT set of the Phase 2 pivotal Cohort 1 and 20 subjects in the mITT set of Cohort 2 have completed the 6 month disease response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first.

3.5.3. Long-term Follow-up

All subjects who received an infusion of axicabtagene ciloleucel will be provided the opportunity to transition to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted adverse events (AEs) and serious adverse events (SAEs) as defined in KT-US-982-5968, presence of replication-competent retrovirus (RCR), and/or insertional mutagenesis for up to 15 years from the time of axicabtagene ciloleucel infusion (also refer to Section 7.13.9).

In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

4. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved consent form before initiating any study specific procedures or activities that are not part of a subject's routine care. Refer to Section 7 for details.

Each subject who enters the screening period, which starts when the subject signs the informed consent form (ICF), will receive a unique subject identification (ID) number before any study specific procedures or activities are initiated. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened or retreated.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

1) Histologically confirmed aggressive B cell NHL, including the following types defined by WHO 2008 {Campo 2011}:

    a) DLBCL not otherwise specified; T cell/histiocyte rich large B cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly;

    or

    i) primary mediastinal (thymic) large B cell lymphoma

    ii) transformation of follicular lymphoma to DLBCL will also be included

2) Chemotherapy-refractory disease, defined as one or more of the following:

    a) No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy chemotherapy are excluded

    i) Progressive disease (PD) as best response to first-line therapy

    ii) Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy

    or

    b) No response to second or greater lines of therapy

    i) PD as best response to most recent therapy regimen

    ii) SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy

    or

    c) Refractory post-ASCT

    i) Disease progression or relapsed ≤ 12 months of ASCT (must have biopsy proven recurrence in relapsed subjects)

    ii) if salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy

3) Subjects must have received adequate prior therapy including at a minimum:

   a) anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and

   b) an anthracycline containing chemotherapy regimen;

   c) for subjects with transformed FL must have chemorefractory disease after transformation to DLBCL

4) At least 1 measurable lesion according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma {Cheson 2007}. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

5) Magnetic resonance imaging (MRI) of the brain showing no evidence of central nervous system (CNS) lymphoma

6) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).

7) Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)

8) Age 18 or older

9) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

10) Absolute neutrophil count (ANC) ≥ 1000/uL

11) Platelet count ≥ 75,000/uL

12) Absolute lymphocyte count ≥ 100/uL

13) Adequate renal, hepatic, pulmonary and cardiac function defined as:

   a) Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min

   b) Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 upper limit of normal (ULN)

   c) Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome

d) Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings

e) No clinically significant pleural effusion

f) Baseline oxygen saturation >92% on room air

14) Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

Additional criteria specific for Phase 2 safety management study **(**Cohorts 3, 4, 5 and 6):

15) Relapsed or refractory large B-cell lymphoma including DLBCL, PMBCL, TFL, and HGBCL after two systemic lines of therapy

NOTE: Cohort 6 is not open for enrollment in Germany.

5.2. Exclusion Criteria

201) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years

202) History of Richter's transformation of CLL

203) Autologous stem cell transplant with therapeutic intent within 6 weeks of planned axicabtagene ciloleucel infusion

204) History of allogeneic stem cell transplantation

205) Prior CD19 targeted therapy with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for re-treatment

206) Prior chimeric antigen receptor therapy or other genetically modified T cell therapy

207) History of severe, immediate hypersensitivity reaction attributed to aminoglycosides

208) Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management.

209) History of human immunodeficiency virus (HIV) infection or acute or chronic active hepatitis B or C infection. Subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines or applicable country guidelines.

210) 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

211) Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases

212) History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement

213) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

214) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment

215) Expected or possible requirement for urgent therapy within 6 weeks due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome)

216) Primary immunodeficiency

217) History of symptomatic deep vein thrombosis or pulmonary embolism requiring systemic anticoagulation within 6 months of enrollment

218) Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

219) History of severe immediate hypersensitivity reaction to any of the agents used in this study

220) Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen

221) Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

222) Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of conditioning chemotherapy

223) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

224) 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

6. PROTOCOL TREATMENT

6.1. Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- Bridging therapy refers to treatment used to control a subject's disease prior to conditioning chemotherapy
- Debulking therapy refers to treatment used to reduce a subject's disease prior to conditioning chemotherapy
- The conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The investigational product for this study is named axicabtagene ciloleucel.
- The term study treatment refers to all protocol required therapies.

6.2. Study Treatment

6.2.1. Bridging Therapy for Phase 2 Safety Management Study, Cohort 3 (retreatment), Cohort 4, and Cohort 6

Bridging therapy will be supplied by the investigative site unless otherwise noted. Sites should refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management of bridging therapy.

At the discretion of the investigator, bridging therapy may be considered for subjects retreated in Cohort 3 or enrolled in Cohort 4 and Cohort 6 with high disease burden at screening or baseline assessments (eg, bulky disease or rapidly progressing disease). Allowed bridging therapy regimens are outlined in Table 2. Other bridging regimens may be considered but need to be discussed with the medical monitor on a case-by-case basis.

NOTE: Cohort 6 is not open for enrollment in Germany.

Table 2. Bridging Therapy Regimens

Type	Therapy Regimens[a]	Timing and Washout Requirements
Corticosteroid	Dexamethasone at a dose of 20 mg to 40 mg or equivalent, either PO or IV daily for 1 to 4 days. Choice of corticosteroid and dose can be adjusted for age/comorbidities or per local or institutional guidelines	May be administered after apheresis/enrollment and must be completed prior to the start of conditioning chemotherapy *Note:* Chemistry panel and CBC with differential must be repeated prior to start of conditioning chemotherapy to confirm eligibility to proceed therapy.
HDMP + Rituximab {Castro 2009}	1 gram/m^2 of high dose methylprednisolone (HDMP) for 3 days in combination with rituximab at 375 mg/m^2 weekly for 3 weeks	May be administered after enrollment and completed at least 7 days prior to the start of conditioning chemotherapy *Note:* Chemistry panel and CBC with differential must be repeated prior to start of conditioning chemotherapy to confirm eligibility to proceed.
Combination Chemotherapy {Vacirca 2014} {Ohmachi 2013}	B-R: Bendamustine (90 mg/m^2, Day 1+2); Rituximab (375 mg/m^2, Day 1)	May be administered after enrollment and completed at least 14 days prior to the start of conditioning chemotherapy, and subjects must remain eligible per the eligibility criteria outlined in Section 5 prior to the start of conditioning chemotherapy *Note:* Chemistry panel and CBC with differential must be repeated prior to start of conditioning chemotherapy to confirm eligibility to proceed.

Abbreviations: IV, intravenous; CBC, complete blood count.
a The bridging therapy regimen may be chosen at the discretion of the investigator

6.2.2. Debulking Therapy for Phase 2 Safety Management Study, Cohort 5

Subjects enrolled into the Phase 2 Safety Management Study, Cohort 5 should receive debulking therapy to reduce lymphoma burden. Debulking therapy options are outlined in Table 3. Other debulking treatment options may be considered in select cases and must be discussed with the Kite medical monitor. The goal of the debulking therapy should be to optimally reduce lymphoma burden.

Table 3. Debulking Therapy Regimens

Type	Proposed Regimen[a]	Timing/Washout
R-CHOP {Feugier 2005}	Rituximab 375 mg/m2 Day 1 Doxorubicin 50 mg/m2 Day 1 Prednisone 100 mg Day 1 through Day 5 Cyclophosphamide 750 mg/m2 Day 1 Vincristine 1.4 mg/m2 Day 1	Should be administered after leukapheresis/enrollment and should be completed at least 14 days prior to the start of conditioning chemotherapy
R-ICE {Gisselbrecht 2010}	Rituximab 375 mg/m2 Day 1 Ifosfamide 5 g/m2 24h-CI Day 2 Carboplatin AUC5 Day 2 maximum dose 800 mg Etoposide 100 mg/m2 /d Days 1 through Day 3	
R-GEMOX {Mounier 2013}	Rituximab 375 mg/m2 Day 1 Gemcitabine 1000 mg/m2 Day 2 Oxaliplatin 100 mg/m2 Day 2	
R-GDP {Crump 2004} {Gopal 2010}	Rituximab 375 mg/m2 Day 1 (or Day 8) Gemcitabine 1 g/m2 on Day 1 and Day 8 Dexamethasone 40 mg on Day 1 through Day 4 Cisplatin 75 mg/m2 on Day 1 (or carboplatin AUC5 on Day 1)	
Radiotherapyb	Per local standard up to 20 to 30 Gy	Should be administered after leukapheresis/enrollment and should be completed at least 5 days prior to the start of conditioning chemotherapy

Abbreviations: AUC, area under the curve.
a Other debulking treatment options may be used, but must be discussed with the medical monitor. Supportive care with hydration, anti-emesis, mesna, growth factor support, and tumor lysis prophylaxis according to local standard may be used. More than 1 cycle allowed.
b At least 1 target lesion should remain outside of the radiation field to allow for tumor measurements

6.2.3. Conditioning Chemotherapy

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted. Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of chemotherapy agents.

6.2.3.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.2.3.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges from 3-12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

6.2.3.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient in mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$.

Mesna should be administered per institutional guidelines. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.2.4. Axicabtagene Ciloleucel

Refer to the most current IB regarding axicabtagene ciloleucel and clinical experience. This section contains general information and is not intended to provide specific instructions. Refer to the investigational product manual for details and instruction on storage and administration.

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing axicabtagene ciloleucel arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

Axicabtagene ciloleucel is a subject-specific product and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (e.g., initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of axicabtagene ciloleucel infused, the thaw start/stop time, and axicabtagene ciloleucel administration start/stop time, will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion. Refer to the Investigational Product Manual for details and instruction on storage, thawing, and administration of axicabtagene ciloleucel.

To date, subjects have received doses of anti-CD19 CAR T cells ranging from 1-30 x 10^6 anti-CD19 CAR T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of axicabtagene ciloleucel or any products that support the management of axicabtagene ciloleucel (eg, cryostorage bags, subject identification labels) required in this study are identified, please log on to www.kitepharma.com to report the complaint.

6.2.5. Concomitant Therapy

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care except those medications listed in Section 6.2.6.

All concurrent therapies, including medications, intubation, dialysis, oxygen, and blood products, will be recorded from the date of the informed consent through 3 months after completing treatment with axicabtagene ciloleucel. After 3 months of follow-up, only targeted concomitant medication will be collected for 24 months after axicabtagene ciloleucel infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

For subjects who are enrolled but not dosed with axicabtagene ciloleucel, concurrent therapies will only be recorded from the date of the informed consent through 30 days after the last study specific procedure (e.g., leukapheresis, conditioning chemotherapy). For subjects who are not enrolled (e.g., screen failure or not leukapheresed), only concurrent therapies related to any SAE(s) will be recorded.

Specific concomitant medication collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.2.6. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis, and 5 days prior to axicabtagene ciloleucel administration. For the prophylactic use of steroid for Cohort 6, refer to Section 7.13.7.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after axicabtagene ciloleucel administration, unless used to manage axicabtagene ciloleucel related toxicities (refer to the most current version of the IB). Other medications that might interfere with the evaluation of the investigational product, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

Treatment for lymphoma such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited, except as needed for treatment of disease progression after the axicabtagene ciloleucel infusion.

If permissibility of a specific medication/treatment is in question, please contact the Kite Pharma Medical Monitor.

NOTE: Cohort 6 is not open for enrollment in Germany.

6.2.7. Subsequent Therapy

Subsequent therapy administered after the axicabtagene ciloleucel infusion for a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy, will be recorded for all subjects until one of the following happens: the subject transitions to the KT-US-982-5968 LTFU study, is considered lost to follow-up, withdraws consent, or dies. For subjects who are enrolled, but do not receive axicabtagene ciloleucel infusion, any additional anti-cancer therapy will also be collected until the subject completes their participation in the current study, is considered lost to follow up, withdraws consent, or dies, whichever occurs first.

6.3. Study Treatment Schedule

6.3.1. Leukapheresis (Within Approximately 5 Days of Eligibility Confirmation)

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the cell processing facility (CPF) overnight as described in the Investigational Product Manual**.** Once a subject commences leukapheresis, the subject is considered enrolled in the study.

Mononuclear cells will be obtained by leukapheresis (12-15 liter apheresis with a goal to target approximately 5-10 x 10^9 mononuclear cells). The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the investigational product manual.

Upon arrival at the CPF, each subject's leukapheresed product will be processed to enrich for the T cells containing PBMC fraction. T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the investigational product per CPF standard operating procedures (SOPs). Once the product has passed certain release tests, it will be shipped back to the treating facility. Following completion of each subject's conditioning chemotherapy regimen, subjects will receive their respective axicabtagene ciloleucel infusion.

6.3.2. Study Treatment

6.3.2.1. Chemotherapy General Instructions

Subjects will receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel *in vivo*. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day -5 (or Day -7 for Cohort B) through Day -1. The 5-day conditioning chemotherapy regimen may be administered in an outpatient setting. The 7-day conditioning chemotherapy regimen may be administered as an outpatient or inpatient regimen per investigator's discretion.

Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy. In general, subjects should be kept well-hydrated but closely monitored to prevent fluid overload.

For subjects enrolled into the Phase 2 Safety Management Study, Cohort 5 and Cohort 6:

Subjects who have not recovered their white blood cell (WBC) count by the time conditioning chemotherapy is scheduled to start, may skip the conditioning chemotherapy if the WBC is ≤ 1000/μL at this time. This option must be discussed with the Kite medical monitor.

NOTE: Cohort 6 is not open for enrollment in Germany.

6.3.2.2. Axicabtagene Ciloleucel General Instructions

All subjects will receive axicabtagene ciloleucel infusion at a healthcare facility, followed by daily monitoring at a healthcare facility for at least 7 days unless otherwise required by country regulatory agencies (refer to Appendix 2) to monitor for signs and symptoms of CRS and neurologic toxicities. Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following axicabtagene ciloleucel infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

Alternatively, subjects may be hospitalized to receive their axicabtagene ciloleucel infusion and be observed for CRS and neurologic toxicities in the hospital setting, if deemed appropriate by the investigator.

If subjects are hospitalized, subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities resolve to ≤ Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (e.g., renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain in a hospital for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing neurologic toxicities > Grade 1, or if deemed necessary by the investigator.

The following medications should be administered approximately 1 hour prior to axicabtagene ciloleucel infusion. Alternatives to the recommendations below should be discussed with the medical monitor.

- Acetaminophen 500 to 1000 mg PO
- Diphenhydramine (12.5 to 25 mg IV or 25 mg PO)

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of axicabtagene ciloleucel. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of axicabtagene ciloleucel are outlined in the Investigational Product Manual. The Investigational Product Manual must be reviewed prior to administration of axicabtagene ciloleucel.

Research sites should follow institutional guidelines for the infusion of cell products.

6.3.3. Rationale for Study Treatment Dosing

6.3.3.1. Rationale for Conditioning Chemotherapy Dose in Phase 1 Cohort A1

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T cell expansion and function in pre-clinical models. The depth and duration of the lymphodepletion in preclinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific CD8+ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine is a potent lymphodepleting regimen. Optimizing the doses of cyclophosphamide and fludarabine to improve the depth and duration of lymphodepletion may enhance the activity of axicabtagene ciloleucel.

As described in the IB**,** the NCI study (09-C-0082; IND 13871) evaluated three groups of subjects based on conditioning regimens. Group 3 evaluated cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2), both given for 3 concurrent days followed by 1-2 x 10^6 anti-CD19 CAR T cells. Eleven subjects were treated with this regimen.

The DLT definition in the KTE-C19-101 study was applied to the NCI study (09-C-0082; IND 13871) data in group 3. There were no DLTs. The subject incidences of Grade 3, 4, 5, and serious adverse events attributed to CAR+ T-cells were 3 (27%), 0 (0%), 0 (0%), and 1 (9%). The ORR in this cohort was 60%, including 10% complete responses. Many subjects, however, did not achieve blood lymphocyte counts of zero with this conditioning regimen.

To improve the depth and duration of lymphocyte depletion, the conditioning chemotherapy dose in Phase 1 Cohort A1 will be cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days with the target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. This regimen is currently being evaluated in the NCI study (09-C-0082; IND 13871). Cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days has been studied and tolerated in subjects with B cell malignancies {O'Brien 2001}. Similar total doses of cyclophosphamide (900 to 2,000 mg/m^2) and fludarabine (90 to 150 mg/m^2) have been given as a reduced non-myeloblative conditioning regimen in subjects with B cell malignancies receiving allogeneic stem cell transplants {Khouri 1998}. The cyclophosphamide dose used in this regimen (Cohort A1 and currently in the NCI study 09-C-0082; IND 1387) is approximately 38% lower than that used in the Group 2 cyclophosphamide 30 mg/kg conditioning regimen from the NCI study (incidence of DLT 29%), with the same lower dose of fludarabine dose as Group 3. Evaluation of higher conditioning chemotherapy doses and/or varying anti-CD19 CAR T cell doses would proceed based on the incidence of DLT and evaluation of benefit-risk.

6.3.3.2. Rationale for Conditioning Chemotherapy Dose in Phase 1 Cohort B1

Fifteen subjects were treated in the NCI protocol (09-C-0082; IND 13871) in group 2. Group 2 included subjects with leukemia and lymphoma, 2 different doses of cyclophosphamide

(cumulative 60 and 120 mg/kg), and a range of CAR T cell doses (1-5 x 10^6/kg). The DLT definition in the KTE-C19-101 study was applied to the NCI study data for subjects in group 2 with B-cell lymphomas, dosed at ≤ 2.5 x 10^6 anti-CD19 CAR T cells, and 60 mg/kg cumulative dose of cyclophosphamide to reflect the KTE-C19-101 protocol. Seven subjects met these DLT criteria.

The subject incidence of DLT was 29%. Subject 1010014, with a best objective response of CR, had specific DLTs of Grade 3 renal insufficiency and hypoxia and Grade 4 hypotension and somnolence requiring intubation. Subject 1010021, with a best objective response of CR, had a specific DLT of Grade 3 motor neuropathy. All events were reversible. The subject incidence of Grade 3, 4, 5, and serious adverse events attributed to CAR T cells were 1 (14%), 2 (29%), 0 (0%), and 2 (29%). The Grade 4 events were Grade 4 hypotension, Grade 4 somnolence, and Grade 4 aphasia/dysphasia (3 events in 2 subjects) (data on file, Kite Pharma). The subject incidence ORR in this cohort was 6 (86%), including 5 (71%) complete responses of which 4 are ongoing.

The duration and depth of lymphodepletion appeared to be improved with this higher dose of cyclophosphamide conditioning chemotherapy (data on file, Kite Pharma). While the sample sizes are small, the data suggest that greater objective and complete response rates may be attained with a higher dose of conditioning chemotherapy regimen. Therefore, the regimen in Cohort B1 may be explored if the incidence of DLT in Cohort A1 is acceptable to further evaluate the impact of conditioning chemotherapy on benefit/risk.

Table 4. Incidence of DLT and Response among Subjects with B-cell Lymphomas and Dosed with Group 2 and Group 3 Conditioning Chemotherapy and ≤ 2.5 x 10^6 anti-CD19 CAR T Cells

Group	N	Incidence of DLT[a] – n(%)	ORR - n(%)	CR Rate – n(%)
Group 2 Conditioning (30 mg/kg Cy x 2 days, 25 mg/m^2 Flu x 5 days)	7	2 (29)	6 (86)	5 (71)
Group 3 conditioning (300 mg/m^2 Cy x 3 days, 30 mg/m^2 Flu x 3 days)	10[b]	0 (0)	6 (60)	1 (10)

a DLT as determined by the definition proposed in the KTE-C19-101 study
b 11 subjects treated in Group 3; 10 were followed through Day 30 at data cutoff

Table 5. DLT[a] Events among Subjects with B-cell Lymphomas and Dosed with ≤ 1-2.0 x 10^6 anti-CD19 CAR T Cells and Cyclosphosphamide 30 mg/kg x 2 Days-Fludarabine 25 mg/m^2 x 5 Days

Subject	Event
1010014	Grade 3 renal insufficiency, duration 9 days Grade 4 hypotension, duration 3 days Grade 3 hypoxia, duration 18 days Grade 4 somnolence, duration 10 days, intubation required
1010021	Grade 3 motor neuropathy, duration 18 days

a DLT as determined by the definition proposed in the KTE-C19-101 study

6.3.3.3. Rationale for Patient Population to be Included in Phase 2 Pivotal Study Cohort 1 and Cohort 2

In the multicenter randomized Phase 3 CORAL study where subjects were randomized to R-ICE or R-DHAP second-line therapy followed by ASCT with or without rituximab maintenance, 203 subjects across both arms did not proceed with ASCT. These subjects were ineligible for ASCT for multiple reasons including chemorefractory disease, early relapsed disease, residual masses after salvage therapy and intolerance to therapy. The median overall survival of these 203 ASCT ineligible subjects after salvage chemotherapy was only 4.4 months {Van Den Neste 2016}. Therefore, the efficacy of axicabtagene ciloleucel will be estimated in this population which represents a significant unmet need for more effective therapies.

6.3.3.4. Rationale for Including Phase 2 Safety Management Study Cohort 3, Cohort 4, Cohort 5, and Cohort 6

6.3.3.4.1. Cohort 3

CRS and neurologic toxicities are two identified risks associated with axicabtagene ciloleucel. Both CRS and neurologic toxicities have led to Grade 4 or Grade 5 events in the context of anti-CD19 CAR T cells {Schuster 2015, Turtle 2016}. The pathophysiology of CRS is well described, but the etiology of the neurologic toxicities remains unclear. Currently it is hypothesized that there are two potential mechanisms of the pathophysiology of neurologic toxicities: 1) peripheral systemic cytokine release followed by cytokine diffusion across the blood brain barrier (BBB) and/or 2) peripherally activated anti-CD19 CAR T cells translocate across the BBB and elicits a local inflammatory effect. The later hypothesis is supported by emerging evidence of CAR T-cells trafficking to the CSF. To further elucidate the pathophysiology of neurologic toxicities, serial CSF collections will be analyzed in this study for cytokines/chemokines/effector molecules and anti-CD19 CAR T cells. In addition, in an attempt to mitigate the onset and severity of CRS and neurologic toxicities, prophylactic tocilizumab and levetiracetam will be administered in Cohort 3 (see Section 6.3.4). It is hypothesized that tocilizumab may lead to fewer activated CAR T-cells trafficking to the CNS and levetiracetam may reduce the risk of clinical or subclinical seizures. Lastly, in an effort to mitigate the severity and/or duration of the neurologic toxicities, IT-Ara C with corticosteroids is recommended to be administered at the onset of Grade 3 neurologic toxicities (see Section 6.4.1).

6.3.3.4.2. Cohort 4 and Cohort 6

In the Phase 2 pivotal study portion of ZUMA-1 (n = 101), CAR T-cell levels were associated with response (P = 0.0002), with a 5.4-fold higher area under the curve (AUC) within the first 28 days post-treatment for responders versus non-responders. However, CAR T-cell levels and specific cytokines, including IL-2, GM-CSF, and ferritin, were only associated with Grade 3 or higher neurologic toxicity suggesting that distinct mechanisms may underlie the pathogenesis of these adverse events, as shown in Figure 4 and {Locke 2017}. While there is a theoretical concern for the use of immunosuppressive agents to manage CRS or neurologic toxicities, tocilizumab and/or corticosteroids usage did not appear to affect negatively the overall response in ZUMA-1 and CAR T-cell levels (Table 6). Prophylactic tocilizumab use in Cohort 3 appeared to lower the rate of Grade 3 or higher CRS but not neurologic toxicities (Table 7). To further

refine the use of corticosteroids to treat CRS and neurologic toxicities, Cohort 4 and Cohort 6 will recommend corticosteroids at lower toxicity grades to determine the impact on incidence and severity of CRS and neurologic toxicities (Section 6.4.1). Cohort 6 will further build on this rationale by initiating corticosteroids as prophylactic treatment on Day 0, Day 1, and Day 2. Prophylactic tocilizumab will not be used in Cohort 4, Cohort 5, or Cohort 6 (Section 6.3.4).

NOTE: Cohort 6 is not open for enrollment in Germany.

Figure 4 **Axicabtagene Ciloleucel Expansion and Correlations with Response and Adverse Events**

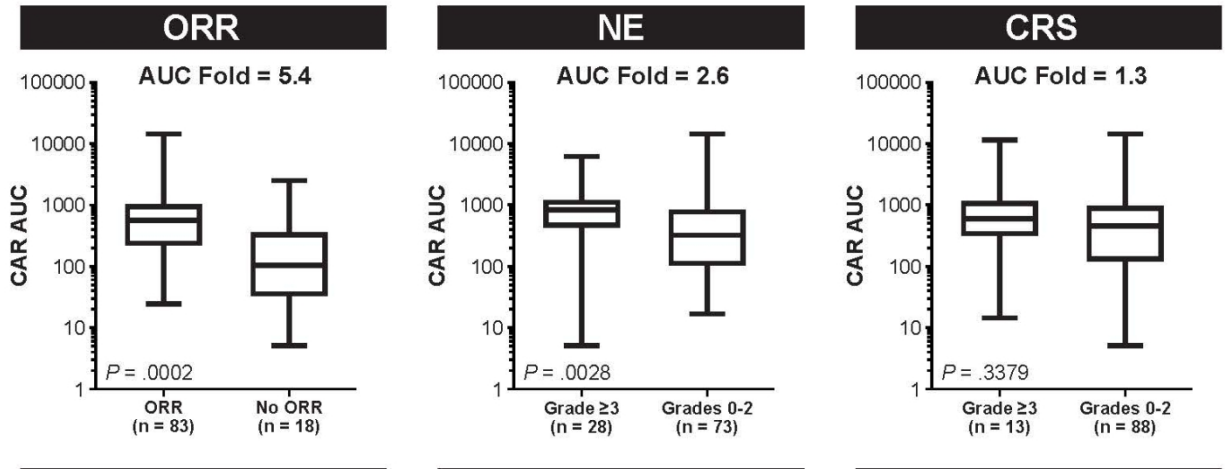


Table 6. **Tocilizumab and Corticosteroids Use in ZUMA-1 Phase 2 Pivotal Study Primary Analysis**

	No Tocilizumab n = 58	Tocilizumab n = 43	*P* Value	No corticosteroids n = 74	Corticosteroids n = 27	P Value
ORR, n (%)	47 (81.0)	36 (83.7)	.8	62 (83.8)	21 (77.8)	.56
CR, n (%)	33 (56.9)	22 (51.2)	.69	40 (54.1)	15 (55.6)	1
Ongoing, n (%)	28 (48.3)	16 (37.2)	.31	33 (44.6)	11 (40.7)	.82
Median peak CAR levels, cells/µL (range)	26.52 (1.25-1226.36)	61.06 (0.84-1513.69)	.0011	32.2 (1.25-1226.36)	49.69 (0.84-1513.69)	.0618
Median CAR AUC, cells/µL days (range)	289.49 (16.82-14329.29)	743.85 (5.09-11506.59)	.0022	407.53 (16.82-14329.29)	724.98 (5.09-11506.59)	.0967

{Neelapu 2017}

Table 7. Rates of Neurologic Toxicities and CRS in the Phase 1 and 2 Pivotal Study versus Phase 2 Safety Management Study Cohort 3

	ZUMA-1 Phase 1+ Phase 2 Pivotal Cohorts 1+2 (N = 108)	ZUMA-1 SMS Cohort 3 (N = 34)
Any Neurologic toxicity[a]	70 (65)	29 (85)
Worst Grade 1	23 (21)	9 (26)
Worst Grade 2	15 (14)	6 (18)
Worst Grade 3	**29 (27)**	**12 (35)**
Worst Grade 4	**3 (3)**	**1 (3)**
Worst Grade 5	**0 (0)**	**1 (3)**
due to disease progression	**0 (0)**	**0 (0)**
Worst Grade >= 3	**32 (30)**	**14 (41)**
Any CRS[b]	101(94)	32 (94)
Worst Grade 1	41 (38)	12 (35)
Worst Grade 2	45 (42)	19 (56)
Worst Grade 3	**9 (8)**	**0 (0)**
Worst Grade 4	**4 (4)**	**1 (3)**
Worst Grade 5	**1 (1)**	**0 (0)**
due to disease progression	**0 (0)**	**0 (0)**
Worst Grade >= 3	**14 (13)**	**1 (3)**

Data cut for Phase 1, Phase 2 Cohort 1 and 2: Primary Analysis, DCO 27JAN2017.
Data cut of SMS Cohort 3: Updated Analysis, DCO 11AUG2017.
Neurologic events are graded per CTCAE 4.03; CRS events are graded per Lee grade {Lee 2014}.

a Neurologic AEs were identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy {Topp 2015}. For Phase 1, Phase 2 Cohort 1 and 2, the neurologic toxicities included events with onset between date of first axicabtagene ciloleucel infusion (Day 0) and Day 56; for SMS Cohort 3, the neurologic toxicities included events with onset on or after the date of first conditioning chemotherapy.

b One subject in Phase 1 had CRS symptoms reported but not graded for CRS at the time at the Primary Analysis data cut. This subject was counted in the "Any CRS" row but not by the worst grade.

6.3.3.4.3. Cohort 5

In the pivotal cohorts of ZUMA-1, Phase 2 (Cohorts 1 and 2; n = 101), subjects with relapsed and refractory aggressive B-cell lymphoma were not permitted to receive anti-cancer therapy between leukapheresis and conditioning chemotherapy. However, a subsequent retrospective analysis suggested a relationship between lymphoma burden (estimated by the sum of the product of diameters [SPD] of index lesions) and clinical outcomes {Locke 2018}. Subjects with the lowest SPD had the highest rates of ongoing response at 1 year and the lowest rates of CRS and neurological events. Thus, Cohort 5 will be used to prospectively assess the impact of debulking therapy, administered after leukapheresis but prior to conditioning chemotherapy, on the safety and efficacy of axicabtagene ciloleucel. The goal of the debulking therapy will be to reduce lymphoma burden and assess clinical outcomes.

Furthermore, the majority (90%) of patients with relapsed/refractory (r/r) DLBCL who were included in another CAR T-cell therapy study {KYMRIAH 2018} received the investigator's choice of bridging therapy that may have had a debulking effect. Although debulking was not explicitly tested, 8 of these patients had no measurable disease following bridging therapy. The overall results from this study suggested that the inclusion of the investigator's choice of bridging therapy was well-tolerated, as no new safety signals were identified using this approach. Toxicities observed within the JULIET study were consistent with other CD19-targeted CAR T-cell therapies.

In conclusion, the goal of Cohort 5 is to improve the benefit-risk ratio of axicabtagene ciloleucel by reducing lymphoma burden prior to administration of axicabtagene ciloleucel. This approach is justified by a retrospective analysis of outcome by tumor burden in ZUMA-1 and data from other CD19-targeting CAR T-cell products. The specific safety regimens studied in Cohorts 3 and 4 will not be continued in Cohort 5.

6.3.4. Study Treatment by Phase

Phase 1 Study

The study will begin with Cohort A1. Subsequent cohorts may be explored as depicted in Figure 3 and outlined in Section 9.10.

Conditioning Chemotherapy

Cohorts A1/A2: Subjects will receive the following 5-day chemotherapy regimen:

- IV hydration with 1 L of 0.9% sodium chloride (NaCl) given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500 mg/m^2 IV over 60 minutes on Day -5, Day -4, and Day -3 followed by:
- Fludarabine 30 mg/m^2 IV over 30 minutes on Day -5, Day -4, and Day -3 followed by:
- An additional 1 L of 0.9% NaCl at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

Cohort A3: Subjects will receive the following 5-day chemotherapy regimen:

- The IV hydration is 1 L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 300 mg/m^2 IV over 60 minutes on Day -5, Day -4, and Day -3 followed by:
- Fludarabine 30 mg/m^2 IV over 30 minutes on Day -5, Day -4, and Day -3 followed by:

- An additional 1 L of 0.9% NaCl at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

For subjects enrolled into Cohort A1/A2/A3, Day -2 and Day -1 will be rest days before axicabtagene ciloleucel infusion on Day 0.

Cohorts B1/B2: Subjects will receive the following 7 day chemotherapy regimen:

- IV hydration with 0.9% NaCl. Recommended at 2.6 ml/kg/hr (maximum 200ml/hr) administered as a continuous infusion starting 11 hours pre-cyclophosphamide infusion and continue hydration until 24 hours after last cyclophosphamide infusion:
- Cyclophosphamide 30 mg/kg IV administered on Day -7 and Day -6 infused over 120 minutes followed by:
- Fludarabine 25 mg/m^2 IV administered on Day -5, Day -4, Day -3, Day -2 and Day -1. Each infusion given over 30 minutes
- Add mesna per institutional guidelines

For subjects enrolled into Cohort B1/B2, there will be no rest days between the last day of chemotherapy (Day -1) and the axicabtagene ciloleucel infusion on Day 0.

6.3.4.1.1. Axicabtagene Ciloleucel

Cohorts A1/A3/B1: Subjects will receive axicabtagene ciloleucel treatment consisting of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (± 20%; 1.6×10^6 anti-CD19 CAR T cells/kg to 2.4×10^6 anti-CD19 CAR T cells/kg). A minimum dose of 1×10^6 anti-CD19 CAR T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of 2×10^8 anti-CD19 CAR T cells will be administered.

Cohorts A2/B2: Subjects will receive axicabtagene ciloleucel treatment consisting of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 1×10^6 anti-CD19 CAR T cells/kg (± 20%; 0.8×10^6 anti-CD19 CAR T cells/kg to 1.2×10^6 anti-CD19 CAR T cells/kg). A minimum dose of 0.5×10^6 anti-CD19 CAR T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of either 1×10^8 anti-CD19 CAR T cells will be administered.

6.3.4.2. Phase 2 Pivotal Study:

Based on the safety profile of the 6 DLT evaluable subjects from the Phase 1 portion of the study, the SRT deemed the axicabtagene ciloleucel dosing regimen explored in Cohort A1 to be safe.

In Phase 2, subjects will receive the 5-day conditioning chemotherapy regimen used in Cohort A1 of the Phase 1 portion of the study:

- IV hydration with 1 L of 0.9% NaCl (or isotonic [crystalloid] fluid) given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500 mg/m^2 IV over approximately 60 minutes on Day -5, Day -4, and Day -3 followed by:
- Fludarabine 30 mg/m^2 IV over approximately 30 minutes on Day -5, Day -4, and Day -3 followed by:
- An additional 1 L of 0.9% NaCl (or isotonic [crystalloid] fluid) at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

Axicabtagene ciloleucel will be administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. In addition, subjects who receive doses between 1-2 x 10^6 anti-CD19 CAR T cells/kg will be included in the mITT analysis set. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells will be administered.

Phase 2 Safety Management Study:

For Cohort 3, subjects will receive conditioning chemotherapy and axicabtagene ciloleucel as described above. In addition, subjects will receive levetiracetam (750 mg PO or IV BID) starting on Day 0. At the onset of ≥ Grade 2 neurologic toxicities, levetiracetam should be administered. If a subject does not experience any ≥ Grade 2 neurologic toxicities, levetiracetam should be tapered and discontinued as clinically indicated. Subjects will also receive tocilizumab (8 mg/kg IV over 1 hour [not to exceed 800 mg]) on Day 2. Further tocilizumab (± corticosteroids) is recommended to be administered at the onset of ≥ Grade 2 CRS.

For Cohorts 4 and 6, subjects will receive bridging therapy (if applicable, refer to Section 6.2.1), conditioning chemotherapy, axicabtagene ciloleucel, and levetiracetam, as described above. Tocilizumab will not be administered as prophylaxis, but will be administered based on toxicity management guidance (eg, tocilizumab and corticosteroids) as described in Section 6.4.1, Table 8, Table 9, and Table 10. Corticosteroids will be initiated for toxicity management for Grade 2 CRS and for Grade 1 neurologic toxicities per Table 8 and Table 9, respectively, as described in Section 6.4.1. In addition, in Cohort 6, subjects will receive corticosteroids on Day 0 (pre-infusion), Day 1, and Day 2.

NOTE: Cohort 6 is not open for enrollment in Germany.

For Cohort 5, subjects should receive debulking therapy (refer to Section 6.2.2), conditioning chemotherapy, axicabtagene ciloleucel, and levetiracetam, as described above. Toxicity management guidance is provided in Section 6.4.

6.4. Toxicity Management

To date, the following important risks have been identified with axicabtagene ciloleucel: CRS, neurologic toxicities, infections, hypogammaglobulinemia, and cytopenias. Refer to Section 6 of the current IB for details regarding these events and management guidance.

As the safety experience with axicabtagene ciloleucel increases, the management guidance may be updated. Therefore, it is important to always refer to the most current version of the axicabtagene ciloleucel IB for guidance regarding managing axicabtagene ciloleucel related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with axicabtagene ciloleucel, as well as possible complications associated with malignancy and cancer treatment.

6.4.1. Phase 2 Safety Management Study (Cohort 4 and Cohort 6 only)

To date, the following risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, hypogammaglobulinemia, and cytopenias. For CRS and neurological toxicities, the treatment guidance outlined in Table 8, Table 9, and Table 10 will be used for Cohort 4 and Cohort 6 of the Phase 2 safety management study. Additional safety information and management recommendations for the other identified risks can also be found in the most current version of the IB.

Table 8. Grading and Management of CRS in Cohort 4 and Cohort 6

CRS Grade	Supportive Care	Tocilizumab	Steroids	Follow up
Grade 1: • Symptoms are not life threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	• Supportive care per institutional standard of care	N/A	N/A	**Not improving after 24 hours:** • **Tocilizumab as per Grade 2 guidance (below)** Not improving after 3 days: • Dexamethasone 10 mg x1

CRS Grade	Supportive Care	Tocilizumab	Steroids	Follow up
Grade 2: • Symptoms require and respond to moderate intervention • Oxygen requirement <40% FiO2 or hypotension responsive to fluids or low dose of one vasopressor[a] or Grade 2 organ toxicity[b]	• Continuous cardiac telemetry and pulse oximetry as indicated • IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids • Vasopressor support for hypotension not responsive to IV fluids • Supplemental oxygen as indicated	• Tocilizumab: 8mg/kg over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 4 to 6 hours as needed if not response to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. • Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS	• Dexamethasone 10mg x 1	Improving: • Discontinue tocilizumab • Taper corticosteroids Not Improving: • Manage as Grade 3 (below)
Grade 3: • Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40% FiO2 or hypotension requiring high-dose or multiple vasopressors[a] or Grade 3 organ toxicity or Grade 4 transaminitis[b]	• Management in monitored care or intensive care unit	• Per Grade 2	• Methylprednisolone 1 mg/kg IV BID[c]	Improving: • Discontinue tocilizumab • Taper corticosteroids Not Improving: • Manage as Grade 4 (below)
Grade 4: • Life-threatening symptoms • Requirements for ventilator support or continuous veno-venous hemodialysis (CVVHD) • Grade 4 organ toxicity (excluding transaminitis)[b]	• Per Grade 3 • Mechanical ventilation and/or renal replacement therapy may be required	• Per Grade 2	High-dose corticosteroids: • Methylprednisolone 1000 mg/day IV x 3 days	Improving: • Discontinue tocilizumab • Taper corticosteroids Not improving: • Consider 1 gram BID to TID of methylprednisolone and other immunosuppressives (e.g. siltuximab) and anti-thymocyte globulin (ATG 2mg/kg x 1 and reassess)

NOTE: Cohort 6 is not open for enrollment in Germany.
a High-dose vasopressor doses
b Severity based on CTCAE
c or equivalent dexamethasone

Table 9. Grading and Management of Neurologic Toxicities in Cohort 4 and Cohort 6

Neurologic Toxicities	Supportive Care	Tocilizumab	Corticosteroids	Follow up
Grade 1 examples include: • Somnolence-mild drowsiness or sleepiness • Confusion-mild disorientation • Encephalopathy-mild limiting of ADLs • Dysphagia-not impairing ability to communicate	• Supportive care per institutional standard of care • Closely monitor neurologic status • Consider prophylactic levetiracetam	N/A	• Dexamethasone 10mg x 1	Not improving after 2 days: • Repeat dexamethasone 10mg x 1 • Continue supportive care
Grade 2 examples include: • Somnolence-moderate, limiting instrumental ADLs • Confusion-moderate disorientation • Encephalopathy-limiting instrumental ADLs • Dysphagia-moderate impairing ability to communicate spontaneously • Seizure(s)	• Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Levetiracetam/ antiepileptics if subject has seizures	• **Only** in case of concurrent CRS: • Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 4 to 6 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. • Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS	• Dexamethasone 10mg QID	Improving: • Discontinue tocilizumab • Taper corticosteroids • Not improving: • Manage as Grade 3 (below)

Neurologic Toxicities	Supportive Care	Tocilizumab	Corticosteroids	Follow up
Grade 3 examples include: • Somnolence-obtundation or stupor • Confusion-severe disorientation • Encephalopathy-limiting self-care ADLs • Dysphagia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	• Management in monitored care of intensive care unit	• Per Grade 2	• Methylprednisolone 1 gram daily	Improving: • Discontinue tocilizumab • Taper corticosteroids • Not improving: • Manage as Grade 4 (below)
Grade 4 examples include: • Life-threatening consequences • Urgent intervention indicated • Requirement for mechanical ventilation • Consider cerebral edema	• Per Grade 3 • Mechanical ventilation, may be required	• Per Grade 2	• Methylprednisolone 1 gram BID	Improving: • Taper corticosteroids Not improving: • Consider 1 gram of methylprednisolone TID, alternative immunsuppressive (e.g. siltuximab) and anti-thymocyte globulin (ATG 2mg/kg x 1 and reassess)

NOTE: Cohort 6 is not open for enrollment in Germany.

Table 10. Management of Cerebral Edema in Cohort 4 and Cohort 6

Supportive Care	Tocilizumab	Corticosteroids	Follow up
As above for neurologic toxicities Grade 4, to include: • Intensive care unit supportive therapy • Optimal head position with elevation of head of bed and straight neck positioning • Administration of diuretics and osmotherapy (eg, mannitol, hypertonic saline) • If cerebral edema documented strongly suspected, recommend neurosurgical consult • Early tracheal intubation with controlled mechanical mild hyperventilation and good oxygenation • Maintain cerebral perfusion pressure with mild hypervolemia • Avoid hypertension with use of antihypertensives (labetalol, nicardipine) • Avoid potent vasodilators • Pharmacological cerebral metabolic suppression (barbiturates, sedation, analgesia, and neuromuscular paralysis, as indicated) • Maintain rigorous glycemic control	• Tocilizumab as above in Grade 4 neurologic toxicity management (tocilizumab should be given only if concurrent CRS)	• Methylprednisone 1gram BID	Improving: • Very slow steroid taper recommended; • Repeat neuro-imaging as indicated • Serial neurologic exams as indicated • Consider early neuro-rehabilitation • Discontinue tocilizumab if started Not Improving • Consider Methylprednisolone 1gram TID, alternative immunosuppressive (e.g. siltuximab) and anti-thymocyte globulin (ATG 2 mg/kg x1 and reassess)

NOTE: Cohort 6 is not open for enrollment in Germany.

6.4.2. Phase 2 Safety Management Study (Cohort 5)

To date, the following risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, hypogammaglobulinemia and cytopenias. Please refer to the current version of the IB for details and management.

7. STUDY PROCEDURES

Research staff should refer to the SOAs for an outline of the procedures required. The visit schedule is calculated from axicabtagene ciloleucel infusion on Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

NOTE: Cohort 6 is not open for enrollment in Germany.

7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current IRB/IEC approved ICF prior to any study specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

7.2. Demographic Data

Demographic data will be collected to include sex, age, race, ethnicity**,** and country of enrollment to study their possible association with subject safety and treatment effectiveness.

7.3. Medical and Treatment History

Relevant medical history prior to the start of adverse event reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the subject's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subjects chart should be obtained.

7.4. Physical Exam, Vital Signs, Performance Status, and EQ-5D

Physical exams will be performed during screening and at times noted in the SOA. Changes noted in subsequent exams when compared to the baseline exam will be reported as an adverse event.

During IP administration, vital signs including blood pressure, heart rate, oxygen saturation, and temperature will be monitored before and after the axicabtagene ciloleucel infusion and then routinely per institutional guidelines. If the subject has a fever (temperature 38.3^{o}C or greater), vital signs will be monitored more frequently as clinically indicated.

Performance status as measured by the ECOG scale will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

For subjects enrolled in Cohort 3, Cohort 4, Cohort 5 or, Cohort 6, EQ-5D will be completed by the subject, prior to any other assessment, at the screening visit and at other times noted in the SOA. Subjects who are blind or illiterate may have the EQ-5D questions read to them by the study staff. The study staff, however, cannot interpret any of the questions for the subject. A subject may be exempt from completing the questionnaire if he or she is unable to read the questionnaire in one of the country languages available.

The EQ-5D is a 2 page generic patient questionnaire for assessing the overall health status of a subject. The EQ-5D consists of a 5 dimension descriptive system including questions on mobility, self-care, usual activities, pain/comfort, and anxiety/depression and a visual analogue scale (EQ VAS) which allows the respondent to record health on a vertical scale (eg, best health to worst health) thus allowing a quantitative measure of health outcome.

7.5. Neurological Assessment

For subjects enrolled in Cohort 1, Cohort 2, or Cohort 3, neurological assessments will be standardized by using the Mini-Mental State Examination (MMSE) standard version 2.0. The MMSE neurological assessment will not be required for Phase 2 SMS Cohort 4, Cohort 5, and Cohort 6. The MMSE is a 5-10 minute, 11-question measure that examines various areas of cognitive function: orientation, attention, immediate recall, short-term recall, language, and the ability to follow simple verbal and written commands.

The MMSE is divided into two sections. The first part requires vocal responses to the examiner's questions. In the second part of the exam, the subject is asked to follow verbal and written instructions, write a sentence spontaneously, and copy a geometric figure**.** Every attempt should be made to dedicate a single research staff member trained in the administration of the MMSE to conduct the assessment to minimize variability among different assessors.

A full neurological assessment will be completed during screening to establish a baseline. Subsequent assessments will be performed before axicabtagene ciloleucel administration on Day 0, on Day 1, and then every other day during the 7-day post-infusion monitoring period, as well as at the Week 4 and Month 3 visits.

7.6. Cardiac Function

Each subject's cardiac function, as measured by ECHO will be assessed during the screening period to confirm study eligibility. Both left ventricular ejection fraction (LVEF) and pericardial effusion will be assessed prior to study entrance by ECHO. An ECHO performed following the subject's last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

To establish a baseline, an ECG will also be performed during the screening period.

7.7. Magnetic Resonance Imaging

Each subject will undergo a screening brain MRI**,** with contrast whenever possible or without contrast in case of contraindication, to rule out CNS metastasis during the screening period of the study. An MRI performed following the subject's last chemotherapy treatment and ≤ 28 days before signing the consent may be used for confirmation of eligibility.

Evaluation of any new onset of ≥ Grade 2 neurologic toxicities should include a brain MRI as described in Section 6.4.

7.8. Bone Marrow Biopsy

Bone marrow aspirate/biopsy will be performed at screening if not previously performed to assess bone marrow involvement. For subjects with a potential complete response to axicabtagene ciloleucel, a follow-up bone marrow aspirate/biopsy will be performed in subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. To confirm a complete response, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. Refer to Section 7.10 and

Appendix 1 for treatment response assessment requirements per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}. Bone marrow aspirate/biopsy should also be considered to evaluate hemophagocytic lymphohistiocytosis (HLH) as indicated in the IB. A portion of the bone marrow sample collected to evaluate HLH or other toxicities should be submitted to the central laboratory as outlined in the central laboratory manual.

7.9. Lumbar Puncture

Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture performed at the screening visit for examination of cerebral spinal fluid. In addition, lumbar puncture may be performed as applicable for subjects with new onset of ≥ Grade 2 neurologic toxicities after axicabtagene ciloleucel infusion (see Section 6.4).

For subjects who sign the optional portion of the consent form, on study paired lumbar puncture for collection of CSF samples will be performed at baseline prior to axicabtagene ciloleucel infusion and after axicabtagene ciloleucel infusion per the schedule of assessments. Samples will be submitted to the central laboratory and analyzed for changes in cytokine levels and presence of CAR T cells.

Phase 2 Safety Management Study

For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, or Cohort 6, lumbar punctures for the collection of CSF samples will be performed pre- and post-axicabtagene ciloleucel infusion at times outlined in the SOA. Samples will be submitted to the central laboratory as outlined in the central laboratory manual. Adequate platelet support should be provided prior to performing a lumbar puncture (e.g. platelet >50,000/mm^3).

7.10. Disease Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}. Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Baseline positron emission tomography-computed tomography (PET-CT) scans of the neck, chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. Subjects will undergo additional PET-CT tumor assessments after their axicabtagene ciloleucel infusion. The first of these post-treatment PET-CT tumor assessments will occur 4 weeks after infusion; subsequent assessments will occur at regular intervals throughout the post-treatment and long-term follow-up portions of the study, as highlighted in the SOA.

After axicabtagene ciloleucel administration, disease assessments will be used to determine the time when progressive disease occurs. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA.

A bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR. Per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}, a bone marrow aspirate and biopsy should be performed only when the subject had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology, or if indeterminate by morphology, it must be negative by immunohistochemistry to assign a CR to treatment.

In addition to the investigator's assessment, PET-CT scans of all subjects evaluated for disease response for Phase 2 pivotal study (Cohort 1 and Cohort 2) will be submitted to and reviewed by an independent central reviewer. For subjects who discontinue the study due to an assessment of progressive disease which was not subsequently confirmed by a central radiology reviewer, any additional imaging data, subsequent to the image in question will be submitted to the central reviewer to confirm disease response.

If the subject is eligible for retreatment with axicabtagene ciloleucel, the last scan prior to retreatment will be considered the baseline for the purpose of evaluating the response to retreatment.

Requirements for PET-CT scans and shipping requirements will be outlined in the study imaging manual.

7.11. Laboratory

The below samples will be collected at the time points indicated in the SOA. Additional samples (eg, blood, urine, CSF, tissue, etc) may be collected as needed for further safety testing.

Local lab analysis:

- Sodium (Na), potassium (K), chloride (Cl), total CO_2 (bicarbonate), creatinine, glucose, blood urea nitrogen (BUN) or urea (if BUN test cannot be analyzed by the local lab), albumin, calcium total, magnesium total (Mg), inorganic phosphorus, alkaline phosphatase, ALT/glutamic-pyruvic transaminase (GPT), AST/glutamic-oxaloacetic transaminase (GOT), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), uric acid

- C-reactive protein (CRP)

- Complete blood count (CBC) with differential

- A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma medical monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma Medical Monitor for instructions.

- For EU sites, a serology (eg, HIV, hepatitis B, hepatitis C**,** syphilis) test will be carried out per institutional guidelines and EU regulations. This may be administered within the 30 days prior to leukapheresis and/or on the day of leukapheresis.

Central lab analysis:

- Blood draws for PBMC (lymphocyte subsets, replication-competent retrovirus [RCR], and anti-CD19 CAR T-cell levels) and cytokine analysis will be performed at intervals outlined in the SOA.

- Serum samples will also be evaluated centrally for anti-axicabtagene ciloleucel antibodies.

- For serum samples that demonstrate increased anti-axicabtagene ciloleucel antibodies at the Month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first.

- Archived tumor tissue

- For subjects enrolled in Cohort 4, Cohort 5, and Cohort 6, a block or 30 unstained slides should be submitted to the central laboratory for confirmatory diagnosis, CD19 expression, cell of origin, and determination of double/triple hit high grade lymphoma.

- For subjects who sign the optional portion of the informed consent, fresh tumor samples will be collected for central pathology review and evaluation of prognostic markers specific for large B-cell lymphoma and pertaining to the tumor immune environment. Additional analysis may include CD19 expression, gene expression profiling, and analysis of tumor-specific DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations), RNA, or protein markers.

- CSF and possibly bone marrow samples will also be collected and analyzed at the central laboratory as outlined in the schedule of assessments and per Section 7.12.

- See central laboratory manual for details on sample collection, processing, and shipping instructions.

7.12. Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate pharmacodynamic markers for axicabtagene ciloleucel. Prognostic markers specific for large B-cell lymphoma and related to the tumor immune environment may also be evaluated in archived and fresh tumor biopsies.

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR T cells will be monitored in the blood primarily by polymerase chain reaction (PCR) analysis, complemented by flow cytometry. Expansion and persistence in peripheral blood will also be monitored by a CD19 CAR specific quantitative polymerase chain reaction (qPCR) assay.

Levels of serum cytokines will be evaluated in serum to characterize the pharmacodynamic and safety profile of axicabtagene ciloleucel. The following pro-inflammatory, homeostatic and immune modulating cytokines may be included in the panel: IL-6, IL-15, IL-17a, TNF-α, GM-CSF, IFN-γ, IL-12p40/p70 and IL-13; immune effector molecules: Granzyme A, B and Perforin; correlates of acute phase response: CRP and SAA; Chemokines MIP-1α, MIP-1β, MCP-1, IP-10, and IL-8. In addition, IL1Ra, IL2Rα, and ferritin will also be measured.

CSF, as well as additional samples (eg, pleural fluid), may be harvested from subjects who develop neurologic toxicities or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable, lymphocyte populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of axicabtagene ciloleucel.

Phase 2 Pivotal Study

For subjects in Cohort 1 and Cohort 2 who sign the optional portion of the consent form, on-study paired lumbar puncture for collection of CSF samples will be performed at baseline prior to axicabtagene ciloleucel infusion and after axicabtagene ciloleucel infusion per the schedule of assessments. Samples will be analyzed for changes in cytokine levels and presence of CAR T cells.

Phase 2 Safety Management Study

For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, or Cohort 6**,** lumbar punctures for collection of CSF samples will be performed at the following time points: after eligibility is confirmed and prior to start of conditioning chemotherapy, after axicabtagene ciloleucel infusion on Day 5 (± 3 days), and at the Week 4 visit (± 3 days). Collection of CSF samples will enable measurement of baseline cytokine levels prior to axicabtagene ciloleucel infusion. Changes in levels of cytokines after axicabtagene ciloleucel infusion will be measured at the time of peak CAR T-cell expansion (Day 5) and at Week 4 when it is anticipated that cytokine levels would return to baseline levels. Infiltration of CAR T cells will also be assessed by flow cytometry in post-axicabtagene ciloleucel infusion CSF samples. Exploratory analysis of cells, analytes, or immune cell markers within the CSF will be analyzed in conjunction with the clinical data to better understand the pathogenesis of neurologic toxicities.

For subjects enrolled in Cohort 4, Cohort 5, and Cohort 6, additional blood will be collected on Day 1 (Cohort 6 only), Day 2 (Cohort 6 only), Day 3, Day 7, Day 10, and Week 3 after axicabtagene ciloleucel infusion. The intent of the additional blood samples is to enable early monitoring of anti-CD19 CAR T-cell and serum cytokine levels in the blood of subjects treated more aggressively with tocilizumab and corticosteroids. To balance the total amount of blood drawn over the first 3 months of therapy, blood volumes have been reduced at pre-specified time points (refer to the central laboratory manual for details).

Phase 2 Pivotal Study and Safety Management Study

Bone marrow samples may be collected for subjects who develop toxicities after axicabtagene ciloleucel infusion and will be analyzed centrally by immunohistochemistry for evidence of disease, treatment emergent toxicities (e.g. HLH, pancytopenia) and presence of anti-CD19 CAR T cells.

Because axicabtagene ciloleucel comprises retroviral vector transduced T cells, the presence of RCR in the blood of treated subjects will be monitored.

In addition, baseline leukapheresis and final axicabtagene ciloleucel samples will be banked and may be analyzed by immunophenotyping, qPCR, and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of immune-related DNA, RNA, or protein markers.

Archived tumor tissue will be collected for central pathology review. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA, RNA, or protein markers.

For subjects who sign the optional portion of the consent form (and for all subjects with accessible tumor), on-study paired core biopsies of tumor will be performed at baseline and after axicabtagene ciloleucel infusion when we expect expansion and tumor infiltration with CAR T cells. In addition, persisting, relapsing or emerging lesions could also be biopsied to help determine eligibility for re-treatment or mechanisms of tumor resistance. Exploratory analysis of tumor or immune cell markers that correlate with response to axicabtagene ciloleucel or disease prognosis will be analyzed.

The above samples and any other components from these samples may be stored up to 15 years to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who in turn can contact the sponsor. The investigator should provide the sponsor the study and subject number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

7.13. Description of Study Periods

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled or the reason for why the subject failed screening.

7.13.1. Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through confirmation of enrollment. Informed consent must be obtained before completion of any non-standard of care study specific procedures. Procedures that are part of standard of care are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA.

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled in the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA:

- Medical history and disease assessment
- Physical examination including height and weight
- Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, and Cohort 6, EQ-5D questionnaire (prior to any other assessments/procedures being performed)
- For subjects enrolled in Cohort 1, Cohort 2, or Cohort 3, neurological assessment including MMSE
- ECG
- ECHO for LVEF and pericardial effusion assessment
- An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility
- Imaging Studies
- Brain MRI
- Baseline PET-CT of the neck, chest, abdomen and pelvis
- PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility**.**
- If PET CT is performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the scans must be repeated to establish a new baseline. For subjects in Cohort 5, if no conditioning chemotherapy is being administered, a PET-CT must be repeated to establish a new baseline prior to the axicabtagene ciloleucel infusion**.** PET-CT should be performed as close to enrollment as possible.
- Bone marrow aspirate/biopsy as needed (if not done at initial diagnosis or between diagnosis and screening)
- Labs
- Chemistry panel

- CBC with differential
- β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- Once eligibility confirmed, collection of archived tumor sample, as well as fresh tumor sample**(s)** and CSF samples (for subjects who signed the optional portion of the consent)
- For subjects assigned to Cohort 3, Cohort 4, Cohort 5, and Cohort 6, lumbar puncture for collection of CSF samples to be performed after eligibility confirmed and prior to start of conditioning chemotherapy

7.13.2. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the 28-day screening period will be permitted to rescreen one time. Subjects will retain the same subject identification number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, only the procedure(s)/assessment(s) that did not originally meet the eligibility criteria needs to be repeated; all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs, or leukapheresis is delayed, more than 28 days from the signing of the original informed consent, subjects must be reconsented and repeat all screening procedures/assessments.

7.13.3. Enrollment/Leukapheresis

If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and results are outside the eligibility criteria listed in Section 5, contact the Kite medical monitor prior to proceeding with leukapheresis.

Before leukapheresis commences, the following criteria must be met. If criteria are not met, leukapheresis must be delayed until the event resolves. If leukapheresis is delayed beyond 5 days, baseline CBC with differential and chemistry panel must be repeated. If results are outside eligibility criteria listed in Section 5, contact the Kite medical monitor prior to proceeding with leukapheresis**.**

- No evidence or suspicion of an infection
- Corticosteroid therapy at a pharmacologic dose (≥5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis.

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

The following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Weight
- Labs (to be drawn prior to leukapheresis, on the day of or day before leukapheresis)
- Chemistry panel
- CBC with differential
- CRP; if CRP is ≥ 100 mg/L a call must be made to the Kite medical monitor before proceeding with conditioning chemotherapy
- Anti-CD19 CAR T cells
- Lymphocyte subsets
- Cytokine levels
- Anti-axicabtagene ciloleucel antibodies
- Leukapheresis
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

7.13.4. Bridging Therapy Phase 2 Safety Management Study

If prescribed, bridging therapy must be administered after enrollment and completed prior to initiating conditioning chemotherapy per the specifications outlined in Section 6 for bridging therapy.

- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

7.13.5. Debulking Therapy Phase 2 Safety Management Study, Cohort 5

Debulking chemotherapy must be administered after enrollment and should be completed at least 14 days prior to initiating conditioning chemotherapy or at least 14 days prior to axicabtagene ciloleucel administration in case conditioning chemotherapy is omitted. Radiotherapy must be administered after enrollment and should be completed at least 5 days prior to initiating conditioning chemotherapy or at least 5 days prior to axicabtagene ciloleucel administration in case conditioning chemotherapy is omitted.

7.13.6. Conditioning Chemotherapy Period

If any screening assessments or procedures are repeated between screening and the start of conditioning chemotherapy and results are outside the eligibility criteria (Section 5), contact the Kite medical monitor for approval prior to proceeding with conditioning chemotherapy.

If PET-CT will be older than 28 days at the initiation of conditioning chemotherapy or if the subject receives any anti-cancer therapy with therapeutic intent (eg, radiation, supraphysiologic doses of steroids, chemotherapy) between the last PET-CT and initiation of conditioning chemotherapy, the PET-CT must be repeated to establish a new baseline.

Subjects in Cohort 5 and Cohort 6 may proceed with conditioning chemotherapy in absence of measurable disease in the new baseline PET-CT if they have received preceding bridging or debulking therapy (Cohort 5).

The investigational product (axicabtagene ciloleucel) must be available before initiation of conditioning chemotherapy.

7.13.6.1. Requirements for Initiating Conditioning Chemotherapy

Administration of anti-CD19 CAR T cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion. Signs, symptoms or abnormal laboratory results attributed to the malignancy (eg "tumor fever," elevated CRP) are diagnoses of exclusion that require a documented workup to establish. Conditioning chemotherapy and axicabtagene ciloleucel infusion should only be initiated after it is reasonably assured that cell infusion can safely proceed.

If any of the following criteria are met prior to initiation of conditioning chemotherapy, then the work-up listed in Section 7.13.7.3 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°Celsius within 72 hours of conditioning chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- WBC count or WBC differential that is suggestive of infectious process, and is observed between enrollment and the initiation of conditioning chemotherapy (eg WBC > 20,000/µL, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy.

- Complete history and physical exam including head, ears, eyes, nose, and throat (HEENT) exam, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.

- The subject must not have received systemic antimicrobials for the treatment of known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of antimicrobials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If the subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator and in consultation with infectious disease service (if applicable).

- The most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stood studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with conditioning chemotherapy.

7.13.6.2. Conditioning Chemotherapy Administration

The following procedures will be completed during Day –5 to Day –3 at the time points outlined in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature

- Labs (to be drawn prior to chemotherapy)

- Chemistry Panel

- CBC with differential

- Fludarabine and cyclophosphamide administration

- Adverse/Serious Adverse Event reporting

- Concomitant medications documentation

- Cytokine levels (Cohort 5 only)

7.13.7. Investigational Product Treatment Period

7.13.7.1. Requirements for Initiating Axicabtagene Ciloleucel Infusion

If any of the following criteria are met prior to the initiation of axicabtagene ciloleucel infusion, then the work-up listed in Section 7.13.7.3 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°Celsius within **72** hours of axicabtagene ciloleucel infusion.
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- WBC count or WBC differential, that is suggestive of infectious process, and is observed between enrollment and the initiation of axicabtagene ciloleucel infusion (eg, WBC > 20,000/μL, rapidly increasing WBC, or differential with high percentage or segments/bands)
- Additionally: If any screening assessments or procedures are repeated between confirmation of eligibility and the start of axicabtagene ciloleucel infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with axicabtagene ciloleucel infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy)
- Complete history and physical exam including HEENT exam, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before axicabtagene ciloleucel infusion (prophylactic use of antimicrobials is allowed)
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable).
- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

After the above criteria are met, then the subject can proceed with administration of axicabtagene ciloleucel**.** For Cohort 6 only, dexamethasone 10 mg by mouth should be given prior to axicabtagene ciloleucel infusion (refer to Section 7.13.7.2).

If the axicabtagene ciloleucel infusion is delayed > 2 weeks from the planned infusion date, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

7.13.7.2. Monitoring After Axicabtagene Ciloleucel Infusion

All subjects will receive axicabtagene ciloleucel infusion at a healthcare facility followed by daily monitoring at a healthcare facility for at least 7 days unless otherwise required by country regulatory agencies (refer to Appendix 2) to monitor for signs and symptoms of CRS and neurologic toxicities. Alternatively, subjects may be hospitalized to receive their axicabtagene ciloleucel infusion and be observed for CRS and neurologic toxicities in the hospital setting, if deemed appropriate by the investigator.

If subjects are hospitalized, subjects should not be discharged from the hospital until all axicabtagene ciloleucel related non-hematological toxicities return to ≤ Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (eg, renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain in a hospital for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing central neurologic toxicities > Grade 1, or if deemed necessary by the investigator.

Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following axicabtagene ciloleucel infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphagia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

During this period, the following procedures will be completed at the time points outlined in the SOA:

- Neurological assessment including MMSE for subjects enrolled in Cohort 1, Cohort 2, or Cohort 3
- MMSE will be administered before treatment with axicabtagene ciloleucel on Day 0, and then on Day 1 and every other day during the 7-day post-infusion monitoring period.
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature, daily at a health care facility for at least 7 days
- Labs (before axicabtagene ciloleucel infusion, as described in the SOA)
- Chemistry Panel

- CBC with differential
- Lymphocyte subsets
- Cytokine levels
- Anti-CD19 CAR T cells
- RCR analysis
- Cohort 6 only: Dexamethasone 10 mg by mouth on Day 0 (in the morning before the axicabtagene ciloleucel infusion), Day 1, and Day 2
- Infusion of axicabtagene ciloleucel
- For subjects enrolled in Cohort 3, administer tocilizumab at a dose of 80 mg/kg IV over 1 hour (not to exceed 800 mg) on Day 2. See Section 6.3.4 for further details on additional tocilizumab administration for toxicity management.
- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, and Cohort 6, administer levetiracetam at a dose of 750 mg (PO or IV) BID starting on Day 0. See Section 6.4 for further details on administration and discontinuation of levetiracetam for toxicity management. If subject does not experience any neurologic toxicities ≥ Grade 2, taper and discontinue levetiracetam as clinically indicated.
- For subjects assigned to Cohort 3, Cohort 4, Cohort 5, and Cohort 6, lumbar puncture for collection of CSF samples at Day 5 (± 3 days)
- Subjects in Cohort 5 and Cohort 6 may proceed with axicabtagene ciloleucel if the new baseline PET-CT shows an absence of measurable disease**.**
- As applicable, lumbar puncture, for subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion or subjects who signed the optional portion of the consent, should be completed for examination of CSF.
- Collection of fresh tumor sample(s) for subjects who signed the optional portion of the consent (anytime between Day 7 and Day 14) Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regards to CRS/neurologic toxicities. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and for at least 7 days at a healthcare facility. In addition, lactate should be monitored as clinically indicated.

7.13.7.3. Requirements for Work-up Potential Infectious and/or Inflammatory States

In the absence of an identified source of infection (eg, line infection, pneumonia on chest x-ray), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or axicabtagene ciloleucel consists of the following:

- Call Kite medical monitor
- Infectious disease service consult (if available)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x 2 bottles each) and urinalysis and urine culture. Deep/induced sputum culture if clinically indicated.
  - All indwelling lines, such as central venous catheters, should be examined for any signs of infection and additional cultures should be drawn from the line
  - Nasopharyngeal-throat swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus [CMV])
- If a central nervous system process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed.
- Any additional sign or symptom-directed investigation should be performed as clinically indicated.

Prior to proceeding with conditioning chemotherapy and/or axicabtagene ciloleucel infusion, the above workup must not suggest the presence of an active infection and all requirements for conditioning chemotherapy and/or axicabtagene ciloleucel infusion must be satisfied. If the axicabtagene ciloleucel infusion is delayed > 2 weeks following conditioning chemotherapy, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

If the above workup was triggered due to CRP > 100 mg/L, CRP should be repeated. If CRP continues to increase significantly, an evaluation should be performed for any other potential infectious or inflammatory condition that was not previously evaluated.

7.13.8. Post-treatment Assessment Period

After completing axicabtagene ciloleucel infusion and completing the minimum 7-day observation period, all subjects will be followed in the post-treatment assessment period. Counting from Day 0 (axicabtagene ciloleucel infusion), subjects will return to the clinic at the following intervals.

- Week 2 (± 2 days)
- Week 3 (± 2 days) for subjects enrolled in Cohort 4 only
- Week 4 (± 3 days)
- Month 2 (± 1 week)
- Month 3 (± 1 week)

Subject will allow key sponsor contacts to continue to access medical records so that information related to subjects health condition and initial treatment response may be obtained. The following procedures will be completed for subjects as outlined in the SOA:

- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, and Cohort 6, EQ-5D questionnaire (prior to any other assessments/procedures being performed)
- For subjects enrolled in Cohort 1, Cohort 2, or Cohort 3, neurological assessment including MMSE
- PET-CT for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated. Refer to the imaging charter for detailed instructions.
- As applicable, bone marrow aspirate/biopsy to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment)
- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs
- Chemistry Panel
- CBC with differential
- β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Anti-axicabtagene ciloleucel antibodies

- Cytokine levels
- Lymphocyte subsets
- Anti-CD19 CAR T cells
- RCR analysis
- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, and Cohort 6, taper or discontinue levetiracetam as clinically indicated. See Section 6.4 for further details.
- For subjects assigned to Cohort 3, Cohort 4, Cohort 5, and Cohort 6, lumbar puncture for collection of CSF samples at Week 4 (± 3 days)
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is admitted to the hospital during the 7-day observation period, discharged, and is subsequently re-admitted to the hospital with any axicabtagene ciloleucel related adverse event(s), the following labs will be collected on the day of hospital re-admission and then weekly through and including on the day of discharge:

- PBMCs (anti-CD19 CAR T cells)
- Cytokines

At any time during the post treatment assessment period, if a subject progresses and is either not eligible for re-treatment or chooses not to pursue re-treatment, the subject will proceed directly to the Month 3 visit and be followed for survival, subsequent therapy and disease outcomes in the long-term follow-up period. A PBMC (for anti-CD19 CAR T cells) and serum sample (for cytokine evaluation) should be collected at the time of progression, prior to starting any subsequent anti-cancer therapy.

Upon disease progression, sites are encouraged to collect a tumor biopsy and submit a portion of the tumor tissue to the central laboratory for exploratory biomarker analysis.

7.13.9. Long-term Follow-up Period

All enrolled subjects will be followed in the long-term follow-up period for survival and disease status per this protocol SOA, if applicable, until the transition to the LTFU study, KT-US-982-5968. Subjects will begin the long-term follow-up period after completion of the Month 3 visit, following axicabtagene ciloleucel infusion.

- Every 3 months (± 2 weeks) through Month 18
- Every 6 months (± 1 month) between Month 24 - Month 60

- Beginning with year 6, Month 72 (± 3 months), subjects will return to the clinic 1 time annually up to 15 years.

Subjects will be given the opportunity to transition to the separate LTFU study, KT-US-982-5968, after providing signed informed consent for the LTFU study and after completing at least 24 months of assessments in the parent study.

The following procedures will be completed for subjects who are enrolled and receive axicabtagene ciloleucel at the time points outlined in the SOA (Table 11):

- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, and Cohort 6, EQ-5D questionnaire (prior to any other assessments/procedures being performed)
- Physical exam
- PET-CT/ Disease assessment through 24 months or until disease progression, whichever occurs first. If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per institutional standard of care.
- Survival status
- Labs
- CBC with differential
- Anti-axicabtagene ciloleucel antibodies (refer to Section 7.11)
- Lymphocyte subsets
- Anti-CD19 CART-cell levels
- RCR analysis
- Subsequent therapy for the treatment of NHL
- Refer to Sections 9.2 and 9.4 for targeted adverse/serious adverse event reporting
- Neurological, hematological, infections, autoimmune disorders, and secondary malignancies
- Targeted concomitant medication documentation (for 24 months or until disease progression, whichever occurs first)
- Gammaglobulins, immunosuppressive drugs, anti-infectives, and vaccinations

Subjects may be contacted by telephone to confirm survival status and report targeted concomitant medication use.

If a subject progresses in the long-term follow-up (LTFU) phase of this study, the subject will continue to be followed for survival status and subsequent therapy for the treatment of NHL. A PBMC sample (for anti-CD19 CAR T cells) and serum (for cytokine evaluation) should be collected at the time of progression, prior to starting any subsequent anti-cancer therapy.

Upon disease progression, sites are encouraged to collect a tumor biopsy and submit a portion of the tumor tissue to the central laboratory for exploratory biomarker analysis.

Subjects who are enrolled, but do not receive axicabtagene ciloleucel will be followed only until the end of this study. These subjects will undergo the following assessments at the time points outlined in the SOA (Table 11):

- Subsequent therapy for the treatment of NHL
- Survival status
- Disease assessment per standard of care
- Adverse/Serious Adverse Event reporting and concomitant medication documentation until 30 days after last procedure (e.g., leukapheresis, conditioning chemotherapy).

Should the subject fail to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact the subject will be considered lost to follow-up and no additional contact will be required.

7.13.10. Retreatment

Subjects who achieve a partial response (PR) or complete response (CR) and subsequently experience disease progression, will have an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel while enrolled in this study. .

The following criteria must be met in order to be considered for retreatment:

- Subject had a PR or CR
- Subjects disease subsequently progress
- Subject received initial axi-cel infusion ≤ 24 months ago
- CD19 tumor expression confirmed locally by biopsy after disease progression and prior to re-treatment. A portion of the biopsy should be sent to the central laboratory.
- Subject continues to meet the original study eligibility criteria with exception of prior axicabtagene ciloleucel use in this study. Screening assessments should be repeated if clinically indicated, as determined by the investigator, to confirm eligibility.

- Subject has not received subsequent therapy for the treatment of lymphoma
- Subject did not experience a DLT in Phase 1 or a comparable toxicity in Phase 2
- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to re-treatment
- Subject does not have known neutralizing antibodies (exception: if a non-neutralizing antibody develops subject may be retreated if they meet the original study eligibility criteria)

The decision to administer retreatment should be made in consultation with the Kite Medical Monitor. In addition, a discussion regarding benefits and risks of retreatment and including the potential need to undergo leukapheresis a second time for the manufacturing of axicabtagene ciloleucel should occur with the subject prior to performing any study related procedures or treatment. This conversation should also be recorded in the subject's source document.

A maximum of 1 retreatment course may occur per subject. Subjects who are retreated will follow the same treatment schedule and procedural requirements per the initial treatment.

Subjects enrolled in Phase 2 will receive the same axicabtagene ciloleucel regimen as the original target dose. Subjects enrolled in Phase 1 will receive the axicabtagene ciloleucel regimen selected for Phase 2 if they are retreated. If the Phase 2 regimen has not yet been selected, subjects will receive the last axicabtagene ciloleucel regimen that was determined safe by the SRT.

Allowance for retreatment is based on clinical experience reported in the 2 studies conducted at the pediatric {Lee 2015} and Surgery Branch {Kochenderfer 2015} of the NCI where 6 subjects in total have been re-treated upon progression. Three of the re-treated subjects (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression.

Table 11. Schedule of Assessments

Procedures	Screening	Enrollment/ Leukapheresis	Debulking Therapy (Cohort 5)	Conditioning Chemotherapy Period					IP Administration Period[12]		Post Treatment Follow-up (each visit calculated from Day 0)				
Day	Within 28 days of enrollment	Within approx. 5 days of eligibility confirmation	After enrollment and at least 14 days prior to Day -5	-5	-4	-3	-2	-1	0	1 - 7	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Medical history	X														
ECOG Performance Status	X														
EQ-5D Questionnaire (Cohort 3,4, 5, and 6 only)[14]	X												X		X
Neurological assessment including Mini Mental Status Exam (MMSE)[5,14]	X								X	QOD [5]			X		X
ECG	X														
ECHO	X														
Archival/Fresh tumor[1,14]		X								between Day 7 & Day 14					
Brain MRI	X														
PET-CT/ disease assessment [2]	X												X		X
Physical exam	X										X		X	X	X
Vital signs (BP, HR, O_2 sat, temp)	X	X		X	X	X			X	X	X		X	X	X
Weight (plus Height at screening)	X	X													
Pregnancy test (serum or urine)	X														X
Lumbar Puncture[6,14]		X								X			X		
Blood draw for Chemistry panel	X	X		X	X	X			X	X	X		X	X	X
Blood draw for CBC w/differential	X	X		X	X	X			X	X	X		X	X	X
Blood draw for C-reactive protein (CRP)		X													
Blood draw for Anti-axicabtagene ciloleucel antibodies [3]		X											X		X
Blood draw for Lymphocyte subsets		X							X				X		X

Procedures	Screening	Enrollment/ Leukapheresis	Debulking Therapy (Cohort 5)	Conditioning Chemotherapy Period					IP Administration Period[12]		Post Treatment Follow-up (each visit calculated from Day 0)				
Day	**Within 28 days of enrollment**	**Within approx. 5 days of eligibility confirmation**	**After enrollment and at least 14 days prior to Day -5**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1 - 7**	**Week 2 (± 2 days)**	**Week 3 (± 2 days)**	**Week 4 (± 3 days)**	**Month 2 (± 1 week)**	**Month 3 (± 1 week)**
Blood draw for Cytokines [7, 11,14]		X		X [11]					X	QOD [11]	X		X		
Blood draw for Anti-CD19 CAR T cells[7, 10,14]		X							X	Day1[10],2[10], 3, 7, 10	X	X	X		X
Blood draw for RCR analysis [4]									X						X
Leukapheresis		X													
Debulking Therapy (Cohort 5 only)			X												
Fludarabine/Cyclophosphamide				X	X	X									
Prophylactic Steroid[13] (Cohort 6 only)[14]									X[13]	X[13]					
Axicabtagene ciloleucel infusion IV									X						
Tocilizumab[8]										Day 2					
Levetiracetam[9,14]									Starting on Day 0						
Adverse events/ Concomitant medication	X	X		→											

1. Archival/Fresh tumor sample: Either FFPE tumor block or up to 20 unstained slides. For subjects enrolled in Cohort 4 Cohort 5, and Cohort 6, a block or 30 unstained slides. Fresh tumor sample for subjects who sign the optional portion of consent. Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. Post treatment fresh tumor samples (if applicable) will be collected/submitted anytime between Day 7 and Day 14. See Section 7.11 and 7.12 and central laboratory manual for details
2. PET-CT (Neck-Chest-Abdomen-Pelvis)/disease assessment PET-CT performed following last line of therapy (>28 days from enrollment) may be used for confirmation of eligibility. If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. As applicable, bone marrow aspirate/biopsy will be performed to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). Bone marrow samples may also be collected and analyzed centrally for subjects who develop toxicities post axicabtagene ciloleucel. See Section 7.10 and Section 7.12
3. Blood draw for Anti-axicabtagene ciloleucel antibodies: Baseline antibody sample to be collected prior to start of leukapheresis. Post axicabtagene ciloleucel antibody sample to be collected at Week 4 and Month 3 visits. See Section 7.11 for further details
4. Blood draw for RCR: on Day 0 prior to administration of axicabtagene ciloleucel and at Month 3, 6 and 12; then collect yearly for up to 15 years. Yearly samples will only be analyzed if positive at Month 3, 6, or 12.

5. MMSE and Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1 and then every other day during the 7 day post infusion monitoring period for Cohort 1, Cohort 2, and Cohort 3. MMSE will not be required for Cohort 4 **,** Cohort 5, and Cohort 6.
6. Lumbar Puncture: subjects with symptoms of CNS malignancy (e.g., new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade ≥ 2 neurologic symptoms post axicabtagene ciloleucel infusion will have lumber puncture performed to assess cerebral spinal fluid. In addition, subjects who sign the optional portion of the consent, will have lumbar puncture for the collection of CSF performed at baseline prior to axicabtagene ciloleucel infusion and post axicabtagene ciloleucel infusion (Day 5 ± 3 days). For subjects enrolled in Cohort 3,Cohort 4, Cohort 5, and Cohort 6, lumbar punctures for collection of CSF samples will be performed at the following time points: after eligibility is confirmed and prior to start of conditioning chemotherapy, post axicabtagene ciloleucel infusion on Day 5 (±3 days), and at the Week 4 visit (±3 days).
7. If a subject is admitted to the hospital within the 7-day observation period is discharged and then subsequently re-admitted to the hospital with any axicabtagene ciloleucel related adverse events, blood samples for anti-CD19 CAR T cells and cytokines will be collected on day of hospital re-admission and then weekly through and including the day of discharge. Blood samples for anti-CD19 CAR T cells and cytokines should also be collected at the time of disease progression prior to starting any subsequent anticancer therapy.
8. For subjects enrolled in Cohort 3, administer tocilizumab at a dose of 8 mg/kg IV over 1 hour (not to exceed 800mg) on Day 2. See Sections 6.3.4 for further details.
9. For subjects enrolled in Cohorts 3, 4**,** 5, and 6, administer levetiracetam at a dose of 750 mg (PO or IV) BID starting on Day 0. See Sections 6.3.4 and 6.4.1 for further details.
10. For subjects enrolled in Cohorts 4 and 5, blood draw for Anti-CD19 CAR T cells will be collected on Day 3, Day 7, Day 10. For subjects enrolled in Cohort 6, blood draw for anti-CD19 CAR T cells will be collected on Day 1, Day 2, Day 3, Day 7, and Day 10.
11. Blood draw for cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1, and then every other day during the 7 day post infusion monitoring period. For subjects enrolled in Cohort 5, additional cytokine sample after debulking therapy from Day -5 prior to conditioning chemotherapy. For subjects enrolled in Cohort 6, additional cytokine sample will be drawn on Day 2.
12. Refer to Appendix 2 for requirements by country regulatory agencies.
13. For subjects enrolled in Cohort 6, administer dexamethasone 10 mg by mouth on Day 0 (prior to axicabtagene ciloleucel infusion), Day 1, and Day 2.
14. Cohort 6 is not open for enrollment in Germany.

Table 12. Schedule of Assessments (Long-term Follow-up Period)

Procedure	Long-Term Follow-up Period[10] (Each visit calculated from Day 0)												
Visit Frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Thereafter**
EQ-5D Questionnaire (Cohorts 3, 4, 5, and 6 only)[9]	X												
Physical exam[1]	X	X	X	X	X	X							
PET-CT/disease assessment[2]	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for CBC w/differential [3]	X	X	X	X	X	X							
Blood draw for Anti-axicabtagene ciloleucel antibodies [4]	X	X	X										
Blood draw for Lymphocyte subsets [3]	X	X	X	X	X	X							
Blood draw for anti-CD19 CAR T cells[3]	X		X			X							
Blood draw for RCR analysis [5]	X		X			X		X		X		X	X
Targeted AE/SAEs [6]	X	X	X	X	X	X							
Targeted concomitant medication [7]	X	X	X	X	X	X							
Subsequent therapy for NHL[8]	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Physical exams will continue through Month 24
2. PET-CTs/disease assessments will continue through Month 24 or until disease progression, whichever comes first**.** If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per standard of care.
3. Subjects will continue to provide samples for CBC w/diffs, lymphocyte subsets and anti-CD19 CAR T cells through Month 24
4. Anti**-**axicabtagene ciloleucel antibody samples: refer to Section 7.11
5. RCR samples: collect and measured at Month 3, 6 and 12, then collect yearly for up to 15 years. Yearly samples will only be analyzed if positive at Month 3, 6, or 12.
6. Targeted AEs/SAEs will be collected for 24 months or until disease progression (whichever occurs first)
7. Targeted concomitant medications will be collected for 24 months or until disease progression (whichever occurs first)
8. Subsequent therapy administered after axicabtagene ciloleucel infusion for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy must be collected until subject completes the long-term follow up period, is considered lost to follow up, withdraws consent, or dies. Subjects may be contacted by telephone to collect information about subsequent therapy for NHL and to assess survival status.
9. Cohort 6 is not open for enrollment in Germany.
10. After completion of at least 24 months of assessments in the KTE-C19-101 study, subjects who received an infusion of axicabtagene ciloleucel will be provided an opportunity to transition to the LTFU study (KT-US-982-5968) after providing signed informed consent, to complete the remainder of the 15-year LTFU period.

8. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product, study treatment or other protocol required therapies and must discuss options for continued participation, completion of procedures and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and where permitted by local regulations, publically available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole or at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol required investigational products or procedures include any of the following:

- Adverse Event
- Subject request
- Product not available
- Lost to Follow-up
- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9. SAFETY REPORTING

9.1. Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered adverse events. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered adverse events.

The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (e.g., B-Cell Lymphoma).

For situations when an adverse event or serious adverse event is due to the disease under investigation report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as adverse events in the appropriate section of the CRF.

The investigators clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol required therapies or the study due to an adverse event, the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.2. Reporting of Adverse Events

The investigator is responsible for **reporting** all adverse events observed by the investigator or reported by the subject that occur from enrollment (ie, commencement of leukapheresis) through 3 months after treatment with axicabtagene ciloleucel infusion or until the initiation of another anti-cancer therapy, whichever occurs first. After 3 months, targeted adverse events including (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) will be monitored and reported for 24 months after treatment with axicabtagene ciloleucel or until disease progression, whichever occurs first.

For subjects who are enrolled, but do not receive axicabtagene ciloleucel, the adverse event reporting period ends 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy).

The investigator must address the below for adverse events:

- Adverse event diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, conditioning chemotherapy or study procedures
- Action taken

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov). Cytokine Release Syndrome events will also be reported using the grading scale outlined in Section 6.4.

In reviewing adverse events, investigators must assess whether the adverse event is possibly related to 1) the investigational product (axicabtagene ciloleucel), 2) conditioning chemotherapy, or 3) any protocol-required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the adverse event. Additional relevant data with respect to describing the adverse event will be collected in the CRFs.

The investigator is expected to follow reported adverse events until stabilization or resolution. If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started.

9.2.1. Reporting Abnormal Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae, or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Associated with clinical symptoms
- Results in a medical intervention (eg, potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

9.3. Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An adverse event would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility (eg, overnight stay).

Events that require an escalation of care when the subject is already hospitalized should be recorded as a serious adverse event. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization.

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event with the criterion of "other medically important serious event."

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic CRF.

9.4. Reporting of Serious Adverse Events

The investigator is responsible for reporting all serious adverse events observed by the investigator or reported by the subject that occur after signing of the consent through 3 months after the axicabtagene ciloleucel infusion or until the initiation of another anti-cancer therapy, whichever occurs first. After 3 months, only serious targeted adverse events (e.g., neurological, hematological, infections, autoimmune disorders, and secondary malignancies) observed by the investigator or reported by the subject will be reported for 24 months after axicabtagene ciloleucel infusion or until disease progression, whichever occurs first. For subjects who screen fail or are enrolled but do not receive axicabtagene ciloleucel, the reporting period for serious adverse events ends 30 days after the last procedure (e.g., screen procedure, leukapheresis, conditioning chemotherapy).

Serious events that the investigator assesses as related to axicabtagene ciloleucel should be reported regardless of the study period.

All SAEs must be submitted via email to safety_fc@gilead.com within 24 hours following the investigator's knowledge of the event and using a SAE Report Form.

Subsequently, all serious adverse events will be reported to the health authorities per local reporting guidelines.

Progression of the malignancy during the study should not be reported as a serious adverse event. Adverse events associated with disease progression may be reported as serious adverse events. If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy or axicabtagene ciloleucel, then the event leading to death must be recorded as a serious adverse event with CTCAE Grade 5.

Death must be reported if it occurs during the serious adverse event reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of the axicabtagene ciloleucel infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring greater than 3 months after the axicabtagene ciloleucel infusion requires expedited reporting within 24 hours only if it is considered related to treatment.

Following the completion of KTE-C19-101, any relevant information on ongoing SAEs must be submitted to Kite Safety and Pharmacovigilance within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via e-mail to the SAE Reporting mailbox: safety_FC@gilead.com

9.5. Reporting Deaths

Deaths that occur during the protocol-specified adverse event reporting period that are attributed by the investigator solely to progression of underlying lymphoma should be recorded as SAEs with the preferred term "B-cell lymphoma" and must be reported immediately to the sponsor. Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. The term "unexplained death" should be captured if the cause of death is not known. However, every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy). Deaths during the post-study survival follow-up due to underlying cancer should be recorded only on the Survival Status CRF.

9.6. Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the AE form. The exception is for CRS where both the diagnosis and signs and symptoms will be captured on the CRF AE form. For signs and symptoms of the underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

9.7. Pregnancy and Lactation

There is no relevant clinical experience with axicabtagene ciloleucel in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) through at least 6 months after conditioning chemotherapy dosing or axicabtagene ciloleucel dosing, whichever is longer. Male subjects are recommended not to father a child for at least 6 months after completing conditioning chemotherapy dosing or axicabtagene ciloleucel dosing, whichever is longer.

If a pregnancy occurs in a female subject enrolled into the study, or a female partner of a male subject, within 6 months of completing the conditioning chemotherapy or axicabtagene ciloleucel dosing (whichever is longer), the pregnancy must be reported to the key sponsor contact. Information regarding the pregnancy and/or the outcome may be requested by the key sponsor.

The pregnancy should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the pregnancy event.

If a lactation case occurs while the female subject is taking protocol required therapies report the lactation case to the key sponsor contact.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol required therapies through 6 months.

Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

9.8. Hospitalization and Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event as described in Section 9.4.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for palliative care or hospice care
- Planned hospitalization required by the protocol (eg, for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying cancer

9.9. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an adverse event. A vital sign result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the CRF.

9.10. Safety Review Team and Dose-limiting Toxicity

Phase 1 Study

The SRT will be specifically chartered to review safety data during Phase 1 of the study and make recommendations on further study conduct in Phase 1 and progression to Phase 2 based on the incidence of axicabtagene ciloleucel DLT and review of serious adverse events.

Dose-limiting toxicity is defined as the following axicabtagene ciloleucel-related events with onset within the first 30 days following axicabtagene ciloleucel infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer
- Grade 4 thrombocytopenia lasting longer than 35 days from the day of cell transfer
- Any axicabtagene ciloleucel-related adverse event requiring intubation, including Grade 4 confusion requiring intubation for airway protection is considered to be a DLT.
- All other Grade 3 toxicities lasting more than 3 days and all Grade 4 toxicities, with the exception of the following conditions which are not considered DLTs:
- Aphasia/dysphasia or confusion/cognitive disturbance which resolves to Grade 1 or less within 2 weeks and to baseline within 4 weeks
- Fever Grade 3
- Myelosuppression (includes bleeding in the setting of platelet count less than 50 $x10^9$/L and documented bacterial infections in the setting of neutropenia), defined as lymphopenia, decreased hemoglobin, neutropenia and thrombocytopenia unless neutropenia and thrombocytopenia meet the DLT definition described above
- Immediate hypersensitivity reactions occurring within 2 hours of cell infusion (related to cell infusion) that are reversible to a Grade 2 or less within 24 hours of cell administration with standard therapy
- Hypogammaglobulinemia Grade 3 or 4

As noted in Section 6.4 CRS will be graded according to a revised grading system {Lee 2014}. Adverse events attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT.

During Phase 1, approximately 6 to 24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens.

Subjects in each cohort will be evaluated for DLTs within the first 30 days following the completion of their respective axicabtagene ciloleucel infusion. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.5 . The SRT will make recommendations based on the incidence of DLT and overall safety profile of the axicabtagene ciloleucel regimen. If the subject incidence of DLT is ≤ 1 of 6 subjects, Cohort B1 may be explored or the study may proceed to Phase 2 of the trial. This decision will be based on overall benefit/risk and available biomarker data.

However, if 2 of the 6 enrolled subjects present with a protocol defined DLT during Phase 1, the SRT may recommend enrolling 2 additional sets of 3 subjects (up to 12 subjects in total) at the same dose that was administered in the first 6 subjects. In this scenario, progression to an additional cohort or to Phase 2 of the study will proceed if ≤ 2 of the first 9 or if ≤ 3 of the 12 subjects present with a DLT.

If the subject incidence of DLT is > 2/6, > 3/9, or > 4/12 subjects, other axicabtagene ciloleucel regimens may be explored in an additional 6 to 12 subjects (Figure 3). The same DLT rules apply as above.

9.11. Data Safety Monitoring Board

Phase 2 Pivotal Study

An independent DSMB will meet during the Phase 2 pivotal portion of the study when 20 and 50 subjects in the mITT set of Cohort 1 have had the opportunity to complete the 3-month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit.

Phase 2 Safety Management Study

The DSMB will also meet to review safety data when 20 subjects in Cohort 3, Cohort 4, Cohort 5, and Cohort 6 have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days, respectively. The DSMB may meet more often as needed. In addition, Kite Pharma or delegate will submit SAEs or suspected unexpected serious adverse reactions (SUSARs) to the DSMB chair for risk benefit analysis. The DSMB Chair will review reported SAEs at least monthly and SUSARs as soon as received.

NOTE: Cohort 6 is not open for enrollment in Germany.

9.12. Criteria to Pause Enrollment

Phase 2 Pivotal Study

As part of its oversight of the study, the DSMB also will assess criteria to pause enrollment after 10, 20, 30, and 50 subjects in the Phase 2 pivotal portion of the study have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following criteria is met:

225) Subject incidence of Grade 5 axicabtagene ciloleucel-related adverse events within 30 days is > 10%.

or

226) Subject incidence of the following Grade 4 axicabtagene ciloleucel-related adverse events lasting more than 7 days is > 33%:

- Neurologic toxicities

- CRS (per Lee 2014 criteria) {Lee 2014}
- Other non-hematological serious adverse event
- Infection (treatment-related)

10. STATISTICAL CONSIDERATIONS

The primary objective of the Phase 1 Study is to evaluate the safety of axicabtagene ciloleucel regimens. The primary objective of the pivotal Phase 2 portion is to evaluate the efficacy of axicabtagene ciloleucel, as measured by ORR in subjects with DLBCL, PMBCL, and TFL. Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints. Inferential testing will only be performed for efficacy for Phase 2 pivotal study Cohort 1 and Cohort 2. For the Phase 2 safety management study, Cohort 3, Cohort 4, Cohort 5, and Cohort 6, the primary objective is to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, or prophylactic steroids on the rate and severity of CRS and neurologic toxicities.

NOTE: Cohort 6 is not open for enrollment in Germany.

10.1. Hypothesis

Phase 2 pivotal study Cohort 1 and Cohort 2: This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the ORR to axicabtagene ciloleucel in Cohort 1 and Cohort 2 is significantly greater than 20%.

Phase 2 safety management study Cohort 3, Cohort 4, Cohort 5, and Cohort 6: No hypothesis will be tested in Cohort 3, Cohort 4, Cohort 5, and Cohort 6, which will be used to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, or prophylactic steroids on the rate and severity of CRS and neurologic toxicities.

10.2. Study Endpoints

10.2.1. Primary

Phase 1 study: Incidence of adverse events defined as DLT.

Phase 2 pivotal study: ORR, defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by the study investigators. All subjects who do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders.

Phase 2 safety management study: incidence and severity of CRS and neurologic toxicities.

10.2.2. Secondary

Duration of response (DOR): Among subjects who experience an objective response, DOR is defined as the date of their first objective response (which is subsequently confirmed) to disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} or death regardless of cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing.

ORR among subjects in Phase 1 will be summarized.

ORR per Independent Radiological Review Committee **(**IRRC**)** (Phase 2): ORR per IRRC is defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by the IRRC. All subjects that do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders.

Progression-free Survival (PFS): PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

OS: OS is defined as the time from axicabtagene ciloleucel infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

Incidence of adverse events and clinical significant changes in safety lab values.

Incidence of anti-axicabtagene ciloleucel antibodies, levels of anti-CD19 CAR T cells in blood, and levels of cytokines in serum will be summarized.

Additional Phase 2 Safety management study secondary endpoints include the following:

- ORR for subjects treated in the safety management study Cohort 3, Cohort 4, Cohort 5, and Cohort 6
- Changes over time in the EQ-5D scale score and EQ-5D VAS score for subjects treated in Cohort 3, Cohort 4, Cohort 5 and Cohort 6

10.2.3. Exploratory Endpoints

- ORR and duration of second response among subjects retreated with axicabtagene ciloleucel (Section 7.13.10).
- ORR and DOR as determined by IWG Response Criteria for Malignant Lymphoma {Cheson 2014}.
- Biomarkers based on assessment of blood cells, tumor cells and the proposed actions of the investigational product.

10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 268 to 286 subjects.

Phase 1 Study: Six to 24 subjects will be enrolled into each cohort in Phase 1 of this study.

If the study proceeds to Phase 2 pivotal study, approximately 72 subjects will be enrolled into Cohort 1, and approximately 20 subjects will be enrolled into Cohort 2.

In the Phase 2 safety management study, approximately 40 subjects will be enrolled into Cohort 3, approximately 40 subjects will be enrolled and dosed into Cohort 4, approximately 50 subjects will be enrolled and dosed into Cohort 5**,** and approximately 40 subjects will be enrolled and dosed into Cohort 6.

ORR and all analyses based on the objective response (objective response, duration of response, progression-free survival) in the Phase 1 and Phase 2 portions of the study will be based on a mITT population consisting of all subjects who receive the target dose of axicabtagene ciloleucel.

Inferential testing will be performed only for efficacy for Phase 2 pivotal study Cohort 1 and Cohort 2. For Cohort 3, Cohort 4, Cohort 5, and Cohort 6**,** the primary objective will be to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, or prophylactic steroids on the rate and severity of CRS and neurologic toxicities. ORR with axicabtagene ciloleucel treatment in subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL in Cohort 3, Cohort 4, Cohort 5, and Cohort 6 will be a secondary endpoint, and the analysis will be descriptive.

10.3.1. Phase 2 Pivotal Study, Cohort 1, and Cohort 2

This study uses a single arm design to test for an improvement in response rate in the DLBCL cohort (approximately n=72) and in Cohorts 1 and 2 combined (n=92). For the test of efficacy this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha level of 0.025.

The overall 1-sided alpha level of 0.025 will be divided between the inference on Cohort 1 and the inference in Cohorts 1 and 2 combined using the methodology described in {Song 2007, Wang 2007}. The objective response for Cohort 1 will be tested at a 1-sided alpha level of 0.0220 and the objective response in Cohort 1 and 2 combined will be tested at a 1-sided alpha level of 0.0075.

Within Cohort 1, 2 interim and 1 primary analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will be for futility only. This futility analysis is based on a rho (parameter 0.35) beta spending function, with a nominal alpha level for the assessment of futility of 0.393. If the criteria for futility are not met, accrual to Phase 2 will continue. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.

- Interim analysis 2 will be conducted after 50 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will assess early demonstration of efficacy. This interim analysis is based on a Pocock boundary of the Lan-DeMets family of alpha spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.017. Under the alternative hypothesis, the likelihood of achieving the criteria for early efficacy is 84%. If the criteria for early efficacy are not met at this analysis, the planned primary analysis of

Cohort 1 will occur when 72 subjects in the mITT set of Cohort 1 have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion.

- The primary analysis of Cohort 1 will occur after 72 subjects in the mITT set have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion. The nominal alpha level for the assessment of efficacy at the primary analysis is 0.011.

Accrual to the study will continue during interim analysis 1 and interim analysis 2 of Cohort 1.

For Cohorts 1 and 2 combined, 1 primary analysis will be performed when 72 subjects in the mITT set in Cohort 1 and 20 subjects in the mITT set in Cohort 2 have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion. This testing will be performed at a 1-sided alpha level of 0.0075. Descriptive confidence intervals about the ORRs within Cohorts 1 and 2 will be presented with the inferential analysis of Cohorts 1 and 2 combined.

As indicated above, inferential testing of Cohort 1 will occur when 72 subjects in the mITT set in Cohort 1 have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion. The efficacy data from any additional subjects (beyond 72) enrolled into Cohort 1 will be analyzed descriptively. Similarly, inferential testing of Cohorts 1 and 2 will occur when 72 subjects in the mITT set of Cohort 1 and 20 subjects in the mITT set of Cohort 2 have had the opportunity to be followed for 6 months following the axicabtagene ciloleucel infusion. The efficacy data from any additional subjects (beyond 92) enrolled into Cohorts 1 and 2 will be analyzed descriptively.

The derivation of the alpha levels for the test of Cohort 1 and the overall study population were originally obtained under the assumption of 40 subjects enrolled into Cohort 2. These original derivations are retained in this protocol amendment as they result in a more conservative alpha level for the test of Cohort 1.

This procedure preserves the designated alpha level (1-sided) of 0.025 and has ≥ 90% power. Simulation (10,000 replicates) via R version 3.1.0 and EAST version 6.3 were used to evaluate the operating characteristics of this design.

10.3.2. Phase 2 Safety Management Study

The primary objective of Phase 2 safety management study Cohort 3, Cohort 4, Cohort 5, and Cohort 6 is to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, or prophylactic steroids on the rate and severity of CRS and neurologic toxicities. The assessment of ORR is a secondary objective, and the analysis will be descriptive.

10.4. Statistical Assumptions

Phase 1 Study

The primary endpoint for the Phase 1 portion of the study is the incidence of DLT.

Phase 2 Pivotal Study

Cohorts 1 and 2 of this trial will enroll subjects with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

Treatment outcomes for subjects refractory to primary therapy or non-responsive to second line therapy are provided in Section 2.1, Table 1. As indicated, the response to salvage therapy for these patients ranged from 0% to 26%. Additionally, a retrospective review of data in refractory DLBCL from 4 institutions {Crump 2017} indicate a response rate of 26% among 636 patients with refractory disease. Based on these data, it is anticipated that the historical control for the ORR in the chemo-refractory population targeted in this study will be approximately 20%.

Phase 2 Safety Management Study

Analyses of the safety and efficacy endpoints will be descriptive, with no formal statistical testing being performed. Subject incidence rates of treatment-emergent CRS, neurologic toxicities, axicabtagene ciloleucel-related adverse events, and ORRs will be summarized by cohort. DOR, PFS, and OS will also be summarized by cohort.

10.5. Analysis Subsets

10.5.1. Phase 1 Study

Depending on the dosing cohort and results of the Phase 1 portion of the study, axicabtagene ciloleucel may be:

- administered as a single infusion at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg (± 20%). For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells will be administered. A minimum dose of 1 x 10^6 anti-CD19 CAR T cells/kg may be administered; or

- administered as a single infusion at a target dose of 1 x 10^6 anti-CD19 CAR T cells/kg (± 20%) in the Phase 2 portion of the study. In this case, for subjects weighing greater than 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR T cells will be administered. A minimum dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg may be administered.

The DLT evaluable set (Phase 1 only), defined for each dosing cohort in Phase 1, will include subjects treated in the Phase 1 dosing cohort who:

- received the target and were followed for at least 30 days after the anti-CD19 CAR T cell infusion; or

- received a dose of anti-CD19 CAR T cells lower than the target for that cohort and experienced a DLT during the 30 day post-infusion period.

If needed, more subjects will be enrolled to achieve 6 DLT evaluable subjects at the target dose for each cohort.

Safety set: the safety set is defined as all subjects treated with any dose of axicabtagene ciloleucel.

10.5.2. Phase 2 Study

In the Phase 2 portion of the study (including the Phase 2 pivotal study and SMS), subjects are to be dosed at a target of 2 x 10^6 anti-CD19 CAR T cells/kg. A minimum dose of 1 x 10^6 anti-CD19 CAR T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells will be administered. Subjects are considered to have received the target dose if they receive 1 x 10^6 anti-CD19 CAR T cells/kg up to 2 x 10^6 anti-CD19 CAR T cells/kg or, if the subject weighs more than 100 kg, the subject receives 2 x 10^8 anti-CD19 CAR T cells.

Modified Intent-to-Treat Set: the mITT set will consist of all subjects enrolled and treated with axicabtagene ciloleucel at a dose of at least 1 x 10^6 anti-CD19 CAR T cells/kg.

This analysis set will be used for all analyses of objective response and endpoints based on objective response (objective response, duration of response, progression-free survival) for both the Phase 1 and Phase 2 portions of the study (including both pivotal and SMS).

Safety analysis set: the safety analysis set is defined as all subjects treated with any dose of axicabtagene ciloleucel.

Full Analysis set (FAS): the full analysis set will consist of all enrolled subjects and will be used for the summary of subject disposition, sensitivity analyses of ORR and DOR, and subject listings of deaths.

10.6. Access to Individual Subject Treatment Assignments

This is a single arm, open-label study and subjects and investigators will be aware of treatment received. Data handling procedures for the Phase 2 portion of the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan, DSMB charter, and Trial Integrity Document.

10.7. Interim Analysis

10.7.1. Interim Analysis and Early Stopping Rules

Phase 1 Study

The SRT will be chartered to review safety during Phase 1 of the study only and make recommendations on further study conduct in Phase 1 and progression to Phase 2.

Phase 2 Pivotal Study

An independent DSMB will be formed to review accumulating safety and efficacy data 2 times during the Phase 2 pivotal study, when 20 and 50 subjects in the mITT set in Cohort 1 have had the opportunity to complete the 3-month disease assessment.

The DSMB will also monitor criteria to pause enrollment (see Section 9.12).

Phase 2 Safety Management Study

The DSMB will review safety data when 20 subjects treated in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** have had the opportunity to be followed for 30 days, respectively.

10.7.2. Safety Interim Analysis

The DSMB will review AE and SAE information on a regular basis throughout subject treatment in Phase 2 of the study. The DSMB may request additional safety data or to modify the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate timely DSMB review.

10.7.3. Efficacy Interim Analysis

Phase 2 Pivotal Study

Within Cohort 1, two interim analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will be for futility only. This futility analysis is based on a rho (parameter 0.35) beta spending function, with a nominal alpha level for the assessment of futility of 0.393. If the criteria for futility are not met, accrual to Phase 2 will continue. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.

- Interim analysis 2 will be conducted after 50 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will assess early stopping for efficacy. This interim analysis is based on a Pocock boundary of the of the Lan-DeMets family of alpha spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.017. Under the alternative hypothesis, the likelihood of achieving the criteria for early efficacy is 84%. If the criteria for early efficacy are not met at this analysis, the planned primary analysis of Cohort 1 will occur when 72 subjects in the mITT set of Cohort 1 have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion.

Phase 2 Safety Management Study

There is no planned efficacy interim analysis for this portion of the study.

10.8. Planned Method of Analysis

Phase 1 Study

Descriptive analysis of the Phase 1 portion of the study may occur at any time.

Phase 2 Pivotal Study

The primary efficacy analyses of Cohort 1 will be performed when 72 subjects in the mITT set of Cohort 1 have had the opportunity to be evaluated for response 6 months after the axicabtagene ciloleucel infusion. The primary analysis of Cohorts 1 and 2 combined will be performed when 72 subjects in the mITT set of Cohort 1 and 20 subjects in the mITT set of Cohort 2 have had the opportunity to be evaluated for response at 6 months after the target axicabtagene ciloleucel infusion. Additional analyses may occur after the primary analysis. These additional analyses will be descriptive and will occur after inferential testing has been performed. The final analysis will occur when all subjects have completed the study.

The primary endpoint of ORR for all analyses (futility, interim, and primary) will be based on investigator review of disease assessments in the mITT set. For Cohorts 1 and 2, sensitivity analyses of ORR based on central radiologic review of disease assessments will be performed.

Analyses of efficacy endpoints will be summarized by study phase, for Cohort 1 alone, for Cohort 1 and Cohort 2 combined, and for Cohort 3 alone. Analyses of safety endpoints will be evaluated by study phase, cohort, Cohort 1 and 2 combined.

Phase 2 Safety Management Study

The primary analysis of Cohort 3, Cohort 4, Cohort 5, and Cohort 6 will occur after all treated subjects in each cohort have had the opportunity to be followed for 6 months, respectively. The ORR in Cohort 3, Cohort 4, Cohort 5, and Cohort 6 will be based on investigator review of disease assessment in the mITT set. No central radiologic review of disease assessment will be performed for these cohorts.

Descriptive analyses of the Phase 2 SMS Cohort 3, Cohort 4, Cohort 5, and Cohort 6 may occur at any time.

10.8.1. Objective Response Rate

The incidence of objective response and exact 2-sided 95% confidence intervals will be generated. For the Phase 2 pivotal study, Cohort 1 and Cohort 2, an exact binomial test will be used to compare the observed response rate to a response rate of 20%.

10.8.2. Duration of Response

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for duration of response. Estimates of the proportion of subjects in response at 3-month intervals from the first response will be provided**.** The competing-risk analysis method {Fine 1999, Pepe 1991} may be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence of non-disease related mortality (the competing risk) may be estimated along with 2-sided 95% confidence intervals at 3-month intervals.

10.8.3. Progression-free Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for progression-free survival time. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided.

10.8.4. Overall Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

10.8.5. Safety

Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4 Grade 3 or higher and treatment related AEs reported throughout the conduct of the study will be tabulated by preferred term and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

For Cohort 3, Cohort 4, Cohort 5, and Cohort 6, the incidences and severity of CRS and neurologic toxicities may be compared to the rates in Cohort 1 and Cohort 2 combined with a binomial test.

Tables and/or narratives of deaths through the long-term follow-up and treatment related SAEs will be provided.

10.8.6. Long-term Data Analysis

All subjects will be followed for survival status for up to 15 years after receiving axicabtagene ciloleucel. LTFU data analysis will be performed on subjects in this study and after transition to the KT-US-982-5968 LTFU study. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

11. REGULATORY OBLIGATIONS

11.1. Independent Review Board/Independent Ethics Committee

A copy of the protocol, ICF and any additional subject or trial information such as subject recruitment materials must be submitted to each sites respective IRB/IEC for approval. Once approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site specific and study serious adverse events (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2. Subject Confidentiality

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number
- Date of birth or year of birth/age at time of enrollment will be reported according with local laws and regulations

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth or year of birth (as per their local reporting requirements for both initials and date of birth)

Per federal regulations and International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) guidelines, investigators and institutions are required to permit authorization to the sponsor, contract research organization (CRO), IRB/IEC and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records which includes personal information.

11.3. Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the investigators agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact.

Both Kite Pharma and the investigator reserve the right to terminate the investigator's participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at is sole discretion, to determine whether to manufacture axicabtagene ciloleucel T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data and records for which the study data are collected and verified. Examples of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries. CRF entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject identification lists
- Protocols and protocol amendments, IB, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records and experimental product related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator's agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility (ies), review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in study KTE-C19-101 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on
- Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individual who accepts direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma for review and approval. The study contract between the institution, principal investigation and Kite Pharma or its delegate will outline the requirements for publication review.

16. COMPENSATION

Kite Pharma will provide compensation for study related illness or injury pursuant to the information outlined in the injury section of the ICF.

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18. APPENDICES

Appendix 1. Revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}

Complete Remission (CR): CR requires all of the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- Typically FDG-avid lymphoma (large cell, mantle cell and follicular lymphomas are all typically FDG-avid): in subjects with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
- The spleen and/or liver, if considered to be enlarged before therapy on basis of physical exam or CT scan, must should be normal size on CT scan and not be palpable on physical examination and nodules thought to represent lymphoma must no longer be present.
- A bone marrow aspirate and biopsy is performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. The biopsy core sample must be a minimum of 20 mm in length.

Partial Remission (PR): PR requires all of the following:

- ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible and should include mediastinal and retroperitoneal nodes if possible.
- No increase in size of nodes, liver or spleen and no new sites of disease.
- If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for single nodules.

- Bone marrow is irrelevant for determination of a PR. If patient has persistent bone marrow involvement and otherwise meets criteria for CR the patient will be considered a PR.

- Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site. Note: in subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated in subjects with one or at most two residual masses that have regressed by 50% on CT scan.

Stable Disease (SD):

- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PET should be positive in typically FDG-avid lymphomas.

Progressive Disease:

Defined by at least one of the following:

- ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node.

- Appearance of a new lesion greater than 1.5 cm in any axis even if other lesions are decreasing in size

- Greater than or equal to a 50% increase in size of splenic or hepatic nodules

- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

- Lesions should be PET positive in typically FDG-avid lymphomas unless the lesion is too small to be detected by PET (< 1.5 cm in its long axis by CT)

Appendix 2. Monitoring of subjects after IP administration per country regulatory agencies:

Germany:

The post-infusion monitoring of subjects, described in Section 7.13.7.2 in this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 11, column "IP administration period, 1-7". The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see Section 7.4), blood draw for chemistry panel with CRP, blood draw for CBC w/differential (see Section 7.11), and neurological assessment**.** Any observed toxicity will be managed according to Section 6.4 of this protocol.

France:

The post-infusion monitoring of subjects in this protocol will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 11, column "IP administration period, 1-7." The L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) recommends a 10-day hospitalization after infusion of any CAR T-cell product.

The daily monitoring will include vital signs (see Section 6.4), blood draw for chemistry panel with CRP, blood draw for CBC w/differential (see Section 7.11), and neurological assessment. Any observed toxicity will be evaluated according to Section 6.4 of this protocol.

CLINICAL STUDY PROTOCOL

A PHASE 2 MULTICENTER STUDY OF AXICABTAGENE CILOLEUCEL IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA (INHL)

Protocol Number:	KTE-C19-105 (ZUMA-5)
USAN/INN:	Axicabtagene ciloleucel
Company Code:	KTE-C19
IND Number:	016278
ClinicalTrials.gov Identifier	NCT03105336
EUDRACT:	2017-001912-13
Clinical Study Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Key Sponsor Contacts:	The medical monitor name and contact information is provided on the Key Study Team Contact List
Original Protocol Date: **Protocol Amendment #1:** **Protocol Amendment #2:** **Protocol Amendment #3:** **Protocol Amendment #4:** **Protocol Amendment #5:** **Protocol Amendment #6:**	26 Nov 2016 29 Aug 2017 19 Jan 2018 07 Sep 2018 29 Nov 2018 24 Jul 2019 08 Jul 2020
Protocol Amendment Number and Date:	Amendment #7
Date:	22 February 2023

This study will be conducted under United States (US) Food and Drug Administration (FDA) Investigational New Drug (IND) application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the IND application and are not considered to be IND application sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable regulatory and local requirements.

CONFIDENTIALITY STATEMENT

This document contains confidential information of Kite Pharma Inc., a wholly owned subsidiary of Gilead Sciences, Inc. This document must not be disclosed to anyone other than the study site research staff and members of the institutional review board/independent ethics committee, a scientific review board, or an equivalent. The information in this document cannot be used for any purpose other than the conduct of the clinical investigation without the prior written consent of Kite Pharma, Inc.

PROTOCOL SYNOPSIS

Title:	A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (iNHL)
Indication:	Adult subjects with relapsed or refractory (r/r) B-cell iNHL of follicular lymphoma (FL) or marginal zone lymphoma (MZL) histological subtypes.
Study Design:	Study KTE-C19-105 is a Phase 2, multicenter, single-arm, open-label study of axicabtagene ciloleucel in subjects with r/r iNHL. Up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set**,** will be enrolled and treated with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2 x 10^6 autologous, genetically modified, anti-CD19 chimeric antigen receptor (CAR) T cells per kg body weight. Each subject will proceed through the following study periods: • Screening • Enrollment/Leukapheresis • Conditioning chemotherapy • Investigational product (IP) treatment • Post-treatment assessment • Long-term follow-up
Study Objectives:	The primary objective is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR), in subjects with relapsed or refractory (r/r) B-cell iNHL. Key secondary objectives are to characterize the safety profile, complete response (CR) rate, ORR among those subjects with 3 or more lines of prior therapy, CR rate among those subjects with 3 or more lines of prior therapy, and to determine duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Additional secondary objectives will include additional safety and pharmacokinetic/pharmacodynamic endpoints and the time to next therapy endpoint.

Hypothesis:	Four hypotheses will be tested using a fixed sequence procedure in terms of ORR and CR to control the overall type I error at 1-sided alpha level of 0.025 with the following test order: Hypothesis 1 (H_1): test for ORR as determined by central review, if significant then Hypothesis 2 (H_2): test for CR rate as determined by central review, if significant then Hypothesis 3 (H_3): test for ORR as determined by central review in the subjects who have had 3 or more prior lines of therapy, if significant then Hypothesis 4 (H_4): test for CR rate as determined by central review in the subjects who have had 3 or more prior lines of therapy The hypotheses H_1 through H_4 will be assessed at the time of the interim analysis 3, 4, and 5 and the primary analysis. The H_1 is that the ORR, as determined by central review, to axicabtagene ciloleucel is significantly greater than 40% in subjects with the FL histological subtype in the inferential analysis set. The H_2 is that the CR rate, as determined by central review, to axicabtagene ciloleucel is significantly greater than 15% in subjects with the FL histological subtype in the inferential analysis set. The H_3 is that the ORR, as determined by central review, to axicabtagene ciloleucel is significantly greater than 40% in subjects with FL in the inferential analysis set who have had 3 or more prior lines of therapy. The H_4 is that the CR rate, as determined by central review, to axicabtagene ciloleucel is significantly greater than 15% in subjects with FL the inferential analysis set who have had 3 or more prior lines of therapy. No formal hypothesis testing is planned for MZL histological subtype. The analysis will be descriptive.
Primary Endpoint:	ORR, defined as complete response (CR) + partial response (PR) per the Lugano Classification {Cheson 2014} as determined by central review. These assessments will be referred to as “central read” in this document.

Secondary Endpoints:	• CR rate, defined as CR per the Lugano Classification {Cheson 2014} by central read • ORR, defined as CR + PR per the Lugano Classification {Cheson 2014} by central read for those subjects who have had 3 or more prior lines of therapy • CR rate, defined as CR per the Lugano Classification {Cheson 2014} by central read for those subjects who have had 3 or more prior lines of therapy • Incidence of adverse events (AEs) and clinically significant changes in laboratory values • DOR • PFS • OS • Incidence of antibodies to axicabtagene ciloleucel • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines in serum • Time to next therapy
Key Covariates for ORR and Other Key Safety and Efficacy Endpoints:	• Age (< 65, ≥ 65 years) • Gender • Race • Ethnicity • Relapsed vs refractory disease status at study entry • Follicular Lymphoma International Prognostic Index (FLIPI) score • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 • Time to relapse from completion of first anti-CD20-chemotherapy combination therapy (≥ 24 months vs < 24 months) • Disease burden, as defined by Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria • Histological diagnosis by both local and central pathology • Prior PI3K inhibitor • Number of prior lines of therapy (excluding single agent anti-CD20 antibody as a line of therapy) • Double refractory (subjects refractory to the first 2 lines of therapy)

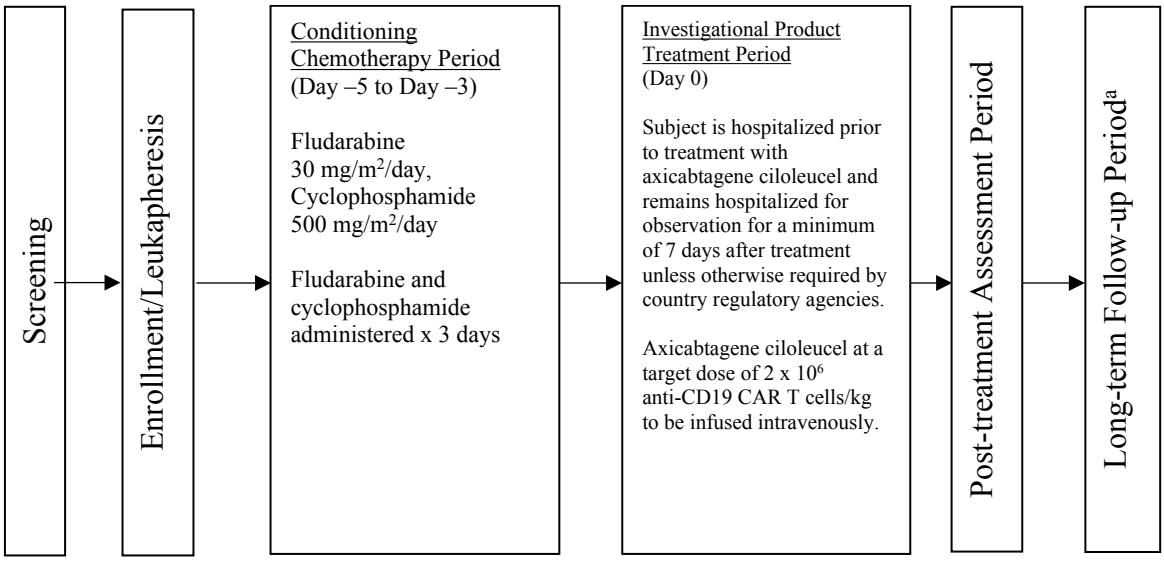
Sample Size:	Up to approximately 160 enrolled and treated subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set.
Duration of Study Participation	The duration of study participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, and survival. After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will transition to a separate Kite Pharma, Inc-sponsored long-term follow-up (LTFU) study, KT-US-982-5968 where they will complete the remainder of the 15 year follow-up assessments. Additional information is available in Section 3.5.
Study Eligibility:	Refer to Section 5 for a detailed list of inclusion and exclusion criteria.
Treatment (IP):	Axicabtagene ciloleucel treatment consists of a single infusion of CAR-transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. Refer to Section 6 for treatment details.
Conditioning Chemotherapy Treatment:	Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.
Procedures:	At specific time points as outlined in the schedule of assessments, subjects will undergo the following procedures: collection of informed consent; general medical history, including previous treatments for B-cell iNHL; physical exam (including neurological exam), including vital signs and performance status; blood draws for complete blood count (CBC); chemistry panels; cytokines; C-reactive protein; lymphocyte subsets; antibodies to axicabtagene ciloleucel; replication-competent retrovirus (RCR); and anti CD19 CAR T-cell analysis. Women of childbearing potential will undergo a urine or serum pregnancy test. Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), a positron emission tomography-computed tomography (PET-CT), possible bone marrow aspirate and biopsy, and leukapheresis.

Data Safety Monitoring Board:	An independent Data Safety Monitoring Board (DSMB) will have ongoing oversight of the study and will monitor data during this study. The DSMB will first meet to review safety data when 10 subjects are enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks from the date of axicabtagene ciloleucel infusion. The DSMB will meet again to review the safety data when 30 subjects are enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks from the date of axicabtagene ciloleucel infusion. The DSMB will meet again to review the safety data when 30 subjects with FL in the inferential set are enrolled and treated with axicabtagene_ciloleucel and have had an opportunity to be followed for 6 months from the date of axicabtagene_ciloleucel infusion. The DSMB will meet again to review the safety data when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months from the date of axicabtagene ciloleucel infusion. The DSMB will meet again to review the safety data when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 9 months from the first disease response assessment. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk vs benefit. The DSMB may meet more often as needed. Refer to Section 9.9.
Statistical Considerations:	The primary endpoint for the study is ORR per the Lugano Classification {Cheson 2014} as determined by central read. The study will enroll and treat up to approximately 160 subjects including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential set. The study uses a single-arm design of the subjects with FL in the inferential analysis set to test for an improvement in response rates (ORR and CR rate), with descriptive analyses being conducted for the subjects with MZL. For the test of primary efficacy in at least 80 subjects with FL in

	the inferential analysis set, this study has approximately 93% power to test the null hypothesis that the ORR is 40% versus the alternative hypothesis that the ORR is 60% with a 1-sided alpha level of 0.0237. The following planned analyses will be performed. • Interim analysis 1 will be conducted after 10 subjects in the safety analysis set (Section 10.5) have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. This analysis will be for safety only. • Interim analysis 2 will be conducted after 30 subjects in the safety analysis set (Section 10.5) have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. This analysis will be for safety only. • Interim analysis 3 will be performed when 30 subjects in the FL inferential set have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion. This interim analysis will be for safety and to assess early demonstration of efficacy. This interim analysis is based on the interpolated alpha spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.0003. The study will not be stopped if early efficacy is demonstrated. The analyses of the efficacy endpoints for MZL will be descriptive. • Interim analysis 4 will be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. The nominal alpha level for the assessment of efficacy for this analysis is 0.0005. The study will not be stopped if early efficacy is demonstrated. The analyses of the efficacy endpoints for MZL will be descriptive. • Interim analysis 5 will be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 9 months after the first disease assessment. The nominal alpha level for the assessment of efficacy for this analysis is 0.0005. The study will not be stopped if early efficacy is demonstrated. The analyses of the efficacy endpoints for MZL will be descriptive.

	• The primary analysis will occur after at least 80 subjects with FL in the inferential analysis set have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 12 months after the first disease response assessment. • Follow-up analysis 1 will be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 18 months after axicabtagene ciloleucel infusion. This analysis will be for safety and efficacy and will be descriptive. • Follow-up analysis 2 will be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 24 months after axicabtagene ciloleucel infusion. This analysis will be for safety and efficacy and will be descriptive. • Additional follow-up analyses may be performed as needed to satisfy regulatory requirements, and to perform long-term efficacy, safety, and survival follow-up. • The final analysis will occur after all subjects transition to the LTFU study, KT-US-982-5869.

Figure 1. Study Schema



Abbreviations: CAR, chimeric antigen receptor.

a. Long-term Follow-up Period: After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will complete the remainder of the 15 year follow-up assessments in a separate Kite Pharma, Inc-sponsored long-term follow-up (LTFU) study, KT-US-982-5968.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CPF	Cell processing facility
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EU	European Union
FAS	Full analysis set
FER	Ferritin
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
GELF	Groupe d'Etude des Lymphomes Folliculaires

GM-CSF	Granulocyte macrophage-colony stimulating factor
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
HDT	High-dose chemotherapy
HEENT	Head, eyes, ears, nose, and throat
Hep	Hepatitis
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
ID	Identification
IFN	Interferon
IL	Interleukin
iNHL	Indolent non-Hodgkin lymphoma
IP	Investigational product
IPI	International Prognostic Index
IPM	Investigational Product Manual
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
qPCR	Quantitative polymerase chain reaction
RCR	Replication-competent retrovirus
r/r	Relapsed or refractory

SAE	Serious adverse event
scFv	Single-chain variable fragment
SCT	Stem cell transplantation
SD	Stable disease
SOA	Schedule of assessment
SUSAR	Suspected unexpected serious adverse reaction
TBI	Total body irradiation
TFL	Transformed follicular lymphoma
TNF	Tumor necrosis factor
UE	Unevaluable
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

The primary objective is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR), in subjects with relapsed or refractory (r/r) B-cell iNHL.

Key secondary objectives are to characterize the safety profile, complete response (CR) rate, ORR among those subjects with 3 or more lines of prior therapy, CR rate among those subjects with 3 or more lines of prior therapy, and to determine duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Additional secondary objectives will include additional safety and pharmacokinetic/pharmacodynamic endpoints and the time to next therapy endpoint.

2. DISEASE BACKGROUND AND RATIONALE

Indolent non-Hodgkin lymphomas comprise approximately one-third of malignant lymphomas {Gribben 2007}. Their presentation is typically insidious, with slow-growing lymphadenopathy, organomegaly, and cytopenias. Systemic B symptoms (fever, weight loss, night sweats) and spontaneous tumor lysis or other oncologic emergencies are uncommon during initial stages {Freedman 2018, Gribben 2007, Tan 2013}. The indolent lymphomas are further subdivided by histology, with FL, MZL (inclusive of splenic, nodal, and mucosa-associated lymphoid tissue subtypes), and small lymphocytic lymphoma making up the bulk of diagnoses {Al-Hamadani 2015, Lunning 2012, The Non-Hodgkin's Lymphoma Classification Project 1997}.

FL is the most common iNHL and represents approximately 17% of non-Hodgkin lymphoma (NHL) cases in the United States {Al-Hamadani 2015}, with an incidence of 3.5 new cases per 100,000 person years {Noone 2017}. Like most iNHL subtypes, it is largely considered to be incurable with standard front-line therapies {Wang 2017}. However, advances in the management of this disease over the last several decades have led to a substantial improvement in long-term survival, with 1 retrospective analysis demonstrating a median OS of nearly 20 years from first diagnosis {Tan 2013}.

Despite these strides made in managing FL, outcomes in FL are quite varied {Kahl 2016}. Prognosis of newly diagnosed FL is predicted by one of several clinical risk stratification scores, such as the Follicular Lymphoma International Prognostic Index (FLIPI) {Solal-Céligny 2004} and the FLIPI-2 {Federico 2009}. These scores are adaptations of the International Prognostic Index (IPI) used in aggressive lymphomas and have been shown to stratify patients by outcome into low-, intermediate-, or high-risk subsets. High-risk patients with ≥ 3 FLIPI criteria have a 5-year overall survival rate of 53%, whereas, low-risk patients with ≤ 1 FLIPI criterion have a 5-year survival rate of over 90%.

Patients with limited stage disease may benefit from involved field radiation therapy, chemotherapy, and rituximab, or, in patients who are ineligible for radiation therapy due to disease site, observation {Freedman 2018}. Low-risk patients with advanced stage disease may also be eligible for a period of close disease observation with regular imaging assessments {National Comprehensive Cancer Network 2018}. The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria are commonly used to trigger treatment in such patients. These criteria include bulky disease, B symptoms, splenomegaly, pleural effusions, peritoneal ascites, cytopenias, and leukemia (> 5.0 x 10^9/L malignant cells) {Brice 1997, National Comprehensive Cancer Network 2018}. Patients with indications for systemic therapy are generally treated with one of a variety of regimens shown in Table 1.

Table 1. Treatment Outcomes in First-line Indolent Lymphoma

Regimen	N	Outcome	Reference
Rituximab + bendamustine	514	Improved PFS vs R-CHOP (69.5 m vs 31.2 m)	{Rummel 2013}
Rituximab + CHOP	38	ORR 100%; DOR 83.5 months	{Czuczman 2004}
Rituximab + CVP	321	Improved TTP vs CVP (34 m vs 15 m)	{Marcus 2008}
Rituximab (maintenance)	379	Improved 3-year PFS vs observation (82% vs 36%)	{Ardeshna 2014}
Rituximab + lenalidomide	103	ORR 90%; 3-year PFS 75.3%	{Fowler 2014}

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, prednisone; DOR, duration of response; m, months; N, number; ORR, overall response rate; PFS, progression-free survival; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; TTP, time to progression.

ORRs with front-line chemoimmunotherapy with an alkylator and anti-CD20 monoclonal antibody combination are nearly 100% {Flinn 2014}. However, Casulo and colleagues recently showed that among 588 patients with FL who received first-line R-CHOP, approximately 20% relapsed within 2 years of diagnosis {Casulo 2015}. Importantly, these patients had significantly worse outcomes overall, with 2-year OS of 64% and 5-year OS of 50%, respectively. In contrast, patients without early disease progression had 5-year OS rates of 90%.

Similar findings were reported by Maurer and colleagues, who examined cases from the Mayo Clinic-University of Iowa Specialized Programs of Research Excellence Molecular Epidemiology Resource (SPORE MER) {Maurer 2016}. Their analysis demonstrated that 17% of patients treated with front-line combination chemotherapy with rituximab did not achieve event-free survival (EFS) at 12 months and 29% of patients did not achieve EFS at 24 months. These patients had poor OS outcomes, because they showed increased mortality when compared with an age- and sex-matched control group drawn from the US general population. By contrast, patients who achieved EFS at 12 months and 24 months had mortality rates that were comparable to rates observed in the control population.

These studies reveal a population of patients who are not accurately identified by existing pretreatment prognostication tools like the FLIPI. Whether current standard high-intensity salvage strategies, such as autologous stem cell transplantation (ASCT), can improve long-term survival outcomes remains to be determined. Therefore, patients with FL who experience disease progression within 2 years of diagnosis and treatment with rituximab and chemotherapy represent a group with high need for new and efficacious treatments.

Another group of patients with a high unmet medical need consists of patients with iNHL who have relapsed following more than 1 line of combination chemotherapy, particularly those who progress rapidly following treatment. Patients with iNHL who progress soon (eg, 6 months) after completing treatment are frequently referred to as refractory to agents contained in the regimen. Such patients may be refractory to chemotherapy, rituximab, or both, and tend to have incomplete and short-lived responses.

In 2014, a PI3Kδ inhibitor, idelalisib, was conditionally approved for use by the Food and Drug Administration (FDA) in patients who have relapsed with FL based on published data {Gopal 2014, ZYDELIG 2016}. In this study, 125 patients who were refractory to rituximab and an alkylating agent (defined as lack of response or had experienced relapse within 6 months of completing therapy) were given idelalisib 150 mg twice daily until disease progression, unacceptable drug toxicity, or patient death. The ORR in the overall population was 57%, with 6% achieving a CR. The ORR in FL was 54% (39/72), and in MZL, it was 47% (7/15). The median PFS was 11 months, with a 12-month PFS rate of < 50%, highlighting the need for new therapies.

The drug was associated with significant gastrointestinal side effects with 43% of all treated patients experiencing any grade diarrhea (13% Grade 3 or higher) and 30% reporting nausea. Additionally, Grade 3 or higher elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were seen in 13% and 8% of patients, respectively. Cytopenias were common as well: 27% of patients had Grade 3 or higher neutropenia, and reductions in hemoglobin and platelets were each seen in roughly a quarter of patients. Treatment was discontinued due to adverse events (AEs) in 25 patients (20%), and 42 patients (34%) required dose reductions. Eleven patients died while receiving the study drug or within 30 days of discontinuation.

In 2017, a second PI3K inhibitor (PI3Kδ and PI3Kα inhibitor), copanlisib, received an accelerated approval by the FDA in patients who have relapsed with FL based on published data {ALIQOPA 2017, Dreyling 2017}. In this study, 142 patients with iNHL who had > 2 prior lines of therapy were enrolled; 104 of these patients had FL. Copanlisib was given intravenously at a dose of 60 mg on Day 1, Day 8, and Day 15 of a 28-day cycle. The ORR in the overall population was 59%, with 12% achieving a CR. The median PFS was 11.2 months, and median DOR was 22.6 months. The ORR in FL was 59% (61/104), and the ORR in MZL was 70% (16/23). The drug was associated with significant side effects, with 41% of patients experiencing Grade 3 or higher hyperglycemia, and 24% experiencing Grade 3 hypertension (> 160 mm Hg). Cytopenias were noted, with 24% of patients Grade 3 or higher neutropenia, and 7% experiencing Grade 3 or higher thrombocytopenia. Grade 3 or higher lung infection was observed in 16% of patients.

A number of agents, which are under investigation in relapsed FL, are summarized in {Kahl 2016} and presented in Table 2.

Table 2. Investigational Treatments in Relapsed or Refractory iNHL

Agent	Classification	N	ORR (%)	CR (%)	PFS/TTP	Reference
Lenalidomide vs Lenalidomide + rituximab	Immunomodulator vs Immunomodulator + anti-CD20 mAb	45 46	53 76	20 39	mTTP (y) 1.1 2	{Leonard 2015}
Duvelisib (IPI-145)	PI3K-δ and PI3K-γ inhibitor	83	41	0	mPFS (mo) 8.3	{Flinn 2016}
Ibrutinib	BTK inhibitor	40	37.5	12.5	mPFS (mo) 14	{Bartlett 2018}
Venetoclax (ABT-199)	BCL-2 inhibitor	29	37.9	13.8	mPFS (mo) 11	{Davids 2017}
Polatuzumab vedotin + Rituximab	Anti-CD79b antibody-drug conjugate 2.4 mg/kg 1.8 mg/kg: + anti-CD20 mAb	25 20	76 75	44 10	mPFS (mo) 15 Not reached	{Advani 2015}
Obinutuzumab vs Rituximab	Anti-CD20 mAbs: Obinutuzumab Rituximab	74 75	44.6 33.3	NR NR	mPFS (mo) 17.6 25.4	{Sehn 2015}

Abbreviations: BCL-2, B-cell lymphoma-2; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CR, complete response; mAb. mo, month; mPFS, median progression-free survival; mTTP, median time to progression; N, number; NR, not reported; ORR, objective response rate; y, year.
Note: Table adapted from {Kahl 2016}

High-dose chemotherapy (HDT) followed by ASCT is an option for patients who experience a disease relapse, and can result in subsequent remissions. Randomized data from the pre-rituximab era suggests improved PFS and OS for patients with relapsed FL who are treated with HDT/ASCT vs those who are treated with conventional chemotherapy alone {Schouten 2003}. Retrospective single-institution data suggest that HDT/ASCT is associated with improved survival outcomes in patients with < 3 previous chemotherapies or low FLIPI scores compared with patients who had ≥ 3 prior chemotherapies or high FLIPI scores {Vose 2008}. This finding is supported in the setting of myeloablative therapy followed by ASCT in a retrospective study of patients treated at Dana Farber Cancer Institute and St. Bartholomew's Hospital {Rohatiner 2007}. This conditioning regimen yielded durable remissions, as 48% of patients were disease-free after 10 years of follow-up. Further, after 12-years of follow-up, the remission duration curve plateaued at 48%, suggesting that some patients may be cured of their lymphoma with this treatment approach. However, this therapy was associated with a high risk of secondary myeloid dysplasia or acute myeloid leukemia, which resulted in 15 deaths in this study. The risk of the development of a secondary myeloid neoplasm is further underscored by Friedberg and colleagues {Friedberg 1999} in which the actuarial incidence of myelodysplastic syndrome (MDS) at 10 years following ASCT after cyclophosphamide/total body irradiation (TBI) was nearly 20%. Furthermore, outcomes following diagnosis of MDS in this population were dismal, with the majority of patients exhibiting poor-risk cytogenetics and a median OS of 9.4 months.

The role of allogenic transplantation in relapsed FL is not clear. Evens and colleagues showed similar failure-free survival, but inferior overall survival, due to increased nonrelapse mortality in patients treated with allogenic transplant compared with those treated with ASCT in the rituximab era {Evens 2013}. Reducing the conditioning regimen for allogenic transplant does not seem to alleviate the treatment-related mortality, as shown in a larger retrospective study in which the 3-year nonrelapse mortality was 5% and 22% for ASCT and reduced-intensity allogenic transplant, respectively {Robinson 2013}. Nevertheless, a small, retrospective, single-institution study suggested that patients with a remission duration of ≤ 12 months prior to initiating salvage therapy may show improved disease control and EFS with allogeneic transplant compared with ASCT {Lunning 2016}.

Although currently available therapies for relapsed/refractory iNHL show some benefit, additional therapies are needed. Anti-CD19 chimeric antigen receptor (CAR) T cells with CD28 and CD3ζ signaling domains have shown promising activity in patients with B-cell cancers. While the majority of patients treated with CAR T cells thus far have had aggressive lymphoma and B-cell precursor leukemia, small numbers of subjects with indolent B-cell lymphomas have also been treated. In 2009, Kite Pharma, Inc., (hereafter referred to as Kite or Kite Pharma) initiated a clinical trial in partnership with the National Cancer Institute (NCI; #NCT00924326) using CAR T cells in subjects with NHL and chronic lymphocytic leukemia (CLL). The CAR T cells in the NCI study were manufactured using the same CAR construct used in axicabtagene ciloleucel. Of the 43 subjects who were treated on that protocol, 7 subjects had iNHL {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017}. The subjects with iNHL had a median age of 57 and a median of 3 prior therapies. Study treatment for the first 4 subjects with iNHL was more intense than current designs and consisted of conditioning chemotherapy with cyclophosphamide (60 to 120 mg/kg) for 2 days followed by fludarabine (25 mg/m^2) for 5 days. This conditioning regimen was followed by a single infusion of 3, 11, 13, or 30 x 10^6 anti-CD19 CAR T cells/kg, which was then followed by high dose interleukin (IL)-2 (720000 IU/kg every 8 hours for 4 to 10 doses, where toxicity precluded additional doses) {Kochenderfer 2012}.

The remaining 3 subjects received CAR T cells generated with an improved short-term culture method (6 to 10 days), at 1, 1, or 2 x 10^6 anti-CD19 CAR T cells/kg, respectively, and received and no post infusion IL-2 {Kochenderfer 2015, Kochenderfer 2017}. One subject received a relatively high dose of conditioning chemotherapy, with 120 mg/kg cyclophosphamide {Kochenderfer 2015}. Two subjects received less intense conditioning chemotherapy, with cyclophosphamide (300 or 500 mg/m^2) for 3 days and with fludarabine (25 mg/m^2) for 3 days {Kochenderfer 2017}.

The ORR and CR rate in the 6 subjects with iNHL evaluable for efficacy was 6/6 (100%) and 4/6 (67%), respectively. At the time of the data cutoff in December 2015, at a median follow-up of 24.9 months, 5/6 subjects with iNHL remained in response with a median DOR of 23.9 (11+ to 64.6+) months. Grade ≥ 3 CAR-related AEs occurred in 50% of subjects; Grade ≥ 3 CAR-related cytokine release syndrome (CRS) and neurotoxicity AEs occurred in 29% and 36% of subjects, respectively. All AEs resolved without routine use of tocilizumab or steroids. There were no CAR-related deaths.

Recently, a CAR T-cell study (utilizing a different anti-CD19 CAR) in lymphoma has reported outcomes for 14 patients with FL. This study utilized the University of Pennsylvania CAR construct of anti-CD19 single-chain variable fragment (scfv) fused to a fragment of the 4-1BB costimulatory molecule and the CD3 zeta chain. Ten of 14 patients (71%) achieved a CR at 6 months. Importantly, these responses were maintained, as none of the patients who achieved a CR at 6 months had relapsed at the time of publication (median follow-up of 28.6 months) {Schuster 2017}.

These results suggest that anti-CD19 CAR T cells may help to meet the unmet medical need for effective treatments of relapsed/refractory iNHL.

2.1. CD19 Target Expression

CD19 is a 95 kD transmembrane protein expressed only in the B-cell lineage. It is expressed in all normal B cells starting at the pro-B-cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B-cell malignancies, including all subtypes of B-cell NHL, CLL, and non-T-cell acute lymphoblastic leukemia (ALL) {Blanc 2011} with the exception of multiple myeloma.

2.2. Anti-CD19 Chimeric Antigen Receptor T-cell Product

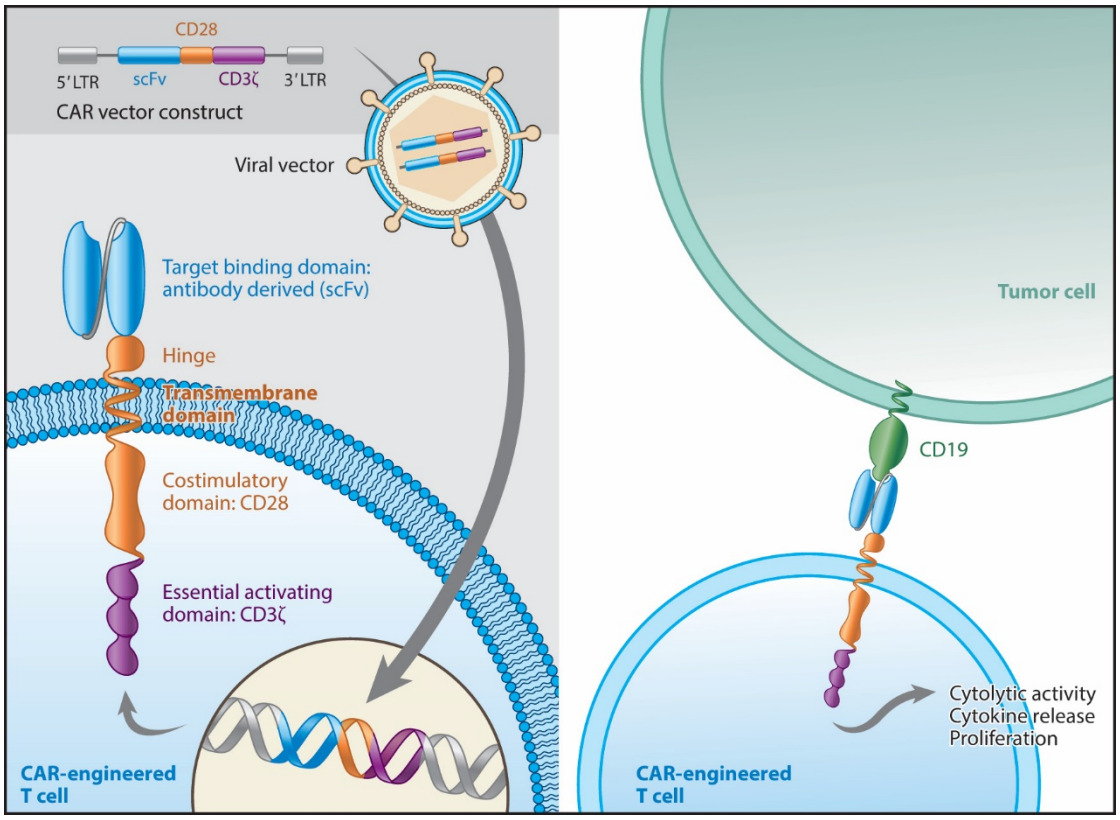
Axicabtagene ciloleucel is an autologous cell therapy product being developed by Kite Pharma. Patient T cells are redirected to recognize CD19 by transducing them with an anti-CD19 CAR. The CAR vector construct utilized in axicabtagene ciloleucel is identical to the one used in NCI protocols (Surgery Branch Protocol 09-C-0082; IND: 13871; Pediatric Branch Protocol 12-C-0112G; IND: 14985). The anti-CD19 CAR vector construct has been designed, optimized, and initially tested at the Surgery Branch of the NCI (Figure 2) {Kochenderfer 2009, Kochenderfer 2010a, Kochenderfer 2010b}.

The anti-CD19 CAR has been engineered to express an extracellular single-chain variable fragment (scFv) with specificity for CD19, linked to an intracellular-signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem. The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 {Nicholson 1997}. A portion of the CD28 co-stimulatory molecule, including the intracellular-signaling domain, is added to the signaling domain of the CD3ζ chain, which is required for T-cell activation {Kowolik 2006}.

The CAR construct is inserted into the T cells' genome by retroviral vector transduction. Briefly, peripheral blood mononuclear cells (PBMCs) are obtained by leukapheresis and Ficoll separation. PBMCs are activated by culturing with an anti-CD3 antibody in the presence of recombinant human IL-2. Stimulated cells are transduced with a retroviral vector containing an anti-CD19 CAR gene and propagated in culture to generate sufficient engineered T cells for administration.

Refer to the current axicabtagene ciloleucel Investigator's Brochure (IB) for additional descriptions of the T-cell product.

Figure 2. Anti-CD19 CAR



Abbreviations: CD, cluster of differentiation; LTR, long terminal repeat; scFv, single-chain variable fragment; CAR, chimeric antigen receptor.

2.3. Axicabtagene Ciloleucel Experience in Diffuse Large B-cell Lymphoma (ZUMA-1 Trial)

ZUMA-1 is a Phase 1/2 multicenter, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in adult subjects with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). The primary analysis for the study, which has been completed, was based on analysis of the data from 101 subjects who had been followed for at least 6 months after infusion of axicabtagene ciloleucel. The study met its primary endpoint: the ORR in these 101 subjects was 82% (95% confidence interval [CI]: 72% to 89%), which was significantly higher than the pre-specified control rate of 20% ($p < 0.001$). The CR rate was 52% {Neelapu 2017}. With a median follow-up of 15.4 months, 42% of subjects had ongoing durable responses.

Refer to the current axicabtagene ciloleucel IB for a summary of the safety and efficacy findings from this study.

2.4. Other Axicabtagene Ciloleucel Study Results

Refer to the current axicabtagene ciloleucel IB for current study results.

3. STUDY DESIGN

3.1. General Study Design

Study KTE-C19-105 is a Phase 2, multicenter, open-label study evaluating the efficacy of axicabtagene ciloleucel in subjects with r/r B-cell iNHL of FL or MZL histological subtypes.

Up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set, will be enrolled and treated with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2×10^6 anti-CD19 CAR T cells per kg body weight.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Conditioning chemotherapy
- Investigational product (IP) treatment
- Post-treatment assessment
- Long-term follow-up (LTFU)

An independent Data Safety Monitoring Board (DSMB) will have ongoing oversight of this study and will review data during this study. The DSMB will first meet to review safety data when 10 subjects in the safety analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. The DSMB will meet for a second time to review safety data after 30 subjects in the safety analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. The DSMB will meet for a third time to review safety and efficacy data after 30 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months. The DSMB will meet for a fourth time when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. The DSMB will meet for a fifth time when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 9 months from the first disease response assessment.

The DSMB will also review serious adverse event (SAE) information and suspected unexpected serious adverse reactions (SUSARs) on a regular basis throughout the study. The DSMB may meet more often as needed.

For details surrounding the DSMB, refer to Section 9.9.

For study requirements assigned to each study period, refer to the schedule of assessments (SOA; Table 3 and Table 4) and Section 7 for details.

A study schema is represented in Figure 1.

3.2. Participating Sites

Approximately 20 centers located in North America and Europe will participate in this study. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

Sites that do not enroll a subject within 3 months of their site being activated will be considered for closure.

3.3. Number of Subjects

Participants in this trial will be referred to as "subjects." It is anticipated that up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set, will be enrolled and treated in this study.

Refer to Section 10 for statistical considerations, including sample size estimations.

3.4. Replacement of Subjects

Clinical trial subjects will continue to be enrolled until the specified numbers are attained in the safety analysis and inferential analysis sets. Subjects who have not received axicabtagene ciloleucel will be retained in the analyses of disposition and safety, where appropriate (see Section 10.5).

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and if applicable, timing of transition to the separate Kite Pharma, Inc-sponsored long-term follow-up (LTFU) study, KT-US-982-5968. After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will transition to the LTFU study.

3.5.2. Completion of Study

Completion of the study is defined as the time at which the last subject transitions to the LTFU study or, while still a participant in this study, is considered lost to follow-up, withdraws consent, or dies. Upon activation of the LTFU study at the subject's study site, the subject will complete LTFU assessments under the LTFU protocol.

3.6. Long-term Follow-up

After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will transition to the LTFU study where they will complete the remainder of the 15 year follow-up assessments. On the LTFU study, subjects will be monitored for the occurrence of late-onset targeted AEs/serious AEs (SAEs) suspected to be possibly related to axicabtagene ciloleucel, occurrence of any product-related SAEs and presence of replication-competent retrovirus (RCR) and/or insertional mutagenesis.

In the LTFU study, subjects will continue assessments at timepoints contiguous with their timepoints in this study.

4. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved consent form before initiating any study-specific procedures or activities that are not part of a subject's routine care. Refer to Section 7 for details.

Each subject who enters the screening period will receive a unique subject identification (ID) number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject.

Furthermore, the subject ID number must remain constant throughout the entire clinical study; it must not be changed after enrollment or if the subject is rescreened or retreated.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

1) Histologically confirmed diagnosis 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 World Health Organization (WHO) 2016 classification

2) Relapsed or refractory disease after 2 or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent. (Single agent anti-CD20 antibody will not count as line of therapy for eligibility.) Stable disease (without relapse) > 1 year from completion of last therapy is not eligible.

3) At least 1 measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma {Cheson 2014}. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy.

4) No known history or suspicion of central nervous system (CNS) involvement by lymphoma.

5) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy and enrollment, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy and enrollment (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists).

6) Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities, such as alopecia).

7) Age 18 or older

8) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

9) Absolute neutrophil count (ANC) ≥ 1000/uL

10) Platelet count ≥ 75000/uL

11) Absolute lymphocyte count ≥ 100/uL

12) Adequate renal, hepatic, pulmonary, and cardiac function defined as:

    a) Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min

    b) Serum ALT/AST ≤ 2.5 upper limit of normal (ULN)

    c) Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome

d) Left ventricular ejection fraction (LVEF) ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant arrhythmias

e) No clinically significant pleural effusion

f) Baseline resting oxygen saturation > 92% on room air

13) Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

5.2. Exclusion Criteria

1) Transformed FL or MZL

2) Small lymphocytic lymphoma

3) FL Histological Grade 3b

4) Lymphoplasmacytic lymphoma

5) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease-free and without anticancer therapy for at least 3 years.

6) ASCT within 6 weeks of planned axicabtagene ciloleucel infusion

7) History of allogeneic stem cell transplantation

8) Prior CD19 targeted therapy, with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for retreatment

9) Prior CAR therapy or other genetically modified T-cell therapy

10) History of severe, immediate hypersensitivity reaction attributed to aminoglycosides

11) Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management.

12) History of human immunodeficiency virus (HIV) infection or active acute or chronic hepatitis (Hep B or Hep C) infection. Subjects with a history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines or applicable country guidelines.

13) Presence of lymphoma that is known to involve the full thickness of the gastric wall.

14) Presence of any indwelling line or drain (eg, 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.

15) Subjects with detectable cerebrospinal fluid malignant cells or known brain metastases or with a history of cerebrospinal fluid (CSF) malignant cells or brain metastases

16) History or presence of non-malignant CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome (PRES), or any autoimmune disease with CNS involvement

17) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

18) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months of enrollment

19) Possible requirement for urgent therapy within 6 weeks after leukapheresis due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome)

20) History of autoimmune disease (eg, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus), resulting in end organ injury or requiring systemic immunosuppression or systemic disease modifying agents within the last 2 years. Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and subjects with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

21) History of symptomatic deep vein thrombosis (DVT) or pulmonary embolism within 6 months of enrollment. History of upper extremity line related DVT within 3 months of conditioning chemotherapy.

22) Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

23) History of severe immediate hypersensitivity reaction to any of the agents used in this study

24) Treatment with a live, attenuated vaccine within 6 weeks prior to the planned start of the conditioning regimen or anticipation of need for such a vaccine during the course of the study

25) Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

26) Subjects of either sex who are not willing to practice birth control from the time of consent through 12 months following conditioning chemotherapy administration or 12 months following axicabtagene ciloleucel infusion, whichever is longer.

27) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

6. PROTOCOL TREATMENT

6.1. Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- The conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The IP for this study is named axicabtagene ciloleucel.
- The term study treatment refers to all protocol-required therapies.

6.2. Study Treatment

6.2.1. Conditioning Chemotherapy

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted. Conditioning chemotherapy should only commence when the product is available, if required by country regulatory agencies. Sites should refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of both agents.

Subjects will receive a conditioning regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel in vivo.

6.2.1.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.2.1.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges from 3 to 12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

6.2.1.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by cyclophosphamide. The active ingredient mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$. Mesna will be administered around the cyclophosphamide dose according to institutional standards. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.2.2. Axicabtagene Ciloleucel

This section contains general information about axicabtagene ciloleucel and is not intended to provide specific instructions. Refer to the Investigational Product Manual (IPM) for details and instruction on storing, thawing, and administering axicabtagene ciloleucel.

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing axicabtagene ciloleucel arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen, and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusing process.

Axicabtagene ciloleucel is a subject-specific product, and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of axicabtagene ciloleucel infused, the thaw start/stop time, and axicabtagene ciloleucel administration start/stop time will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion.

To date, over 280 subjects have received doses of anti-CD19 CAR T cells made using the vector construct used in this study at doses ranging from 0.5 to 30 x 10^6 anti-CD19 CAR T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of axicabtagene ciloleucel or to any products that support the management of axicabtagene ciloleucel (eg, cryostorage bags, subject ID labels) in this study are identified, log on to kitepharma.com to report the complaint.

6.2.3. Concomitant Therapy

Investigators may additionally prescribe any other concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF; granulocyte colony stimulating factor) and routine anti-emetic prophylaxis and treatment, except those medications listed in the excluded medications in Section 6.2.4.

All concurrent therapies, including medications, intubation, dialysis, oxygen, and blood products, should be recorded from the date of the informed consent through 3 months after completing treatment with axicabtagene ciloleucel. After 3 months of follow-up, only targeted concomitant medications will be collected for 24 months after axicabtagene ciloleucel infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

For subjects who are not enrolled (eg, screen failure or who do not undergo leukapheresis), only concurrent therapies related to any SAE(s) will be recorded.

For subjects who are enrolled, but not dosed with axicabtagene ciloleucel, concurrent therapies will only be recorded from the date of the informed consent through 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy). Specific concomitant medications collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.2.4. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to axicabtagene ciloleucel administration.

Systemic corticosteroids may not be administered as premedication to subjects for whom computed tomography (CT) scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). Such subjects should undergo non-contrast CT scans instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after axicabtagene ciloleucel administration unless used to manage axicabtagene ciloleucel-related or other severe toxicities (eg, anaphylaxis). Other medications that might interfere with the evaluation of axicabtagene ciloleucel, such as non-steroidal anti-inflammatory agents, should also be avoided for the same period unless medically necessary.

Treatment for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited, except as needed for treatment of disease progression after axicabtagene ciloleucel.

If permissibility of a specific medication/treatment is in question, contact the Kite medical monitor.

6.2.5. Subsequent Therapy

Subsequent therapy administered after axicabtagene ciloleucel necessary to treat a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplantation (SCT) and radiation therapy, will be recorded until one of the following happens: the subject transitions to the LTFU study, is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled but do not receive axicabtagene ciloleucel infusion, any additional anticancer therapy will also be collected until the subject completes their participation in the current study, is considered lost to follow-up, withdraws consent, or dies, whichever occurs first.

6.3. Rationale for Study Treatment Dosing: Conditioning Chemotherapy and Axicabtagene Ciloleucel Dose

6.3.1. Conditioning Chemotherapy Dose

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in pre-clinical models. The depth and duration of the lymphodepletion in preclinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific $CD8^+$ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine is a potent lymphodepleting regimen.

To improve the depth and duration of lymphocyte depletion, the conditioning chemotherapy dose will be cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days. Cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days have been studied and tolerated in subjects with B-cell malignancies {O'Brien 2001}. This regimen has been evaluated in the NCI study and is the dose of conditioning chemotherapy that is being studied in other studies in NHL at Kite.

6.3.2. Axicabtagene Ciloleucel Dose

The rationale for the axicabtagene ciloleucel dose in this study is based on aggregate safety and efficacy data compiled from the KTE-C19-101 study as outlined in the axicabtagene ciloleucel IB. Based on the favorable benefit/risk ratio observed in KTE-C19-101, a target dose of 2×10^6 anti-CD19 CAR T cells/kg will be used for this protocol.

6.4. Study Treatment Schedule

6.4.1. Leukapheresis

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells [WBCs]) for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the cell processing facility (CPF) overnight as described in the IPM.

Mononuclear cells will be obtained by leukapheresis (approximately 12 to 15 liter apheresis with a goal to target approximately 5 to 10×10^9 mononuclear cells). The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the IPM.

Upon arrival at the CPF, each subject's leukapheresed product will be processed to enrich for the T-cell-containing PBMC fraction. T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the investigational product per CPF standard operating procedures (SOPs). After the product has passed certain release tests, it will be shipped to the treating facility. Following completion of each subject's conditioning chemotherapy regimen, subjects will receive their respective axicabtagene ciloleucel infusion.

6.4.2. Cyclophosphamide and Fludarabine (Days –5 Through –3 Before Infusion of Axicabtagene Ciloleucel)

Subjects will receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel in vivo. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day –5 through Day –3 with 2 rest days before the receiving axicabtagene ciloleucel. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting, as follows:

- IV hydration with 1 L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion (and as needed, according to local institutional guidelines) followed by:
- Cyclophosphamide 500 mg/m^2 IV over 60 minutes (± 15 minutes) followed by:
- Fludarabine 30 mg/m^2 IV over 30 minutes (± 15 minutes) followed by:
- An additional 1 L of 0.9% NaCl at the completion of the cyclophosphamide infusion
- Add mesna per institutional guidelines

At investigator discretion, an alternative balanced crystalloid can be used in place of 0.9% NaCl. Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours). In general, subjects should be kept well hydrated, but closely monitored to prevent fluid overload.

6.4.3. Axicabtagene Ciloleucel (Day 0)

All subjects will be hospitalized to receive treatment with axicabtagene ciloleucel followed by an observation period. Subjects will remain in the hospital at a minimum through Day 7 post-treatment with axicabtagene ciloleucel unless otherwise required by country regulatory agencies. Refer to Section 18.3 for more information.

Subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities return to ≤ Grade 1 or baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (eg, renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1 or if deemed necessary by the treating investigator.

6.4.3.1. Axicabtagene Ciloleucel Premedication Dosing

The following axicabtagene ciloleucel infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the Kite medical monitor.

- Acetaminophen 650 mg PO (eg, Tylenol)
- Diphenhydramine 12.5 to 25 mg IV or PO (eg, Benadryl)

6.4.3.2. Axicabtagene Ciloleucel Dosing

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of axicabtagene ciloleucel and for the hospitalization treatment period. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of axicabtagene ciloleucel are outlined in the IPM. The IPM must be reviewed prior to administration of axicabtagene ciloleucel.

Research sites should follow institutional guidelines for the infusion of cell products.

6.5. Toxicity Management

To date, the following important risks have been identified with axicabtagene ciloleucel: CRS, neurological events, infections, hypogammaglobinemia, and cytopenias. Refer to Section 6 of the current IB for details regarding these events and management guidance.

As the safety experience with axicabtagene ciloleucel increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the axicabtagene ciloleucel IB for guidance regarding managing axicabtagene ciloleucel-related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with axicabtagene ciloleucel as well as possible complications associated with malignancy and cancer treatment.

7. STUDY PROCEDURES

Research staff should refer to the SOAs in Table 3 and Table 4 for an outline of the procedures required. The visit schedule is calculated from axicabtagene ciloleucel infusion on Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7.11. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and the potential risks. Subjects should sign the most current IRB/IEC approved informed consent form (ICF) prior to any study-specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

7.2. Demographic Data

Demographic data will be collected to include sex, age, race, and ethnicity.

7.3. Medical and Treatment History

Relevant medical history prior to the start of AE reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the subject's disease, treatment, and response to treatment will be collected and must date back to the original diagnosis.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subject's chart should be obtained and reviewed.

7.4. Physical Exam, Vital Signs, Performance Status

Physical exams, including neurological exam, will be performed during screening and at times noted in the SOA (refer to Table 3 and Table 4). Changes noted in subsequent exams when compared to the baseline exam will be reported as an AE.

During IP administration/hospitalization, vital signs, including blood pressure, heart rate, oxygen saturation, and temperature, will be monitored before and after the axicabtagene ciloleucel infusion and then routinely (every 4 to 6 hours) while hospitalized. If the subject has a fever (temperature 38.3˚C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

Performance status is measured by the ECOG scale and will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

7.5. Bone Marrow Biopsy

Bone marrow aspirate and biopsy will be performed at screening, if not previously performed, to assess bone marrow involvement.

A repeat bone marrow aspirate and biopsy will be required to confirm a complete response to axicabtagene ciloleucel except among subjects known to be negative for bone marrow involvement.

To confirm a complete response, the bone marrow aspirate and biopsy must show no evidence of disease by morphology, or, if indeterminate by morphology, it must be negative by immunohistochemistry.

Refer to Section 18.3 for treatment response assessment requirements per the Lugano Classification {Cheson 2014}.

7.6. Lumbar Puncture

Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture performed at the screening visit for examination of CSF. In addition, lumbar puncture should be performed for subjects with new onset of ≥ Grade 2 neurological event (see the axicabtagene ciloleucel IB) after axicabtagene ciloleucel infusion. Opening pressures for all lumbar punctures (LPs) should be measured and recorded in the subject's site record whenever possible.

7.7. Disease Response Assessment

Disease assessments will be evaluated for response per the Lugano Classification {Cheson 2014} by the site investigator at times indicated in the SOA (refer to Table 3 and Table 4). All enrolled subjects will be monitored via fluorodeoxyglucose positron emission tomography (FDG–PET) with diagnostic quality contrast-enhanced CT and/or other scans as specified in the imaging manual. Scans will be sent to a central imaging vendor to be reviewed by an independent central reviewer using the Lugano Classification {Cheson 2014}.

For subjects who discontinue the study due to an assessment of progressive disease (PD), any additional imaging data, subsequent to the image in question, may also be submitted to the central imaging vendor. Refer to the study imaging manual for details regarding submission of scans to the imaging vendor.

Flow cytometric, molecular, or cytogenetic studies will not be used to determine response.

Baseline positron emission tomography-computed tomography (PET-CT) scans of the neck, chest, abdomen, and pelvis, along with the appropriate imaging of all other sites of disease, are required. Subjects will have their post-axicabtagene ciloleucel infusion planned PET-CT tumor assessments during the post-treatment and LTFU period per the SOA. Additional CT scans will be performed at regular intervals as highlighted in the SOA during the LTFU portion of the study.

Post-axicabtagene ciloleucel administration disease assessments will be used to determine the time when PD occurs. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule according to the SOA.

For subjects with disease progression who are eligible for retreatment with axicabtagene ciloleucel, the last scan prior to retreatment will be considered the baseline for the purpose of evaluating the response to retreatment, provided it was done within 28 days of retreatment.

7.8. Cardiac Function

Each subject's cardiac function will be assessed by an electrocardiogram (ECG) and ECHO during the screening period to confirm study eligibility. Adequate LVEF and no evidence of pericardial effusion, as required by eligibility criteria, will be documented by ECHO. An ECHO performed following the subject's last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

7.9. Laboratory

The below samples will be collected at the time points indicated in the SOA (refer to Table 3 and Table 4). Additional samples (eg, blood, urine, CSF, tissue) may be collected, as needed, for additional safety testing.

7.9.1. Local Lab Analysis

- Sodium (Na), potassium (K), chloride (Cl), total CO2 (bicarbonate), creatinine, glucose, blood urea nitrogen (BUN) or urea (if BUN test cannot be analyzed by the local lab), albumin, calcium total, magnesium total (Mg), inorganic phosphorus, alkaline phosphatase, ALT/glutamic-pyruvic transaminase (GPT), AST/glutamic-oxaloacetic transaminase (GOT), total bilirubin direct bilirubin, lactate dehydrogenase (LDH), uric acid

- C-reactive protein (CRP), ferritin (FER)

- Complete blood count (CBC) with differential (if WBC counts are adequate per the local lab)

- For European Union (EU) sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.

A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study and the result is positive, the investigator should contact the Kite medical monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting the Kite medical monitor for instructions. See Section 9.6 for details.

7.9.2. Central Lab Analysis

- Blood draws for PBMC (lymphocyte subsets, replication-competent retrovirus [RCR], and anti-CD19 CAR T cells) and cytokine analysis will be performed at intervals outlined in the SOA (refer to Table 3 and Table 4).

- Serum samples will also be drawn for antibodies to axicabtagene ciloleucel.

  — For serum samples that demonstrate increased anti-axicabtagene ciloleucel antibodies at the Week 4 or Month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or become negative) or up to 1 year from the completion of treatment, whichever occurs first. Samples that test positive in the screening enzyme-linked immunosorbent assay will undergo confirmatory analysis in a cell-based assay.

  — Archived tumor tissue will be collected for central confirmatory diagnosis, central pathology review, and evaluation of prognostic markers specific for iNHL and pertaining to the tumor immune environment. If an archival sample is not available, a fresh biopsy sample collection is strongly encouraged.

  — Additional analysis may include CD19 expression, gene expression profiling, and analysis of tumor-specific DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations) or tumor/immune-related RNA and protein markers.

- CSF and possibly bone marrow samples will also be collected and analyzed at the central laboratory as outlined in the schedule of assessments (refer to Table 3 and Table 4) and per Section 7.5 and Section 7.6.

- See central laboratory manual for details on sample collection, processing, and shipping instructions.

7.10. Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate pharmacodynamic markers for axicabtagene ciloleucel. Prognostic markers specific for iNHL and related to the tumor immune microenvironment may also be evaluated in archived and fresh tumor biopsies.

The presence, expansion, persistence, and immunophenotype of the anti-CD19 CAR T cells will be monitored in the blood by flow cytometry. Expansion and persistence will also be monitored by an anti-CD19 CAR-specific quantitative polymerase chain reaction (qPCR) and/or flow cytometry.

Levels of serum cytokines will also be evaluated in the blood. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines, IL-6, tumor necrosis factor alpha (TNF-α), IL-8, IL-1, IL-2, granulocyte macrophage-colony stimulating factor (GM-CSF), IL-15, IL-17a, interferon gamma (IFN-γ), IL-12p40/p70; immune effector molecules granzyme A and B and perforin; correlates of acute phase response CRP; and chemokines, including macrophage inflammatory proteins MIP-1α and MIP-1β, interferon gamma-induced protein 10 (IP-10), and monocyte chemotactic protein 4 (MCP-4). Other analytes may be added to this panel as necessary.

CSF, as well as any additional subject samples (eg, pleural fluid), may be collected from subjects who develop a neurological event or CRS to enable evaluation of inflammatory cytokines and chemokine levels and presence of anti-CD19 CAR T cells. As applicable, lymphocyte and monocyte populations residing in the CSF or other additional subject samples may also be monitored for the purpose of understanding the safety profile of axicabtagene ciloleucel.

Because axicabtagene ciloleucel comprises retroviral vector transduced T cells, the presence of RCR in the blood of treated subjects will be monitored at baseline (prior to infusion) and at Month 3, Month 6, and Month 12 after axicabtagene ciloleucel infusion. In the LTFU, samples will continue to be collected yearly and may be held for up to 15 years from the last subject treated with axicabtagene ciloleucel. Additional testing will be conducted if a sample is positive at baseline, Month 3, Month 6, or Month 12 or as clinically indicated.

In addition, baseline leukapheresis and final axicabtagene ciloleucel samples will be banked and may be analyzed by immunophenotyping, qPCR, and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of immune-related DNA, RNA, or protein markers.

Archived tumor tissue (from most recent biopsy available) will be collected for centralized confirmatory diagnosis, evaluation of prognostic markers specific for iNHL, and pertaining to the tumor immune environment. If an archival sample is not available, a fresh biopsy sample collection is strongly encouraged. Additional analysis may include CD19 expression, gene expression profiling, and analysis of somatic DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations) and tumor/immune-related RNA and protein markers.

For subjects who sign the optional portion of the consent form, on-study paired core biopsies of tumor will be performed at baseline (prior to conditioning chemotherapy) and between Day 7 and Day 14, following axicabtagene ciloleucel infusion, when peak expansion and tumor infiltration with anti-CD19 CAR T cells is expected. In addition, persisting, relapsing, or emerging lesions should also be biopsied to help determine eligibility for retreatment or mechanisms of tumor resistance. Exploratory analysis of tumor or immune cell markers that correlate with response to axicabtagene ciloleucel or disease prognosis will be executed.

These samples, and any other components from these samples, may be stored up to 15 years from the last subject treated with axicabtagene ciloleucel to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who, in turn, can contact the sponsor. The investigator should provide the sponsor the study and subject ID number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor, and any data that may be generated will be entered in the study database.

7.11. Description of Study Periods

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information, such as the date of screening, date the subject was enrolled, or the reason why the subject failed screening.

7.11.1. Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through enrollment. Informed consent must be obtained before completion of any study-specific procedures. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA (refer to Table 3 and Table 4).

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled into the study. If, at any time prior to enrollment, the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure in the electronic CRF system with the reasons for failing screening.

In general, if a subject is screened and enrolled in the study, subjects must continue to meet all study inclusion and exclusion criteria at the time of administration of conditioning chemotherapy and at the time of axicabtagene ciloleucel infusion unless discussed in advance with and approved by the Kite medical monitor.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Medical history
- Physical exam, including neurological exam, height, and weight
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
  - Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture for examination of cerebral spinal fluid
- ECOG performance status
- ECG
- ECHO
- Imaging studies
  - Baseline PET-CT of the neck, chest, abdomen, and pelvis
    - PET-CT performed following the subject's last line of therapy and prior to signing the consent may be used for confirmation of eligibility, provided that the scan was obtained < 28 days before the initiation of conditioning chemotherapy.
    - If PET-CT will be older than 28 days at the initiation of conditioning chemotherapy or if the subject receives any anticancer therapy with therapeutic intent (eg, radiation, supraphysiologic doses of steroids, chemotherapy) between the last PET-CT and conditioning chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET-CT should be performed as close to enrollment as possible.
- Bone marrow aspirate and biopsy as needed if not done previously
- Labs
  - β-HCG pregnancy test (serum or urine) on all women of childbearing potential
  - Chemistry panel
  - CBC with differential
  - For EU sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.

- SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- After eligibility is confirmed, submission of archival tumor tissue to the central lab and collection fresh tumor (for subjects who signed the optional portion of the consent)

7.11.2. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the 28-day screening period may be permitted to rescreen. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days of the signing of the initial informed consent, only the procedures/assessments that did not originally meet the eligibility criteria need to be repeated. All other initial screening procedures/assessments do not need to be repeated.

If rescreening occurs or leukapheresis is delayed more than 28 days from the initial informed consent date, subjects must be re-consented and repeat all screening procedures/assessments. A subject will not be considered a screen failure until it is confirmed that the subject did not meet the eligibility criteria (ie, will not move forward to leukapheresis) and is no longer eligible for rescreening.

7.11.3. Enrollment/Leukapheresis

If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and results are outside the eligibility criteria listed in Section 5, contact the Kite medical monitor prior to proceeding with leukapheresis.

Additionally, the investigator must review the last CBC with differential and chemistry panel drawn prior to the start of leukapheresis to confirm that Inclusion 112 (eg, creatinine clearance, serum ALT/AST, total bilirubin) continues to be met (see Section 5.1).

Before leukapheresis commences, the below criteria must be met. If criteria are not met, leukapheresis must be delayed until the event resolves. If leukapheresis is delayed beyond 5 days, baseline CBC with differential and chemistry panel must be repeated. If results are outside the eligibility criteria listed in Section 5, contact the Kite medical monitor prior to proceeding with leukapheresis.

- No evidence or suspicion of an infection
- Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis.

If leukapheresis is delayed beyond 28 days from the screening visit, screening procedures will be repeated to confirm that the subject remains eligible for enrollment (see Section 7.11.1).

Leukapheresis should occur within approximately 5 days from eligibility confirmation.

After a subject commences leukapheresis, the subject will be considered enrolled into the study.

The following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA (refer to Table 3 and Table 4):

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Weight
- Labs (to be drawn prior to leukapheresis, on the day of, or day before leukapheresis)
  - Chemistry panel
  - CRP, FER
  - CBC with differential
  - Blood draw for PBMCs (includes lymphocyte subsets and baseline RCR), cytokines, and antibodies to axicabtagene ciloleucel
  - Blood draw for leukapheresis
- AE/SAE reporting
- Concomitant medications documentation

7.11.4. Conditioning Chemotherapy and Axicabtagene Ciloleucel Infusion

Administration of CAR T cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion.

Signs, symptoms, or abnormal laboratory results attributed to the malignancy (eg "tumor fever," elevated CRP) are diagnoses of exclusion that require a documented workup to establish.

Conditioning chemotherapy and axicabtagene ciloleucel infusion should only be initiated when it is reasonably assured that cell infusion can safely proceed.

Refer to Section 7.11.4.1 for workup requirements for potential infectious and/or inflammatory states.

7.11.4.1. Requirement to Workup Potential Infections and/or Inflammatory States

In the absence of an identified source of infection (eg, line infection or pneumonia on chest X-ray), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or axicabtagene ciloleucel comprises the following:

- Call Kite medical monitor
- Infectious disease service consult (if applicable)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic; x2 bottles each) and uric acid (UA) and urine culture. Deep/induced sputum culture if clinically indicated.
  - All indwelling lines such as central venous catheters should be examined for any signs of infection and additional cultures should be drawn from the line
  - Nasopharyngeal-throat swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus [CMV])
- If a CNS process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral polymerase chain reaction (PCR) should be performed
- Any additional sign- or symptom-directed investigation should be performed as clinically indicated

Prior to proceeding with conditioning chemotherapy and/or axicabtagene ciloleucel infusion, the above workup must not suggest the presence of an active infection and all requirements for conditioning chemotherapy and/or axicabtagene ciloleucel infusion must be satisfied.

If the axicabtagene ciloleucel infusion is delayed > 2 weeks following conditioning chemotherapy, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

If the above workup was triggered due to CRP > 100mg/L, CRP should be repeated. If CRP continues to increase significantly, an evaluation should be performed for any other potential infectious or inflammatory condition that was not previously evaluated.

7.11.5. Conditioning Chemotherapy Period

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, the workup listed in Section 7.11.4.1 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of conditioning chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- WBC count or WBC differential concerning for infectious process between enrollment to start of conditioning chemotherapy (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy.
- Complete history and physical exam, including head, eyes, ears, nose, and throat (HEENT), and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems, must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of antimicrobials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service consult (if applicable).
- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

After the above criteria are met, then the subject can proceed with conditioning chemotherapy.

The following procedures will be completed during Day –5 to Day –1 at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy)
  - Chemistry panel
  - CBC with differential
- Fludarabine and cyclophosphamide administration
- AE/SAE reporting
- Concomitant medications documentation

7.11.6. Investigational Product Treatment Period

If any of the following criteria are met prior to the initiation of axicabtagene ciloleucel infusion, then the workup listed in Section 7.11.4.1 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of axicabtagene ciloleucel infusion
- CRP > 100 mg/L anytime between enrollment to start of axicabtagene ciloleucel infusion
- WBC count or WBC differential suggestive of infectious process between enrollment and start of axicabtagene ciloleucel infusion (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segments/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of axicabtagene ciloleucel infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with axicabtagene ciloleucel infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam, including HEENT, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems, must not reveal evidence of infection/inflammation.

- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before axicabtagene ciloleucel (prophylactic use of antimicrobials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease service consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service consult (if applicable).

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial or viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

After the above criteria are met, the subject can proceed with administration of axicabtagene ciloleucel.

If the axicabtagene ciloleucel infusion is delayed > 2 weeks, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

Subjects will remain in the hospital through at least Day 7 following treatment with axicabtagene ciloleucel (please also refer to Section 18.2 for France). Subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities return to Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg, renal insufficiency), even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1 or if deemed necessary by the treating investigator.

Given the possibility that a subject could develop CRS or neurological event in the outpatient setting after discharge, subjects and their family members/caregivers should be educated on potential symptoms of these syndromes, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the investigator or seek immediate medical attention.

During this period, the following procedures will be completed at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Daily physical and neurological exams are at the discretion of the investigator during hospitalization unless required by local ethics committees or regulatory agencies.

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature, every 4 to 6 hours during hospitalization

- Labs (before axicabtagene ciloleucel infusion, as described in the SOA)
  - Chemistry panel
  - CBC with differential (if WBCs are adequate per the local lab)
- Blood draw for PBMCs (includes lymphocyte subsets and anti-CD19 CAR T cells) and cytokines
- Infusion of axicabtagene ciloleucel
- As applicable, lumbar puncture for subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion.
- Collection of fresh tumor sample(s) for subjects who signed the optional portion of the consent (any time between Day +7 and Day +14)
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

Monitoring of CRP, FER, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regard to CRS/neurological event. It is, therefore, recommended that CRP, FER, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continued through hospitalization. In addition, lactate should be monitored as clinically indicated.

7.11.7. Post-treatment Assessment Period

After completing axicabtagene ciloleucel infusion and discharged from the hospital, all subjects will be followed in the post-treatment assessment period. Counting from Day 0 (axicabtagene ciloleucel infusion), subjects will return to the clinic at the following intervals.

- Week 2 (± 2 days)
- Week 4 (± 3 days)
- Month 2 (± 1 week)
- Month 3 (± 1 week)

Subjects will allow key sponsor contacts to continue to access medical records so that information related to a subject's health condition and initial treatment response may be obtained. The following procedures will be completed for subjects as outlined in the SOA (refer to Table 3 and Table 4):

- Physical exam, including neurological exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature

- Disease assessment per the SOA (Note: If the PET-CT is not of high enough resolution to accurately quantify lesion size, the scan must be repeated.)
- As applicable, bone marrow aspirate and biopsy to confirm response (ie, for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment)
- Labs
  - β-HCG pregnancy test (serum or urine) on all women of childbearing potential
  - Chemistry panel
  - CBC with differential
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis), cytokines, and anti-axicabtagene ciloleucel antibodies
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is subsequently re-admitted to the hospital with any axicabtagene ciloleucel-related AEs, the following procedures will be performed as outlined in the SOA (refer to Table 3 and Table 4):

- The labs below will be collected on the day of hospital re-admission and then weekly through the date of hospital discharge.
  - Blood draw for PBMCs (anti-CD19 CAR T cells)
  - Blood draw for cytokines
- If the subject has a new or ongoing Grade 3 or higher neurologic event, in addition to the labs above, blood draw for cytokines will be collected every other day through the date of hospital discharge.

At any time during the post-treatment assessment period, if a subject did not respond to treatment (ie, did not achieve a CR or partial response [PR]) or progresses following a response and is either not eligible for retreatment or chooses not to pursue retreatment, the subject will proceed directly to the Month 3 visit and be followed for **s**afety**,** survival, subsequent therapy, and disease outcomes in the LTFU period. A PBMC sample (for anti-CD19 CAR T cells, RCR) and tumor biopsy (for exploratory biomarker analysis) should be collected at the time of progression and prior to starting any subsequent anticancer therapy.

7.11.8. Long-term Follow-up Period

All enrolled subjects will be followed in the LTFU period for safety, survival, and disease status, if applicable. Subjects will begin the LTFU period after they have completed the Month 3 visit following axicabtagene ciloleucel infusion (whether they have responded to treatment or they went straight to the Month 3 visit due to disease progression), and will transition to the LTFU study after providing signed informed consent.

- Month 6 (± 2 weeks)
- Month 9 **(**+ 1 month)
- Month 12 (+ 1 month)
- Month 15 (± 2 weeks)
- Month 18 (± 2 weeks)
- Every 6 months (± 1 month) between Month 24 to Month 60
- If not already transitioned to the LTFU study, every 12 months (± 1 month) from Month 72 to Year 15

The following procedures will be completed for subjects who are enrolled and receive axicabtagene ciloleucel at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Physical exam, including neurological exam, through Month 24
- Disease assessment per the SOA. Diagnostic PET-CT may be used to document disease recurrence or progression if suspected.
- Survival status
- Labs
  - CBC with differential through Month 24
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis) and anti-axicabtagene ciloleucel antibodies (refer to Section 7.9)
- Targeted AE/SAE reporting - (refer to Section 9 for safety reporting guidelines)
- Targeted concomitant medications documentation (for 24 months after axicabtagene ciloleucel infusion or until disease progression, whichever comes first)
  - Including gammaglobulin, immunosuppressive drugs, anti-infective medications, and vaccinations
- Subsequent therapy for the treatment of lymphoma

Subjects may also be contacted by telephone to confirm survival status and report targeted concomitant medications use.

If a subject progresses in the LTFU phase, the subject will continue to be followed for survival status**,** any secondary malignancies**,** and subsequent therapy for the treatment of NHL. A PBMC sample (for anti-CD19 CAR T cells) and tumor biopsy (for exploratory biomarker analysis) should be collected at the time of progression and prior to starting any subsequent anticancer therapy. Also, if a subject develops a secondary malignancy during the study, every effort will be made to assay for RCR in blood and in a biopsy sample of the neoplastic tissue as clinically indicated. Secondary malignancies are defined as new malignancies that are suspected to be possibly related to axicabtagene ciloleucel (ie, plausibly associated with axicabtagene ciloleucel and without compelling alternate etiologies).

Subjects who are enrolled/leukapheresed, but did not receive axicabtagene ciloleucel treatment, will be followed only until the end of this study and will undergo the following procedures/assessments at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Subsequent therapy
- Survival status–subjects may be contacted by telephone to confirm survival status
- Disease assessment per standard of care
- AE/SAE reporting and concomitant medications documentation until 30 days after last procedure (eg, leukapheresis, conditioning chemotherapy)

Should the subject fail to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact, the subject will be considered lost to follow-up, and no additional contact will be required.

Subjects who undergo a consolidation SCT will be contacted to confirm the status of their disease, survival status, and will have blood collected for PBMCs per the LTFU schedule.

7.11.9. Retreatment

Subjects who achieve a response of PR or better at the 3-month disease assessment, but subsequently experience disease progression, may have an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel.

The following criteria must be met to be considered for a repeat course of therapy:

- Subject has at least PR or CR at the Month 3 disease assessment, but subsequently experienced progression of disease at a later time.

- CD19 expression on tumor cells confirmed locally by biopsy after disease progression and prior to treatment

- Subject continues to meet the original study eligibility criteria with the exception of prior axicabtagene ciloleucel use in this study. Screening assessments should be repeated if clinically indicated, as determined by the investigator, to confirm eligibility.

- Subject has not received subsequent therapy for the treatment of lymphoma.

- Subject did not experience Grade 4 CRS, Grade 4 neurological event, or any other life-threatening toxicity during the original course of treatment.

- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to retreatment.

- Subject does not have known neutralizing antibodies (exception: if a non-neutralizing KTE-C19 antibody develops, subject may be retreated if he or she meets the original study eligibility criteria).

Retreatment for all eligible subjects must occur within 24 months after the initial axicabtagene ciloleucel infusion. The decision to retreat with axicabtagene ciloleucel should be made in consultation with the Kite medical monitor. In addition, a discussion regarding benefits and risks of retreatment, including the need to undergo leukapheresis a second time for the manufacturing of axicabtagene ciloleucel, should occur with the subject prior to performing any study-related procedures or treatment. This conversation should also be recorded in the subject's source document.Allowance for retreatment is based on clinical experience reported in the 2 studies conducted at the pediatric {Lee 2015} and Surgery Branch {Kochenderfer 2015} of the NCI where 6 subjects in total have been retreated upon progression. Three (3) of the retreated subjects (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression.

A maximum of 1 retreatment course may occur per subject.

Retreated subjects will remain on this study, following the same treatment schedule and procedural requirements per the initial treatment, until they are eligible to transfer to the LTFU study (please refer to Section 3.6).

Table 3. Schedule of Assessments (1 of 2)

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period					IP Administration Period		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	**Within 28 days of enrollment**		**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1 – 7[11]**	**Week 2 (± 2 days)**	**Week 4 (± 3 days)**	**Month 2 (± 1 week)**	**Month 3 (± 1 week)**
Medical history	X												
Physical exam (with neurological exam)	X							X	X[12]	X	X	X	X
Weight (plus height at screening)	X	X											
Vital signs (BP, HR, O_2 sat, temp)	X	X	X	X	X			X	X	X	X	X	X
Lumbar Puncture[1]	X								X				
ECOG Performance Status	X												
ECG	X												
ECHO	X												
Disease assessment (PET and/or CT, bone marrow **aspirate and** biopsy)[2]	PET-CT										PET-CT		PET-CT
Archival/Fresh tumor to central lab[3,4]	X								between Day 7 & Day 14				
Pregnancy test (serum or urine)	X												X
Viral serologic tests (except for US sites)[10]	X												
Blood draw for chemistry panel[9]	X	X	X	X	X			X	X	X	X	X	X
Blood draw for CBC w/differential	X	X	X	X	X			X	X	X	X	X	X
Blood draw for CRP, Ferritin		X											

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period					IP Administration Period		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	**Within 28 days of enrollment**		**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1 – 7[11]**	**Week 2 (± 2 days)**	**Week 4 (± 3 days)**	**Month 2 (± 1 week)**	**Month 3 (± 1 week)**
Blood draw for anti-KTE-C19 antibody[5]		X									X		X
Blood draw for PBMCs[6,7]		X							Day 7[7]	X	X		X
Blood draw for cytokines[7,8]		X						X	Day 3,7[7]	X	X		
Leukapheresis		X											
Fludarabine/Cyclophosphamide			X	X	X								
KTE-C19 infusion IV								X					
Adverse events/Concomitant medication	X	→											

Abbreviations: BP, blood pressure; HR, heart rate; sat, saturation; temp, temperature; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ECHO, echocardiogram; PET, positron emission tomography; CT, computed tomography; CBC, complete blood count; CRP, C-reactive protein; PBMC, peripheral blood mononuclear cell; IV, intravenous; IP, investigational product.

1 Lumbar Puncture: Subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess CSF for possible CNS involvement. Subjects with new onset Grade ≥ 2 neurologic symptoms post-axicabtagene ciloleucel infusion will have lumbar puncture performed to assess CSF. Opening pressures for all lumbar punctures (LPs) should be measured and recorded whenever possible.

2 PET and/or CT (neck-chest-abdomen-pelvis)/disease assessment: All scans will be submitted to the central imaging vendor to be read by a central independent reviewer. If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy, the baseline PET-CT scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. PET-CT will be performed at the Week 4, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, and Month 24 visits and at any subsequent scheduled or unscheduled visit if there is clinical concern for disease progression. After Month 24, PET-CT will be performed if disease recurrence is suspected. Otherwise, surveillance imaging will be diagnostic CT without PET**.** A bone marrow aspirate and biopsy will be required to confirm a complete response to axicabtagene ciloleucel except among subjects known to be negative for bone marrow involvement within 4 weeks of screening. As applicable, bone marrow aspirate and biopsy will be performed if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. See Section 7.9 and Section 7.11.

3 For archival tumor samples, either formalin-fixed paraffin embedded (FFPE) tumor block or 20 unstained slides is accepted. If not able to send a FFPE block or at least 20 unstained slides, refer to the central lab manual for further instruction. Site must attempt to ship archived tumor samples to the central laboratory after eligibility has been confirmed and prior to the start of conditioning chemotherapy. Fresh tumor sample for subjects who sign the optional portion of consent (refer to Section 7.10) will be collected and shipped after eligibility has been confirmed and prior to the start of conditioning chemotherapy. Post-treatment fresh tumor samples (if applicable) will be collected/submitted any time between Day 7 and Day 14. See Section 7.10.

4 Archived tumor tissue will be collected for central confirmatory diagnosis, central pathology review, and evaluation of prognostic markers specific for iNHL and pertaining to the tumor immune microenvironment. If an archival sample is not available, a fresh biopsy sample collection is strongly encouraged.
5 Blood draw for anti-axicabtagene ciloleucel antibody: Baseline antibody sample to be collected prior to start of conditioning chemotherapy and a post-axicabtagene ciloleucel infusion sample will be collected at the Month 3 visit; see Section 7.9.
6 PBMCs blood draw for the analysis of lymphocytes, anti-CD19 CAR T cells, and RCR. See Section 7.10. Day 7 blood draws for PBMCs that fall on a weekend or public holiday may be drawn on Day 6 or Day 8 (Day 5 only if Day 6 or Day 8 cannot be done).
7 If, following discharge from initial hospitalization, the subject is subsequently re-admitted to the hospital with any axicabtagene ciloleucel-related adverse events, blood samples for PBMCs (anti-CD19 CAR T cells) and cytokines will be collected on day of admission, then weekly while hospitalized, and on the day of discharge. If the subject has a new or ongoing Grade 3 or higher neurological event, blood samples for cytokines will be collected every other day while hospitalized, and on the day of discharge.
8 A blood draw for cytokines will be drawn at Day 3 and Day 7. Day 3 blood draws for cytokines that fall on a weekend or public holiday may be drawn on Day 2 or Day 4 (Day 1 only if Day 2 or Day 4 cannot be done). Day 7 blood draws for cytokines that fall on a weekend or public holiday may be drawn on Day 6 or Day 8 (Day 5 only if Day 6 or Day 8 cannot be done). If the subject experiences Grade 3 axicabtagene ciloleucel-related toxicity, such as Grade 3 CRS or neurological event, one additional blood draw for cytokines will be taken at the time of Grade 3 related toxicity.
9 Urea is an acceptable alternative if BUN cannot be analyzed by the local lab.
10 Except for US sites, viral serologic tests will be done at screening or at the time of leukapheresis or within the 30 days prior to leukapheresis (see Section 7.9.1).
11 Subjects will remain in the hospital through Day 7 after treatment with axicabtagene ciloleucel unless otherwise required by country regulatory agencies (see Section 18.2)
12 Daily physical and neurological exams are at the discretion of the investigator during hospitalization unless required by local ethics committees or regulatory agencies.

Table 4. Schedule of Assessments (2 of 2)

Procedure	LTFU Period[1] (Each visit calculated from Day 0)												
Visit Frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Until Year 15**
	(± 2 weeks)	**(+ 1 month)**	**(+ 1 month)**	**(± 2 weeks)**	**(± 2 weeks)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**
Physical exam (with neurological exam)[2]	X	X	X	X	X	X							
PET/CT disease assessment[3]	PET-CT	PET-CT	PET-CT	PET-CT	PET-CT	PET-CT		CT[3]		CT[3]		CT[3]	CT[3]
Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/differential[4]	X	X	X	X	X	X							
Anti-KTE-C19 antibody[5]													
Blood draw for PBMCs[6]	X		X		X	X		X		X		X	X[5]
Targeted AE/SAEs related to axicabtagene ciloleucel infusion[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted concomitant medication[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for NHL[9]	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: LTFU, long-term follow-up; PET, positron emission tomography; CT, computed tomography; CBC, complete blood count; PBMC, peripheral blood mononuclear cell; AE, adverse event; SAE, serious adverse event; NHL, non-Hodgkin lymphoma.

1 After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will complete the remainder of the 15 year follow-up assessments in a separate Kite Pharma, Inc-sponsored long-term follow-up (LTFU) study, KT-US-982-5968.

2 Physical exams (including neurological exam) will continue through the first 24 months.

3 The Month 9 and Month 12 PET/CT disease assessment should occur at the Month 9 + 1 month and Month 12 + 1 month, respectively. PET-CT scans/disease assessments will continue every 3 months through Month 18 and at Month 24 or until disease progression, whichever comes first. After Month 24**,** PET-CT will be performed if disease recurrence is suspected. Otherwise, surveillance imaging will be diagnostic CT without PET.

4 Subjects will continue to provide samples for CBC w/differentials and lymphocyte subsets through Month 24.

5 Anti-axicabtagene ciloleucel antibodies post-3-month samples; refer to Section 7.9.

6 Blood draw for PBMCs includes the analysis of lymphocytes, anti-CD19 CAR T cells, and RCR. RCR will be tested at baseline, Month 3, Month 6 and Month 12. In the LTFU, samples will be collected yearly and may be held for up to 15 years from the last subject treated with axicabtagene ciloleucel.

7 Targeted AEs and SAEs related to axicabtagene ciloleucel infusion will be collected for 15 years, until disease progression, or until initiation of subsequent anticancer therapy (whichever occurs first).. All new malignancies are to be reported for all subjects through 15 years after initial axicabtagene ciloleucel infusion, including those whose disease progresses and/or those who receive subsequent anticancer therapy.
8 Targeted concomitant medications will be collected for 24 months after axicabtagene ciloleucel infusion or until disease progression (whichever occurs first).
9 Subsequent therapy administered after axicabtagene ciloleucel infusion for a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy, must be collected until subject completes the LTFU period, is considered lost to follow-up, withdraws consent, or dies. Subjects may be contacted by telephone to collect information about subsequent therapy for iNHL and to assess survival status.

8. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study-required treatment and/or other protocol -required procedures at any time during the study, but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from IP, study treatment, or other protocol-required therapies and must discuss options for continued participation, completion of procedures, and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent for a study means that the subject does not wish to receive further protocol-required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and, where permitted by local regulations, publicly available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol-required IPs or procedures include any of the following:

- AE
- Subject request
- Product not available
- Lost to follow-up
- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9. SAFETY REPORTING

9.1. AEs

An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered AEs. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered AEs.

The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, FL).

For situations when an AE or SAE is due to the disease under investigation, report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as AEs in the appropriate section of the CRF.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. In the event a subject requests to withdraw from protocol-required therapies or the study due to an AE, the subject should undergo the procedures outlined in the Month 3 visit of the SOA (refer to Table 3 and Table 4).

9.2. Reporting of AEs

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur from enrollment (ie, commencement of leukapheresis) through 3 months after treatment with axicabtagene ciloleucel infusion or until the initiation of another anticancer therapy, whichever occurs first. After 3 months, targeted AEs (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) related to axicabtagene ciloleucel infusion will be monitored and reported for 15 years after initial treatment with axicabtagene ciloleucel, until disease progression, or the initiation of subsequent anticancer therapy, whichever occurs first.

For subjects who are enrolled, but do not receive axicabtagene ciloleucel, the AE reporting period ends 30 days after the last procedure (eg, leukapheresis, conditioning chemotherapy).

The investigator must provide the information listed below regarding the AEs being reported:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to IP, conditioning chemotherapy, or study procedures
- Action taken

AE grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov). CRS events will be reported using the grading scale outlined in the axicabtagene ciloleucel IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) the IP (axicabtagene ciloleucel), 2) conditioning chemotherapy, or 3) any protocol-required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae, require therapy, or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Associated with clinical symptoms
- Results in a medical intervention (eg, potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

The investigator is expected to follow reported AEs until stabilization or resolution. If a subject begins a new anticancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.

9.3. Definition of SAEs

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility (eg, overnight stay).

Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization.

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each AE recorded on the electronic CRF.

9.4. Reporting of SAEs

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject that occur after signing of the screening informed consent through 3 months after the axicabtagene ciloleucel infusion, until disease progression, or until the initiation of subsequent anticancer therapy, whichever comes first. After 3 months, only serious targeted AEs (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) related to axicabtagene ciloleucel infusion are to be reported for 15 years after initial axicabtagene ciloleucel infusion, until disease progression, or until the initiation of subsequent

anticancer therapy, whichever occurs first. All new malignancies are to be reported for all subjects through 15 years, including those whose disease progresses and/or those who receive subsequent anticancer therapy. New malignancies are defined as the development of any new malignancies occurring after axicabtagene ciloleucel infusion. Secondary malignancies are defined as new malignancies that are suspected to be possibly related to axicabtagene ciloleucel (ie, plausibly associated with axicabtagene ciloleucel and without compelling alternate etiologies).

SAEs that the investigator assesses as related to axicabtagene ciloleucel should be reported regardless of the time period.

For subjects who screen fail or are enrolled, but do not receive axicabtagene ciloleucel, the reporting period for SAEs ends 30 days after the last study-specific procedure (eg, screen procedure, leukapheresis, conditioning chemotherapy).

All SAEs must be reported within 24 hours of the investigator's knowledge of the event. SAEs will be reported through the electronic database capture (EDC) system. This is called eSAE reporting. If the eSAE system is unavailable, reports will be submitted by emailing a completed SAE report form to safety_fc@gilead.com.

After completion of ZUMA-5 study and database closure, any relevant information on ongoing SAEs must be submitted to Kite within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via email to the SAE Reporting mailbox: safety_fc@gilead.com.

Subsequently, all SAEs will be reported to the health authorities per local reporting guidelines.

Disease progression of the malignancy is not considered an AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and being indicated as due to disease progression. If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy or axicabtagene ciloleucel, then the event malignant neoplasm progression must be recorded as an SAE with the outcome fatal.

Death must be reported if it occurs during the SAE reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning and within 3 months of the axicabtagene ciloleucel infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring greater than 3 months after the axicabtagene ciloleucel infusion requires expedited reporting within 24 hours only if it is considered related to treatment.

9.4.1. Reporting Deaths

Deaths occurring during the protocol-specified AE reporting period that investigators attribute solely to progression of underlying lymphoma should be recorded as SAEs and on the AE

electronic CRF with the preferred term "Follicular Lymphoma, Marginal Zone Lymphoma, or B-cell lymphoma" and must be reported to the sponsor immediately. Death is an outcome and not a distinct event. For deaths not due to the underlying malignancy, the event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. The term "unexplained death" should be captured if the cause of death is not known. However, every effort should be made to capture the established cause of death, which may become available later (eg, after autopsy). Deaths occurring during the post-study survival follow-up period that are due to underlying cancer should be recorded on the Survival Status CRF and the Death Summary Page.

9.5. Diagnosis Versus Signs and Symptoms

For AEs, a diagnosis (if known) should be recorded on the AE form in lieu of signs and symptoms. The exception is for CRS, where both the diagnosis and signs and symptoms should be captured on the AE form. Signs and symptoms of the underlying cancer should also be recorded. However, the investigator should state that these signs and symptoms are due to the underlying disease.

9.6. Pregnancy and Lactation

There is no relevant clinical experience with axicabtagene ciloleucel in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 12 months after administration of conditioning chemotherapy or 12 months after axicabtagene ciloleucel dosing, whichever is longer. Male subjects are recommended to not father a child for 12 months after conditioning chemotherapy or 12 months after axicabtagene ciloleucel dosing, whichever is longer. If a pregnancy occurs in a female subject enrolled into the study at any time after infusion or a female partner of a male subject within 12 months of completing conditioning chemotherapy or axicabtagene ciloleucel infusion, whichever is longer, the pregnancy must be reported to the key sponsor contact. Pregnancies should be reported within 24 hours of the investigator's knowledge of the pregnancy event. Information regarding the pregnancy and/or the outcome may be requested by the sponsor.

If a lactation case occurs while the female subject is taking protocol-required therapies, report the lactation case to the key sponsor contact. Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 12 months.

9.7. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE, as described in Section 9.3.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative care or hospice care
- Planned hospitalization required by the protocol (eg, for monitoring the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying cancer

9.8. Abnormal Vital Sign Value

Not all vital sign abnormalities qualify as an AE. A vital sign result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised when deciding whether an isolated vital sign abnormality should be classified as an AE. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the CRF.

9.9. DSMB

An independent DSMB will have ongoing oversight of the study and will monitor data during this study. The DSMB will first meet to review safety data when 10 subjects have been treated with axicabtagene ciloleucel (see Section 10.5) and have had an opportunity to be followed for 4 weeks. The DSMB will meet again to review safety data after 30 subjects have been treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. The DSMB will meet again to review safety and efficacy data after 30 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. The DSMB will meet for a fourth time when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. The DSMB will meet for a fifth time when

80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 9 months from the first disease response assessment.

The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk vs benefit. The DSMB may meet more often as needed.

The DSMB will also review SAE information and SUSARs on a regular basis throughout subject treatment in the study. The DSMB may request additional safety data or modify the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate and ensure timely DSMB review.

At the time of expedited reporting of SUSARs to regulatory authorities, Kite (or designee) will concurrently submit these reports to the DSMB chair. The DSMB chair will also review SAE narrative reports monthly. Finally, the DSMB or Kite may request additional analyses of safety data if a safety concern arises during the course of the trial.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

Four hypotheses will be tested using a fixed sequence procedure in terms of ORR and CR rate as determined by central review to control the overall type I error at 1-sided alpha level of 0.025 with the following testing order:

- Hypothesis 1 (H_1): test for ORR, as determined by central review; if significant then
- Hypothesis 2 (H_2): test for CR rate, as determined by central review; if significant then
- Hypothesis 3 (H_3): test for ORR, as determined by central review, in the subjects who have had 3 or more lines of prior therapy; if significant then
- Hypothesis 4 (H_4): test for CR rate, as determined by central review, in the subjects who have had 3 or more lines of prior therapy

The hypotheses H_1 through H_4 will be assessed at the time of the interim analysis 3**,** 4, and 5 and the primary analysis.

The H_1 is that the ORR, as determined by central review, to axicabtagene ciloleucel is significantly greater than 40% in subjects with FL in the inferential analysis set. The targeted response rate is 60%.

The H_2 is that the CR rate, as determined by central review, to axicabtagene ciloleucel is significantly greater than 15% in subjects with FL in the inferential analysis set.

The H_3 is that the ORR, as determined by central review, to axicabtagene ciloleucel is significantly greater than 40% in subjects with FL in the inferential analysis set who have had 3 or more lines of prior therapy.

The H_4 is that the CR rate, as determined by central review, to axicabtagene ciloleucel is significantly greater than 15% in subjects with FL in the inferential analysis set who have had 3 or more lines of prior therapy.

An alpha spending function will be used to allocate the alpha level between the interim analysis 3, interim analysis 4, and interim analysis 5, and the primary analysis. Using the O'Brien-Fleming boundary of the Lan-DeMets family of alpha spending functions, the nominal 1-sided alpha used to test for efficacy at interim analysis 3, interim analysis 4, and interim analysis 5 are 0.0003, 0.0005, and 0.0005, respectively, and the nominal 1-sided alpha used to test for efficacy at the primary analysis is 0.0237. If the criteria for early efficacy are met for H_1, the same alpha spending function will be applied to test H_2 at each interim analysis; otherwise, H_2 through H_4 will not be tested until the primary analysis. If the criteria for early efficacy are met for H_1 and H_2, the same alpha spending function will be applied to test H_3; otherwise, H_3 and H_4 will not be

tested until the primary analysis. If the criteria for early efficacy are met for H_1, H_2, and H_3, the same alpha spending function will be applied to test H_4; otherwise, H_4 will not be tested until the primary analysis. The study will not be stopped if early efficacy is demonstrated.

No formal hypothesis testing is planned for the MZL histological subtype. The analyses will be descriptive.

10.2. Study Endpoints

10.2.1. Primary

ORR is defined as the incidence of a CR or a PR by the Lugano Classification {Cheson 2014} as determined by the central reader. All subjects who do not meet the criteria for an objective response by the analysis data cutoff date will be considered nonresponders.

10.2.2. Secondary

The CR rate is defined as the incidence of CR as best response to treatment by the Lugano Classification {Cheson 2014} as determined by the central reader.

ORR is defined as the incidence of a CR or a PR by the Lugano Classification {Cheson 2014} as determined by the central reader for those subjects who have had 3 or more lines of prior therapy.

The CR rate is defined as the incidence of CR as best response to treatment by the Lugano Classification {Cheson 2014} as determined by the central reader for those subjects who have had 3 or more lines of prior therapy.

ORR per investigator read is defined as the incidence of a CR or a PR by the Lugano Classification {Cheson 2014} as determined by the investigator. All subjects who do not meet the criteria for an objective response by the analysis cutoff date will be considered nonresponders.

Best objective response is defined as the incidence of CR, PR, stable disease (SD), PD, or non-evaluable (NE) as best response to treatment by the Lugano Classification {Cheson 2014}. Response may be defined per central read or investigator read.

DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression per {Cheson 2014} or death due to any cause. Response and progression may be defined per central read or investigator read. Subjects not meeting the criteria for progression or death due to any cause by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive any subsequent anticancer therapy (including SCT or retreatment with axicabtagene ciloleucel) in the absence of prior documented progression will be censored at the last evaluable disease assessment prior to the subsequent anticancer therapy. The DOR for subjects who progress or die after any subsequent anticancer therapy, including SCT or retreatment with axicabtagene ciloleucel, will be censored at the last evaluable disease assessment prior to the subsequent anticancer therapy.

PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per {Cheson 2014}or death due to any cause. Subjects not meeting the criteria for progression or death due to any cause by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive any subsequent anticancer therapy (including SCT or retreatment with axicabtagene ciloleucel) in the absence of prior documented progression will be censored at the last evaluable disease assessment prior to the subsequent anticancer therapy. The PFS for subjects who progress or die after any subsequent anticancer therapy, including SCT or retreatment with axicabtagene ciloleucel, will be censored at the last evaluable disease assessment prior to the subsequent anticancer therapy.

OS is defined as the time from axicabtagene ciloleucel infusion to the date of death due to any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive prior to the data cutoff date. Survival for subjects known to be alive or determined to have died after the data cutoff date will be censored at the data cutoff date.

Other secondary endpoints are as follows:

- Incidence of AEs and clinically significant changes in laboratory values
- Incidence of anti-axicabtagene ciloleucel antibodies
- Levels of anti-CD19 CAR T cells in blood
- Levels of cytokines in serum
- Time to next therapy: defined as the time from the axicabtagene ciloleucel infusion date to the start of the subsequent new lymphoma therapy or death from any cause. Subjects who have not received subsequent new therapy and are still alive will be censored at the last contact date.

10.2.3. Covariates

The following covariates may be used in efficacy and safety analyses

- Age (< 65, ≥ 65 years)
- Gender
- Race
- Ethnicity
- Histological diagnosis (eg, FL, MZL), by both local and central pathology
- FLIPI (age > 60, Hgb < 12, Stage 3 or 4, > 4 nodal sites, elevated LDH)

- ECOG status (0 vs 1)
- Disease burden as defined by any of the following 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 extra-nodal tumor mass with a diameter of ≥ 7 cm
  - B symptoms
  - Splenomegaly
- Relapsed vs refractory status at study entry
- Time to relapse from completion of first anti-CD20-chemotherapy combination therapy (≥ 24 months, < 24 months)
- Prior PI3K inhibitor
- Number of prior lines of therapy (excluding single agent anti-CD20 antibody as a line of therapy)
- Double refractory (subjects refractory to the first 2 lines of therapy)

10.3. Sample Size Considerations

The trial uses a single-arm design to estimate the ORR in subjects with r/r B-cell iNHL treated with axicabtagene ciloleucel. The target response rate in subjects with FL is 60%.

Up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set, will be enrolled and treated.

The primary efficacy endpoint for this study in at least 80 subjects with FL in the inferential analysis set has 93% power to test the null hypothesis that the ORR is 40% versus the alternative hypothesis that the ORR is 60% with a 1-sided alpha level of 0.0237.

Within the inferential analysis set, interim analysis 3, 4, and 5 will be performed when 30 subjects with FL have had the opportunity to be followed for response for 6 months after axicabtagene ciloleucel infusion, when 80 subjects with FL have had the opportunity to be followed for response for 6 months after axicabtagene ciloleucel infusion, and when 80 subjects with FL have had the opportunity to be followed for response 9 months after the first disease response assessment. These interim analyses will be for safety and to assess early demonstration of efficacy. The interim analyses are based on the interpolated alpha spending function. The nominal alpha levels for the assessment of efficacy are 0.0003, 0.0005, and 0.0005. The study will not be stopped if early efficacy is demonstrated and the primary analysis will occur after at

least 80 subjects with FL in the inferential analysis set and have had the opportunity to be followed for 12 months after the first disease response assessment.

10.4. Statistical Assumptions

Treatment outcomes for subjects with r/r iNHL who have had > 2 prior regimens are exemplified by the clinical trials of the PI3K-inhibitors, idelalisib (Zydelig®) {Gopal 2014}, and copanlisib (Aliqopa) {Dreyling 2017}. In these trials, the ORRs were 57% and 59%, respectively, with CR rates of 6% and 12%, respectively. See Section 2.

In the current trial, it is anticipated that most subjects will have had prior treatment with at least one of these agents; thus, an ORR < 40% or CR < 15% would not be of clinical interest.

10.5. Analysis Subsets

The following analysis sets are defined:

The pivotal cohort is defined by the eligibility criteria specified below:

1) Histologically confirmed diagnosis 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

2) Relapsed or refractory disease after 2 or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent. (Single agent anti-CD20 antibody will not count as a line of therapy for eligibility). Stable disease (without relapse) > 1 year from completion of last therapy is not eligible.

    a) The safety analysis set will consist of all subjects treated with any dose of axicabtagene ciloleucel.

    b) The inferential analysis set will consist of all enrolled subjects who meet the eligibility criteria for the pivotal cohort and were treated with any dose of axicabtagene ciloleucel. This analysis set will be used for all analyses of objective response and endpoints based on objective response (best overall response, DOR, PFS).

    c) The full analysis set (FAS) will consist of all enrolled subjects and will be used for the summary of subject disposition, sensitivity analyses of ORR and PFS, and subject listings of deaths.

10.6. Access to Individual Subject Treatment Assignments

This is a single-arm, open-label study, and subjects and investigators will be aware of treatment received. Data handling procedures for the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan, DSMB charter, and trial integrity document.

10.7. Interim Analysis

The DSMB will review safety data after 10 subjects in the safety analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks for safety. This analysis will be for safety only.

The DSMB will meet again to review safety data after 30 subjects in the safety analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. This analysis will be for safety only.

The DSMB will meet again to review safety and efficacy data after 30 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. This analysis will be for safety and efficacy.

The DSMB will meet again to review the safety data when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion.

The DSMB will meet again to review the safety data when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 9 months from the first disease assessment date.

The DSMB will also review SAE information and SUSARs on a regular basis throughout the study. The sponsor may request additional reviews by the DSMB if safety concerns are identified. The DSMB may meet more often as needed.

10.8. Planned Methods of Analysis

The interim analysis 5 will be performed when at least 80 subjects with FL in the inferential analysis set have had the opportunity to be followed for 9 months after the first disease response assessment. The primary efficacy analysis of response rate will be performed when at least 80 subjects with FL in the inferential analysis set have had the opportunity to be followed for 12 months after the first disease response assessment. A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). The CSR will be written based on the data collected and analyzed from the primary analysis. Kite will ensure that the report meets the standards set out in the International Conference on Harmonisation (ICH) Guideline for Structure and Content of Clinical Study Reports (ICH E3). After the primary analysis, additional follow-up analyses of efficacy and safety will be performed as needed to satisfy regulatory requirements and to perform long-term efficacy, safety, and OS follow-up. The final analysis will occur when all subjects have completed the study.

The primary analysis for ORR as primary endpoint will be based on central review of disease assessments per the Lugano Classification {Cheson 2014}. The ORR based on investigator review of the disease assessment will be used as the sensitivity analysis for ORR.

Efficacy summaries will be presented by histological subtype (eg, FL and MZL) and overall.

10.8.1. ORR

The subject incidence of objective response will be calculated and 2-sided 95% confidence intervals will be calculated with the Clopper-Pearson method. An exact binomial test will be used to compare the ORR per central read among the subjects with FL and among the subjects with FL who have had 3 or more lines of prior therapy to the hypothesized historical control rate of 40%.

The incidence of subjects with CR, PR, SD, PD, and NE as best overall response to treatment and exact 2-sided 95% confidence intervals about the incidence will be generated.

10.8.2. CRR

The subject incidence of CR will be calculated. The 2-sided 95% confidence intervals will be provided about the CR rate, calculated with the Clopper-Pearson method. An exact binomial test will be used to compare the observed CR rate per central read among the subjects with FL and among the subjects with FL who have had 3 or more lines of prior therapy to the hypothesized historical control rate of 15% if ORR is statistically significant.

10.8.3. DOR

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for DOR. Kaplan-Meier estimates will be provided for the proportion of subjects who are alive and progression-free at 3-month time intervals. The number of subjects censored or having events will be summarized, as well as the reasons for censoring and the event type (PD or death). Analyses will be generated for DOR per central read and per investigator read. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR.

10.8.4. PFS

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for PFS. Kaplan-Meier estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided. The number of subjects censored or having events will be summarized, as well as the reasons for censoring and the event type (PD or death).

10.8.5. OS

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month, 6-month, and 12-month intervals will be provided.

10.8.6. Time to Next Therapy

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for time to next therapy.

10.8.7. Safety

Safety summaries will be provided by FL, MZL, and overall. AEs will be graded using the CTCAE version 4.03 or above. Subject incidence rates of all AEs, including serious AEs, fatal AEs, Grade 3 or higher AEs, and treatment -related AEs will be reported throughout the conduct of the study and will be tabulated by preferred terms and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medication use will be summarized.

Tables and/or narratives of deaths through the LTFU and treatment-related SAEs will be provided.

10.8.8. Long-term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject receives his or her last axicabtagene ciloleucel infusion. LTFU data analysis will be performed on subjects in the study and after transition to the LTFU study. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

10.8.9. Follow-up Analysis

After the primary analysis, additional follow-up analyses of efficacy and safety will be performed as needed to satisfy regulatory requirements and to perform long-term efficacy, safety, and OS follow-up.

11. REGULATORY OBLIGATIONS

11.1. IRB/IEC

A copy of the protocol, ICF, and any additional subject or trial information, such as subject recruitment materials, must be submitted to each site's respective IRB/IEC for approval. After approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site-specific and study SAEs (provided to the site by the key sponsor contact), along with any protocol deviations, to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2. Subject Confidentiality

Subject confidentiality must be maintained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique ID number
- Date of birth or year of birth/age at time of enrollment will be reported in accordance with local laws and regulations

For reporting of SAEs, subjects will be identified by their respective subject ID number, initials, and date of birth or year of birth (as per their local reporting requirements for both initials and date of birth).

Per regulations and International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) guidelines, investigators and institutions are required to permit authorization to the sponsor, contract research organization (CRO), IRB/IEC, and regulatory agencies to access subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which includes personal information.

11.3. Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the investigator's agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties is to be submitted to the key sponsor contact.

Both Kite and the investigator reserve the right to terminate the investigator's participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the sponsor with a copy of the correspondence.

Kite reserves the unilateral right, at its sole discretion, to determine whether to manufacture axicabtagene ciloleucel T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data, and records for which the study data are collected and verified. Examples of such source documents may include, but are not limited to, hospital records and patient charts; laboratory, pharmacy, and radiology records; subject diaries; microfiches; correspondence; and death registries. CRF entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all subject records that are readily retrieved to be monitored and/or audited at any time by the key sponsor contact, regulatory authorities, and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject ID lists
- Protocols and protocol amendments, IB, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records, and experimental product-related correspondence

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

Traceability records for the product, from procurement through manufacture to the administration of the product, should be kept by each relevant party (eg, the sponsor and the investigator/institution) for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by agreement with the sponsor. Before, during, and after completion or termination of the trial, each party should hold the necessary information available at all times to ensure bidirectional traceability, linking the subject information at the procurement site to the product and subject information at the study site to product, while ensuring the data protection legally required for the subject.

If the investigator cannot provide this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Kite to store these records securely away from the site so that they can be returned sealed to the investigator in the case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

If a subject is transferred to another study site, the investigator must notify Kite in advance before assigning the subject's study records to another party or moving them to another location.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors, or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy, and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator's agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH, GCP, and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility (ies), review of subject and study-related records, and compliance with protocol requirements as well as ICH/GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English, and concomitant medications should be identified by trade names. For additional details surrounding the completion of CRFs, refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in study KTE-C19-105 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on:
  - Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work and
  - Drafting the article or revising it critically for important intellectual content; and
  - Final approval of the version to be published; and
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data, or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite for review and approval. The study contract among the institution, principal investigator, and Kite or its delegate will outline the requirements for publication review.

16. COMPENSATION

Kite will provide compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

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18. APPENDICES

18.1. Sponsor and Investigator Signature Page

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGMENT

A PHASE 2 MULTICENTER STUDY OF AXICABTAGENE CILOLEUCEL IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA (INHL)

Amendment 7.0, 22 February 2023

This protocol has been approved by Kite Pharma, Inc. The following signature documents this approval.

Olga Nikolajeva	*[Refer to the appended electronic signature]*
Kite Medical Monitor Name (Printed)	Signature
[Refer to the appended electronic signature]	
Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner, and dependent children)
- Subinvestigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma, Inc.

Principal Investigator Name (Printed)	Signature
Date	Study Site Number

18.2. Country-specific Regulatory Agency Requirements - France

The postinfusion monitoring of subjects in this protocol will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 3, column "IP Administration Period, D1 to 7". The L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) recommends a 10-day hospitalization after infusion of any CAR T-cell product.

The daily monitoring will include vital signs (see Section 7.4), blood draw for chemistry panel with CRP (see Section 7.11.6), blood draw for CBC w/differential (see Section 7.9), and physical/neurological assessment. Any observed toxicity will be managed according to Section 6.5 of this protocol.

18.3. Lugano Classification

Refer to the imaging manual and {Cheson 2014} for details of assessment.

5-Point Scale (5PS) {Barrington 2014}

Score	Description
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma.

18.3.1. Complete Remission

18.3.1.1. Complete Metabolic Response (CMR) for Positron Emission Tomography-computed (PET-CT) Based Response

The designation of complete metabolic response (CMR) requires all of the following:

- A 5PS (5-point scale) score of 1, 2, or 3, with or without a residual mass
  - In Waldeyer's ring or extra-nodal sites with high physiologic uptake or with activation within spleen or marrow, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
- No new sites of disease should be observed.
- No evidence of FDG-avid disease in bone marrow

18.3.1.2. Complete Radiologic Response for CT-based Response

The designation of complete radiologic response (CRR) requires all of the following:

- Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion (LDi)
- No extra-lymphatic sites of disease
- Absent non-measured lesion
- Organ enlargement regress to normal
- No new sites of disease should be observed.

- Bone marrow normal by morphology; if indeterminate, immunohistochemistry (IHC) negative

18.3.2. Partial Remission

18.3.2.1. Partial Metabolic Response for PET-CT-based Response

The designation of partial metabolic response (PMR) requires all of the following:

- A 5PS score of 4 or 5, with reduced uptake compared to baseline (screening), and residual mass (es) of any size.

  Note:

  — At interim, these findings suggest responding disease.

  — At end of treatment (EOT), these findings suggest residual disease.

- No new sites of disease should be observed.

- Residual uptake higher than uptake in normal bone marrow, but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed)

If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with magnetic resonance imaging (MRI) or biopsy or an interval scan.

18.3.2.2. Partial Radiologic Response for CT-based Response

The designation of partial radiologic response (PRR) requires all of the following:

- ≥ 50% decrease in sum of the product of the perpendicular diameters (SPD) of up to 6 target measurable nodes and extra-nodal sites.

  — When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value.

  — When no longer visible, 0 x 0 mm

  — For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation.

- Absent/normal, regressed, but no increase of non-measured lesions

- Spleen must have regressed by > 50% in length beyond normal.

- No new sites of disease should be observed.

18.3.3. Stable Disease

18.3.3.1. No Metabolic Response for PET-CT-based Response

The designation of no metabolic response (NMR) requires all of the following:

- A 5PS score of 4 or 5, with no significant change in FDG uptake compared to baseline (screening), at an interim time point or end of treatment
- No new sites of disease should be observed.
- No change from baseline in bone marrow

18.3.3.2. Stable Radiologic Disease for CT-based Response

The designation of stable radiologic disease (SRD) requires all of the following:

- < 50% decrease from baseline in the sum of the product of the perpendicular diameters (SPD) of up to 6 dominant, measurable nodes and extra-nodal sites; no criteria for progressive disease are met
- No increase consistent with progression in non-measured lesion and organ enlargement.
- No new sites of disease should be observed.

18.3.4. Progressive Disease

18.3.4.1. Progressive Metabolic Disease for PET-CT-based Response

The designation of progressive metabolic disease (PMD) requires at least 1 of the following:

- A 5PS score of 4 or 5 with an increase in intensity of uptake from baseline, and/or
- New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment
- New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
- New or recurrent FDG-avid foci in bone marrow

18.3.4.2. Progressive Radiologic Disease for CT-based Response

The designation of progressive radiologic disease (PRD) requires at least 1 of the following:

- An individual node/lesion must be abnormal with:
  - Longest traverse diameter (LDi) > 1.5 cm, and
  - Increase by ≥ 50% from cross-product of LDi and perpendicular diameter (PPD) nadir, and
  - An increase in LDi or SDi, shortest axis perpendicular to the LDi, (SDi) from nadir
    - 0.5 cm for lesions ≤ 2 cm
    - 1.0 cm for lesions > 2 cm
  - In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline.
  - New or recurrent splenomegaly
- New or clear progression of pre-existing non-measured lesions
- New lesion
  - Regrowth of previously resolved lesions
  - A new node > 1.5 cm in any axis
  - A new extra-nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
  - Assessable disease of any size unequivocally attributable to lymphoma
- New or recurrent bone marrow involvement

18.4. Protocol Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below, with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summaries of changes for previous amendments are available upon request.

A separate tracked change (red-lined) document comparing the original protocol ([Amendment 6]) to this amendment will be made available upon the publication of this protocol.

12.10.1. Amendment [7] (22Feb2023) Section Number and Name	High-level Description of Change	Brief Rationale
Synopsis, Study Schema, Sections 3.5, 3.6, 6.2.5, 7.11.8, 7.11.9, 10.8.8, Table 4	The timing of subject transition to a separate long-term follow-up protocol (KT-US-982-5968) was defined.	New guidance added to reference transition to the LTFU study.
Section 9.2, 9.4, Table 4	Timeline for reporting targeted AEs and SAEs was lengthened. Additionally, clarification was added that only targeted AEs and SAEs related to axicabtagene ciloleucel need to be reported from 3 months through 15 years, until disease progression, or until the initiation of subsequent anticancer therapy.	Timeline for reporting targeted AEs and SAEs was lengthened due to regulatory agency feedback. Clarification that only targeted AEs and SAEs need to be reported from 3 months to 15 years added due to regulatory agency feedback.
Section 7.11.8, Section 9.4	Updated definition of secondary malignancies	Clarification.
Section 9.4	Included details for SAE reporting after completion of study and database closure.	Clarification.
Section 6.2.5	Language added clarifying collection of anticancer therapy information for subjects who are enrolled but do not receive axicabtagene ciloleucel infusion.	Clarification.
Section 7.11.9	Retreatment limited to 24 months after initial axicabtagene ciloleucel infusion.	Retreatment limit added to align with other Kite studies.
Section 5.2, 9.6	Updated contraception language from 6 months to 12 months.	Contraception language updated due to regulatory agency feedback.
Section 13	Study documentation and archive language updated.	Clarification.
Section 18.8	Pandemic Risk Assessment and Mitigation Plan Language added.	New section added to summarize potential risks associated with

12.10.1. Amendment [7] (22Feb2023) Section Number and Name	High-level Description of Change	Brief Rationale
		subjects being unable to attend study visits.
Section 6.4.3, 7.11.6, 18.2	Added country-specific regulatory agency requirements for post-infusion monitoring of subjects in France.	Addition of appendix previously added to a country-specific French protocol amendment to the global amendment. (Consolidation of PA6 & PA 6.1 [France] protocols)
Throughout, as needed	Minor changes.	Clarification/correction.

18.5. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Subject safety monitoring and follow-up:

   a) Subjects may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

      Mitigation plan: For subjects who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the subjects within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

      i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AEs/SAEs.

      ii) Review the current list of concomitant medications and document any new concomitant medications.

      iii) If applicable, confirm electronic/paper diary questionnaires and patient reported outcomes have been completed and transmitted.

   b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, blood draws, imaging, physical exams).

      Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study because of the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible. Central lab kits may be sent to subject's local hospital lab for sample collection. Relevant imaging (eg, PET-CT, CT) can be done at the subject's local hospital and images transferred or sent to the investigative site. Physical exams can be completed by a local physician with results sent to investigative site.

   c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

      Mitigation plan: The site staff will follow their approved informed consent process and remain in compliance with the local ethics committee/institutional review board and national laws and regulations. Remote consent will be allowed if it has been approved by

the local ethics committee/institutional review board. The consent process will be documented and confirmed by normal consent procedure at the investigative site at the earliest opportunity.

2) Protocol and monitoring compliance:

   a) Protocol deviations may occur in situations where scheduled visits or procedures cannot be conducted as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure at a protocol-specified time point, an unscheduled visit should be conducted as soon as possible when conditions allow so that the required procedure can be performed. The situation should be recorded and explained as a protocol deviation. Any missed subject visits must be reported in the eCRF, if possible, and recorded as deviations to the protocol because of the pandemic, so that they can be appropriately documented and described in the clinical study report. Any remote study visits that are conducted in lieu of clinic visits because of the pandemic will be documented as protocol deviations related to the pandemic.

   b) Study monitors may be unable to carry out source data review or source data verification, study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure ongoing data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring study visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on-site must be tracked centrally and updated on a regular basis.

3) Missing data and data integrity:

   There may be an increased amount of missing data because of a subject's missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

   Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

   Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit/risk assessment of axicabtagene ciloleucel in study subjects remains unchanged.

PROTOCOL TITLE: A PHASE 1-2 MULTI-CENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF KTE-C19 IN COMBINATION WITH ATEZOLIZUMAB IN SUBJECTS WITH REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Protocol Number:	KTE-C19-106 (ZUMA-6)
Kite Investigational Product	Axicabtagene ciloleucel
Clinical Study Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Key Sponsor Contacts:	Ioana Kloos, M.D. Sr. Director, Clinical Development Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 Email: ikloos@kitepharma.com Yuni Kim, Ph.D. Program Manager, Clinical Operations Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 Email: ykim12@kitepharma.com
Amendment 2:	04 August 2021

Confidentiality Notice

Investigators Agreement

A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Combination with Atezolizumab in Subjects with Refractory Diffuse Large B-Cell Lymphoma (DLBCL) (ZUMA-6) dated **04 Aug 2021** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner and dependent children)
- Sub-Investigators (including, if applicable their spouse, legal partner and dependent children)

at the start of the study and for up to one year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma Inc.

_____
Signature

_____
Name of investigator

_____
Date

PROTOCOL SYNOPSIS

TITLE

A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Combination with Atezolizumab in Subjects with Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

INDICATION

Treatment refractory DLBCL in adult subjects.

STUDY DESIGN

This is a Phase 1-2, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with atezolizumab in subjects with refractory DLBCL. The trial will be separated into two distinct Phases designated as Phase 1 and Phase 2.

During Phase 1, approximately 3-9 subjects with refractory DLBCL will be enrolled in up to 3 cohorts to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens. A safety review team (SRT) that is internal to the study sponsor and Phase 1 investigators, will review safety data after all subjects in each Phase 1 cohort have had the opportunity complete the dose-limiting toxicities (DLT) window. The SRT will make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 3 and outlined in Section 9.6.

In Phase 2**,** approximately 22 subjects will be enrolled to receive combination treatment with axicabtagene ciloleucel and atezolizumab based on the dose and schedule selected to move forward from the Phase 1 portion of the study as recommended by the SRT.

Independent of the cohort or Phase of the study, each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Conditioning chemotherapy
- Combination treatment (axicabtagene ciloleucel and atezolizumab)
- Post treatment assessment
- Long term follow-up

For study requirements assigned to each study period, please refer to Section 7 for details.

STUDY OBJECTIVES

The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens.

The primary objective of Phase 2 is to evaluate the efficacy of axicabtagene ciloleucel and atezolizumab, as measured by complete response rate in subjects with refractory DLBCL. Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and atezolizumab and additional efficacy, biomarker, pharmacokinetic, and anti-therapeutic antibody endpoints.

HYPOTHESIS

No formal hypothesis will be tested in this study. The Phase 2 portion of the study is designed to estimate the true CR rate in patients with refractory DLBCL treated with the axicabtagene ciloleucel followed by atezolizumab.

PRIMARY ENDPOINT

- Phase 1: Incidence of dose-limiting toxicities (DLT)
- Phase 2: Complete response rate (complete response [CR] per the revised International Working Group [IWG]) Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by study investigators.

SECONDARY ENDPOINT(S) FOR PHASE 1 AND 2

- Objective Response Rate (CR + PR) per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}
- Duration of Response
- Progression Free Survival
- Overall Survival
- Incidence of adverse events and clinically significant changes in safety lab values
- Levels of axicabtagene ciloleucel in blood and incidence of anti-KTE-C19 antibodies
- Atezolizumab pharmacokinetics and incidence of anti- atezolizumab antibodies in serum
- Levels of cytokines and other markers in serum

EXPLORATORY ENDPOINT(S) FOR PHASE 1 AND 2

- Objective response rate based on PD-L1 expression on tumor cells or infiltrating immune cells
- Investigation of potential biomarker development based on assessment of product cells, blood cells, tumor tissue at baseline and post-treatment, and the proposed actions of the investigational product

- Frequency of atezolizumab dose delays for ongoing acute toxicities following axicabtagene ciloleucel

SAMPLE SIZE

Approximately 3-31 subjects

Phase 1: approximately 3-9 subjects

Phase 2: approximately 22 subjects

STUDY ELIGIBILITY

Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both Phases of the study.

TREATMENT

Conditioning Chemotherapy Treatment:

- Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m2/day and cyclophosphamide 500 mg/m2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.

Investigational Product(s):

- Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 **anti-CD19 CAR T cells/kg**. Subjects who receive between 1.0 and 2.4 x 10^6 anti-CD19 CAR T cells/kg will be considered evaluable in the efficacy set. Under circumstances where subjects initially respond and subsequently relapse, subjects may be eligible for a second course of conditioning chemotherapy and axicabtagene ciloleucel. Refer to Section 6 for treatment and Section 7.12.8 for retreatment details.

- Atezolizumab treatment consists of an intravenous infusion of 1200 mg given every 21 days for 4 doses. In the Phase 1 portion of the study, the first dose of atezolizumab will be administered 21 days following axicabtagene ciloleucel infusion (Cohort 1), 14 days following axicabtagene ciloleucel infusion (Cohort 2), or 1 day following axicabtagene ciloleucel infusion (Cohort 3).

Additional axicabtagene ciloleucel and atezolizumab schedules or regimens may be explored in Phase 1.

The axicabtagene ciloleucel and atezolizumab treatment in Phase 2 will follow the dosing schedule with the best overall benefit/risk profile tested in Phase 1 as determined by the safety review team (see Figure 3).

PROCEDURES

At specific time points as outlined in the schedule of assessments, subjects will undergo the following procedures: collection of informed consent, general medical history including previous treatments for NHL, physical exam **(including neurological assessment)** including vital signs and performance status. Subjects will also undergo blood draws for complete blood count (CBC), chemistry panels, cytokines, C-reactive protein, lymphocyte subsets, anti-KTE-C19 antibodies, anti-atezolizumab antibodies, replication competent retrovirus (RCR) and anti-CD19 CAR T cell analysis. Women of child-bearing potential will undergo a urine or serum pregnancy test.

Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), brain magnetic resonance image (MRI), a positron emission tomography–computed tomography (PET-CT), and leukapheresis.

Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events and will have their disease assessed.

SAFETY REVIEW TEAM

A safety review team (SRT), internal to the study sponsor and Phase 1 investigators, will review the safety data following each Phase 1 cohort and make recommendations on further study conduct of Phase 1 and progression to Phase 2.

The SRT will also meet 1 time during the Phase 2 portion of the study when 6 subjects have had the opportunity to complete their 1-month disease assessment. The SRT will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. The SRT may meet more often as needed. Refer to Section 9.6.

STATISTICAL CONSIDERATIONS

The primary endpoint for the Phase 1 portion of the study is the incidence of DLT.

The primary endpoint for the Phase 2 portion of the study is complete response rate per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by the study investigators.

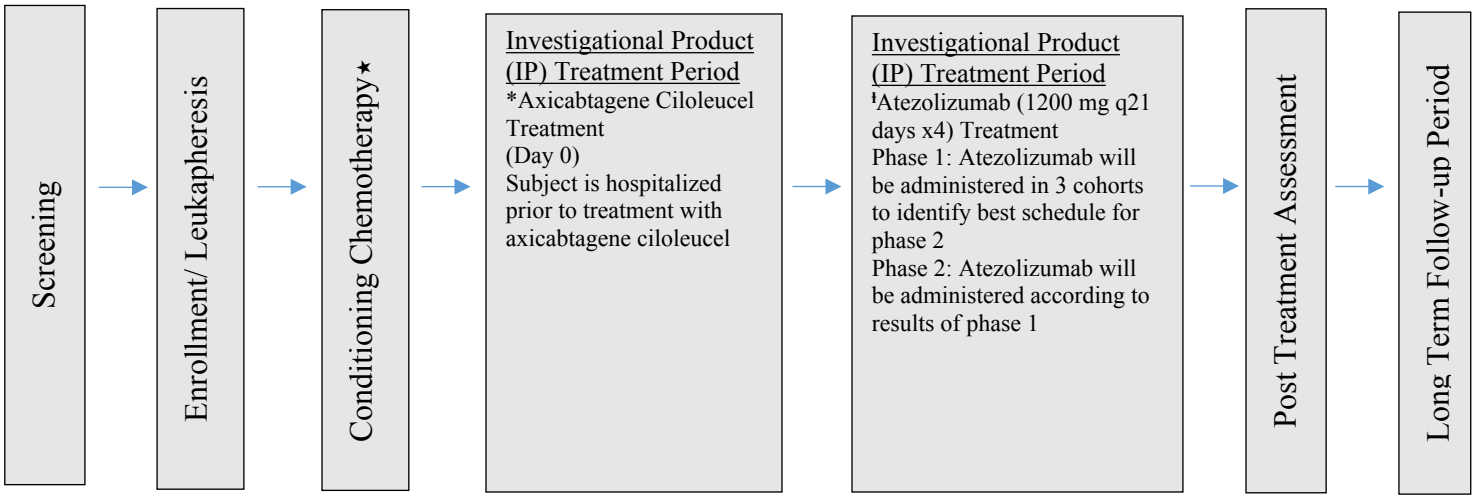
This study uses a single-arm design to estimate the true complete response rate in patients with DLBCL treated with the combination of axicabtagene ciloleucel and atezolizumab at the dosing schedule closest to concomitant administration tested in Phase 1 and deemed safe by the SRT. With a total sample size of 25 patients at a given dosing schedule, of which at least 3 will have been treated in the Phase 1 portion, an observed CR rate of 70% will yield 95% confidence that estimate of the true CR rate is between 51% and 88%. Refer to Section 10 for additional discussion.

STUDY GLOSSARY

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
ATAs	anti-therapeutic antibodies
AUC	area under the curve
Axicabtagene ciloleucel / KTE-C19	autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3 zeta chimeric antigen receptor
CAR	chimeric antigen receptor
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPF	central processing facility
CR	complete response / **Complete Remission**
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
eACT™	engineered autologous cell therapy
EBV	epstein-Barr virus
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	eastern cooperative oncology group
End of Study for individual subject	Defined as when the last day that protocol specified assessments are conducted for an individual subject
End of Study (primary completion)	Defined as when the last subject is assessed or received an intervention for the purposes of final collection of data for the primary endpoint at Month 6
End of Study (end of trial)	Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments
FAS	full analysis set
FL	follicular lymphoma
HAMA	human anti-mouse antibodies
HLH	hemophagocytic lymphohistiocytosis
ICF	informed consent form
ICU	intensive care unit
IP	investigational product

Abbreviation or Term	Definition/Explanation
IRB/IEC	institutional review board/independent ethics committee
IWG	International working group
LMWH	low-molecular-weight heparin
LTFU	long term follow-up
mITT	modified intend to treat
MMSE	mini mental status exam
MRI	magnetic resonance imaging
MSGV1	murine stem cell virus-based vector
NaCl	sodium chloride
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
OS	overall survival
PET-CT	positron emission tomography–computed tomography
PBMC	peripheral blood mononuclear cells
PMBCL	primary mediastinal B cell lymphoma
PD	progressive disease
PK	pharmacokinetic
PR	partial response / **Partial Remission**
RCR	replication competent retrovirus
scFv	single chain variable fragment
SOA	schedule of assessments
SD	stable disease
SRT	safety review team
SUSAR	suspected unexpected serious adverse reactions
Study day 0	Defined as the first day that **axicabtagene ciloleucel** is administered to the subject
TEAEs	treatment emergent adverse events
TFL	transformed follicular lymphoma
ULN	upper limit of normal

Figure 1. Study Schema (Phase 1 and Phase 2)



⋆ Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.

* Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously on Day 0 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg

ǂAtezolizumab treatment consists of an intravenous infusion of 1200 mg given every 21 days for 4 doses. In the phase 1 portion, the first dose of atezolizumab will be administered in 3 cohorts:

- Cohort 1: Beginning on day 21 following axicabtagene ciloleucel/KTE-C19 infusion
- Cohort 2: Beginning on day 14 following axicabtagene ciloleucel/KTE-C19 infusion
- Cohort 3: Beginning on day 1 following axicabtagene ciloleucel/KTE-C19 infusion

Atezolizumab treatment in phase 2 will follow the dosing schedule from phase 1 agreed upon by the study sponsors and the SRT.

Note: After the end of KTE-C19-106, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in a separate Long-term Follow-up study, KT-US-982-5968

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1. OBJECTIVES

The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens.

The primary objective of Phase 2 is to evaluate the efficacy of axicabtagene ciloleucel and atezolizumab, as measured by complete response rate in subjects with refractory diffuse large B-cell lymphoma (DLBCL). Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and atezolizumab and additional efficacy, biomarker, pharmacokinetic, and anti-therapeutic antibody endpoints.

2. DISEASE BACKGROUND AND RATIONALE

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes or natural killer cells. In the United States, B-cell lymphomas represent 80-85% of cases reported. In 2013, approximately 69,740 new cases of NHL and over 19,000 deaths related to the disease were estimated to occur. Non-Hodgkin lymphoma is the most prevalent hematological malignancy and is the seventh leading site of new cancers among men and women and account for 4% of all new cancer cases and 3% of deaths related to cancer {SEER 2014}.

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for approximately 30% of NHL cases. There are approximately 22,000 new diagnoses of DLBCL in the United States each year. In the past two decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of CHOP and immunotherapy. The addition of rituximab into combination therapies for DLBCL have greatly improved patient outcomes. However, patients with chemotherapy-refractory DLBCL following treatment under the current standards of care still have a particularly dire prognosis, with no curative treatment options {Flowers 2010}.

The population with the highest unmet need continues to consist of patients that do not respond to first line combination chemotherapy (typically R-CHOP) or do not respond to their most recent course of combination chemotherapy, as the disease is mostly insensitive to subsequent combination chemotherapy (typically R-ICE, R-ESHAP) (Table 1). In a review of 64 patients with DLBCL with disease progression during first line chemotherapy or only transient response (≤90 days) after end of induction treatment, the response rate to second line therapy was 15% and the median overall survival (OS) was 6 months, and no patient survived more than 26 months after first diagnosis {Josting 2000}. An analysis of outcome in 1126 patients with DLBCL after first line R-CHOP included 33 patients with primary refractory DLBCL who received second line therapy with curative intent. Only 3 (9%) were able to receive autologous stem cell transplantation (ASCT), and only 1 (3%) patient achieved long term survival {Hitz 2010}. Seshadri et al analyzed 120 patients who did not respond to second line platinum-based chemotherapy regimens (e.g., R-ICE) and showed that only 14% responded to their third line therapy {Seshadri 2008}. Ardeshna et al followed 19 patients with aggressive NHL, and 9 patients with transformed follicular lymphoma (TFL) that did not respond to second line chemotherapy. Only 5 of the 28 total patients (18%) responded to third line chemotherapy {Ardeshna 2005}.

Table 1. Historical Responses in Refractory NHL (SD or PD to Last Line of Therapy)

Setting	Outcome to Subsequent Therapy
Refractory to 1st line	
Phillip et al 1995 (n=28)	ORR 21%
Josting et al 2000 (n=64)	ORR 15%, median OS 6 mos
Ardeshna et al 2005 (n=5)	ORR 0%
Hitz et al 2010 (n=33)	Proceeded to ASCT 9%, 3% survived > 1 year
Telio et al 2012 (n = 111)	ORR 23%, median OS 10 mos
Matasar et al 2013 (n=10)	ORR 10%
Refractory to 2nd line	
Moskowitz et al 1999 (n=55)	Median OS 5 mos
Ardeshna et al 2005 (n=28)	ORR 18%, median OS (aggressive NHL) <6 mos
Seshadri et al 2008 (n=73)	ORR 14%
Relapsed post ASCT	
Nagle et al 2013 (N=45)	Median OS 8 mos

These results suggest that once a patient with DLBCL has become refractory to cytotoxic chemoimmunotherapy, the likelihood of achieving a response of any significant duration with subsequent lines of chemotherapy is low. New treatment paradigms are therefore needed in these refractory patients.

Immunotherapy is an emerging category of cancer therapy that employs the patient's own immune system to combat his or her cancer. Two distinct immunotherapeutic approaches to the care of patients with chemo-refractory lymphoma, engineered T cell therapy and immune checkpoint blockade have shown promise in pilot trials {Kochenderfer 2015, Lesokhin 2014}.

This trial will enroll patients with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

2.1. Anti-CD19 CAR T cell Product

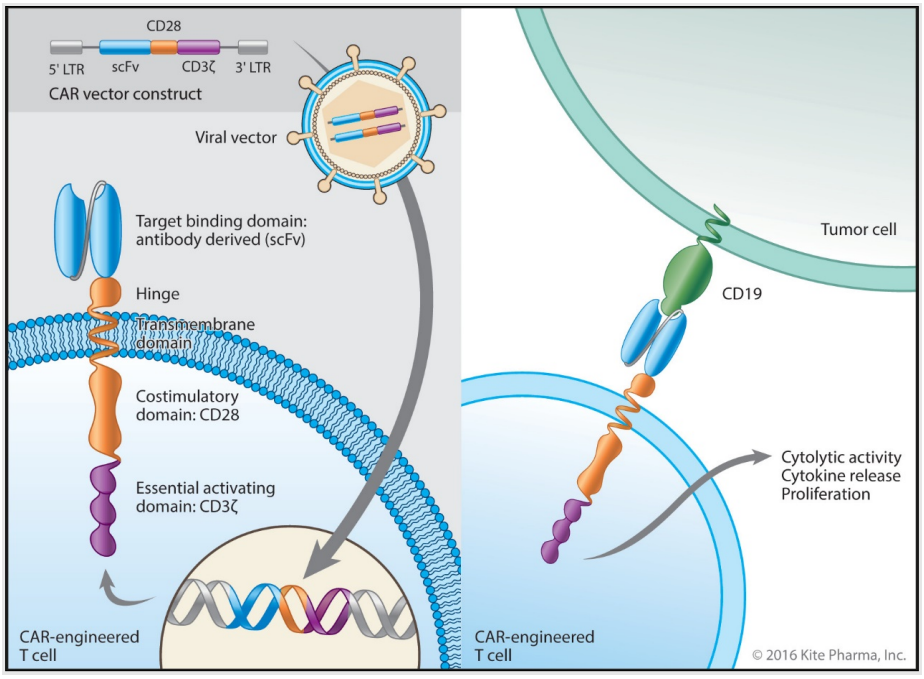
Anti-CD19 chimeric antigen receptor (CAR) T cells are autologous human T cells that have been engineered to express an extracellular single chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem.

An anti-CD19 CAR vector construct has been designed, optimized and initially tested at the Surgery Branch of the National Cancer Institute (NCI, IND 13871) (Figure 2); {Kochenderfer

2009, Kochenderfer 2010}. The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 {Nicholson 1997}. A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and persistence of anti-CD19 CAR T cells {Kowolik 2006}. The signaling domain of the CD3-zeta chain is essential for T cell activation. These fragments were cloned into the murine stem cell virus-based (MSGV1) vector, utilized to genetically engineer the autologous T cells. Treatment with anti-CD19 CAR T cells was administered to subjects with CD19+ B cell malignancies in NCI protocol (09-C-0082; IND 13871) and in several Kite-sponsored clinical trials. The same CAR vector construct will be used in this study.

The CAR construct is inserted into the T cells' genome by retroviral vector transduction. Briefly, peripheral blood mononuclear cells (PBMCs) are obtained by leukapheresis and Ficoll separation. Peripheral blood mononuclear cells are activated by culturing with an anti-CD3 antibody in the presence of recombinant interleukin 2 (IL-2). Stimulated cells are transduced with a retroviral vector containing an anti-CD19 CAR gene and propagated in culture to generate sufficient engineered T cells for administration.

Figure 2. Anti-CD19 Chimeric Antigen Receptor Construct and Mechanism of Action



2.2. Anti-CD19 chimeric antigen receptor (CAR) T cells

2.2.1. CD19 and Expression

CD19 is a 95 kD transmembrane protein expressed only in the B cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19

expression is maintained in B cell malignancies including all subtypes of B cell NHL, chronic lymphocytic leukemia (CLL), and non-T cell acute lymphoblastic leukemia (ALL) {Blanc 2011} with the exception of multiple myeloma.

2.2.2. Prior experience with axicabtagene ciloleucel and other anti-CD19 CAR T cells

The design and rationale of this study is in part derived from prior experience with axicabtagene ciloleucel on another Kite-sponsored study, ZUMA-1, and on a single-center study conducted at the National Cancer Institute. Please see the most current axicabtagene ciloleucel/KTE-C19 investigator's brochure for details.

2.3. Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and in cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma and for the treatment of non−small cell lung cancer.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

2.3.1. Summary of Nonclinical Studies for Atezolizumab

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to evaluate the safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were performed with atezolizumab.

The safety, PK, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical PK and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway; heightened immune responses and the potential to increase immune-associated inflammatory lesions were identified as possible safety risks in patients.

Refer to the Atezolizumab IB for details on the nonclinical studies.

2.3.2. Summary of Clinical Studies for Atezolizumab

For information on the additional ongoing studies, see the latest version of the Atezolizumab IB.

2.3.2.1. Clinical Safety for Atezolizumab

Single-Agent Clinical Safety in Study PCD4989g

Study PCD4989g, in which atezolizumab is being used as a single agent in subjects with locally advanced or metastatic solid tumors or hematologic malignancies, provides the majority of data (with 558 safety-evaluable patients as of the data extraction date of 11 May 2015) for the safety profile of atezolizumab as monotherapy.

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications. The most common cancer types for these patients include NSCLC, urothelial bladder cancer, melanoma, and renal cell carcinoma. Safety data for NSCLC are also derived from Studies GO28625 (FIR) and GO28753 (POPLAR).

Adverse Events

Of the 558 patients, 520 patients (93.2%) experienced at least one adverse event, including 376 patients (67.4%) who experienced one treatment-related adverse event. Commonly reported events (reported in > 10% of all patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, and cough (see Table 2).

Table 2. Study PCD4989g: Adverse Events with Frequency > 10% of Patients for All Grades

Preferred Term	All Grades n (%)	All Grades Related n (%)	Grade 3/4 n (%)	Grade 3/4 Related n (%)
Any adverse event	520 (93.2)	376 (67.4)	239 (42.8)	66 (11.8)
Fatigue	192 (34.4)	115 (20.6)	13 (2.3)	6 (1.1)
Decreased Appetite	142 (25.4)	62 (11.1)	4 (0.7)	0 (0.0)
Nausea	136 (24.4)	65 (11.6)	5 (0.9)	2 (0.4)

Preferred Term	All Grades n (%)	All Grades Related n (%)	Grade 3/4 n (%)	Grade 3/4 Related n (%)
Pyrexia	117 (21.0)	63 (11.3)	2 (0.4)	0 (0.0)
Constipation	116 (20.8)	8 (1.4)	2 (0.4)	0 (0.0)
Cough	113 (20.3)	11 (2.0)	1 (0.2)	1 (0.2)
Dyspnea	112 (20.1)	18 (3.2)	18 (3.2)	4 (0.7)
Diarrhea	110 (19.7)	53 (9.5)	2 (0.4)	1 (0.2)
Anemia	104 (18.6)	26 (4.7)	23 (4.1)	5 (0.9)
Vomiting	96 (17.2)	28 (5.0)	3 (0.5)	2 (0.4)
Asthenia	88 (15.8)	53 (9.5)	8 (1.4)	4 (0.7)
Back Pain	85 (15.2)	9 (1.6)	8 (1.4)	1 (0.2)
Headache	83 (14.9)	32 (5.7)	2 (0.4)	1 (0.2)
Arthralgia	79 (14.2)	35 (6.3)	2 (0.4)	0 (0.0)
Pruritus	75 (13.4)	55 (9.9)	0 (0.0)	0 (0.0)
Rash	73 (13.1)	53 (9.5)	0 (0.0)	0 (0.0)
Abdominal Pain	63 (11.3)	12 (2.2)	8 (1.4)	0 (0.0)
Insomnia	62 (11.1)	7 (1.3)	1 (0.2)	0 (0.0)
Peripheral edema	59 (10.6)	7 (1.3)	-	-
Chills	57 (10.2)	31 (5.6)	0 (0.0)	0 (0.0)

1. Note: '-' refers to missing Common Terminology Criteria Grade.

Grade 3/4 adverse events (on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) were reported in 239 patients (42.8%), of which 66 (11.8%) were considered related. Grade 3 and 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased gamma-glutamyl transferase (GGT), lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia.

Refer to the Atezolizumab IB for details on adverse events observed in patients treated with atezolizumab.

Immune-Mediated Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, gastrointestinal, and respiratory events.

Refer to the Atezolizumab IB for details on immune-mediated adverse events that were observed in patients treated with atezolizumab. Guidelines for the management of immune-mediated adverse events are described in the Atezolizumab IB.

For additional information, refer to the Atezolizumab IB.

Single-Agent Clinical Safety in Patients with NSCLC in the POPLAR Study

The Phase II POPLAR study interim analysis, as of the 30 January 2015 data cutoff, included data from 142 patients treated with atezolizumab as a fixed dose of 1200 mg IV every 3 weeks and 135 patients treated with docetaxel 75 mg/m2 IV every 3 weeks. The frequency of patients in the POPLAR study who reported any adverse event regardless of attribution was 96.5% for the atezolizumab arm and 95.6% for the docetaxel arm. A higher number of Grade ≥3 adverse events were observed in the docetaxel arm (55.6% vs. 43.0%), explained primarily by the difference in adverse events due to bone marrow suppression.

For additional information, refer to the Atezolizumab IB.

Clinical Safety in Combination with Bevacizumab or Platinum-Based Doublet Chemotherapy

Study GP28328 is a Phase Ib study of atezolizumab in combination with bevacizumab or cytotoxic chemotherapy in patients with multiple tumor types including NSCLC, TNBC, and colorectal cancer. As of 10 February 2015, 144 patients had been enrolled in this study: 39 in Arm A (atezolizumab, bevacizumab), 36 in Arm B (atezolizumab, bevacizumab, and FOLFOX), 14 in Arm C (atezolizumab, carboplatin, and paclitaxel), 24 in Arm D (atezolizumab + carboplatin and pemetrexed), 20 in Arm E (atezolizumab, carboplatin, and nab-paclitaxel), and 11 in Arm F (atezolizumab + nab-paclitaxel). The treatment combinations have been generally well tolerated. No DLTs have been reported during the dose-escalation stage in any study arm. Patients are being enrolled in safety and biopsy expansion cohorts in Arms A and B as well as in additional arms testing atezolizumab in combination with commonly used NSCLC chemotherapy doublets.

A total of 141 of 144 patients (97.9%) reported at least one adverse event while receiving study drug. The majority of these events were Grade 2 and 3 in severity. The five most commonly reported adverse events across the study arms (>10% of patients) included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. The adverse events were consistent with the known safety profile of each agent (atezolizumab monotherapy and chemotherapy). No additive effects were observed when atezolizumab was administered with chemotherapy.

All 39 patients who were enrolled in Arm A reported one or more adverse event. The five most frequently reported events were consistent with the overall population and included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. There were 36 patients enrolled in Arm B, and 97% of patients reported at least one adverse event. The most frequently reported adverse events (> 20% of patients) included fatigue, pyrexia, peripheral neuropathy, neutropenia, anemia, diarrhea, decreased appetite, temperature intolerance, constipation, vomiting, and nausea.

All patients who were enrolled in Arms C and D experienced an adverse event; 95% of patients who were enrolled in Arm E experienced an adverse event, and 83.3 % of patients enrolled in Arm F experienced an adverse event. The adverse events commonly reported in 2 or more patients in Arms C, D, and E included anemia, decreased appetite, hypomagnesemia, nausea,

neutropenia, constipation, vomiting, fatigue, rash, cough, and diarrhea. Adverse events commonly reported in 2 or more patients in Arm F included dermatitis, upper respiratory infection, alopecia, peripheral sensory neuropathy, fever, constipation, neutrophil count decreased, anemia, diarrhea, headache, nausea, and fatigue.

2.3.2.2. Clinical Activity for Atezolizumab

As of May 10, 2015 relevant clinical data for atezolizumab are mainly available from seven clinical trials in patients with solid tumors and hematologic malignancies. For all of these studies, treatment and/or analyses are ongoing. These include:

- Monotherapy: One Phase Ia (Study PCD4989g) and two-Phase II studies (Studies GO28625[FIR] and GO28753 [POPLAR])
- Combination Therapy: Three Phase Ib studies (Studies GP28328, GP28363 and GP28384), and one Phase II (WO29074 [IMmotion150]) study.

Additional safety information is also gleaned from the entire development program from atezolizumab. Further details of all ongoing and planned studies with atezolizumab can be found in the Atezolizumab Investigator's Brochure.

2.3.2.3. Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03-20 mg/kg), atezolizumab appeared to show linear PK at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent clearance (CL) and the mean volume of distribution at steady state (Vss) had a range of 3.11 to 4.14 mL/kg and 48.1 to 67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) to atezolizumab has been observed in patients in all dose cohorts and was associated with changes in PK for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and adverse events or infusion reactions has been observed.

For additional information on atezolizumab please refer to the Investigator's Brochure.

2.4. Rationale for Combination Therapy

Preclinical and translational results have suggested that T cells that have been engineered to express anti-CD19 chimeric antigen receptors, such as axicabtagene ciloleucel, rapidly upregulate markers of activation, including programmed cell death-1 (PD-1) {Perez 2015}, upon target engagement. Signaling through PD-1 is known to deliver a suppressive stimulus on the activated T-cells, giving rise to a phenotype commonly referred to as T-cell "exhaustion." Exhausted T cells have diminished proliferative and cytolytic capacity {John 2013}. Therefore, PD-1 expression and signaling on CAR T cells may lead to reduced clinical activity.

Conversely, a growing body of literature suggests that PD-L1 is expressed on a variety of human cancers and tumor-infiltrating immune cells, including in DLBCL {Chen 2013, Herbst 2014, Kiyasu 2015}. Furthermore, PD-L1 expression on DLBCL tends to associate with known markers of poor prognosis including activated B cell (ABC) phenotype and has been shown in retrospective series to be associated with shortened survival {Chen 2013, Kiyasu 2015}. Early results of PD-1 blockade with a monoclonal antibody, nivolumab, suggests that inhibition of this signaling cascade yields clinical responses in lymphoma {Lesokhin 2014}, although with limited OR (36%) and CR (9%) rates. The expression of PD-L1 on tumor cells and within the tumor microenvironment coupled with the activation-dependent expression of PD-1 on engineered T cells given to patients with refractory DLBCL led to the hypothesis that blockade of PD-1 ligation would augment the activation, proliferation, and cytolytic activity of CAR T cells.

As an additional safeguard against the potential of added toxicity in patients treated with the combination of anti-CD19 CAR T cells and atezolizumab, we have adopted a 3+3 “schedule compression” Phase 1 run-in in this study design. By staggering the doses of axicabtagene ciloleucel and atezolizumab, we aim to mitigate the potential additive or synergistic toxicities related to the combination.

3. STUDY DESIGN

3.1. General Study Design

This is a Phase 1-2, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with atezolizumab in subjects with refractory DLBCL. The trial will be separated into two distinct Phases designated as Phase 1 and Phase 2.

During Phase 1, approximately 3-9 subjects with refractory DLBCL will be enrolled in up to 3 cohorts to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens. A SRT that is internal to the study sponsor and Phase 1 investigators, will review safety data after all subjects in each Phase 1 cohort have had the opportunity complete the DLT window. The SRT will make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 3 and outlined in Section 9.6.

In Phase 2**,** approximately 22 subjects will be enrolled to receive combination treatment with axicabtagene ciloleucel and atezolizumab based on the dose and schedule selected to move forward from the Phase 1 portion of the study as recommended by the SRT.

Independent of the Phase of the study, each subject will proceed through the following study periods:

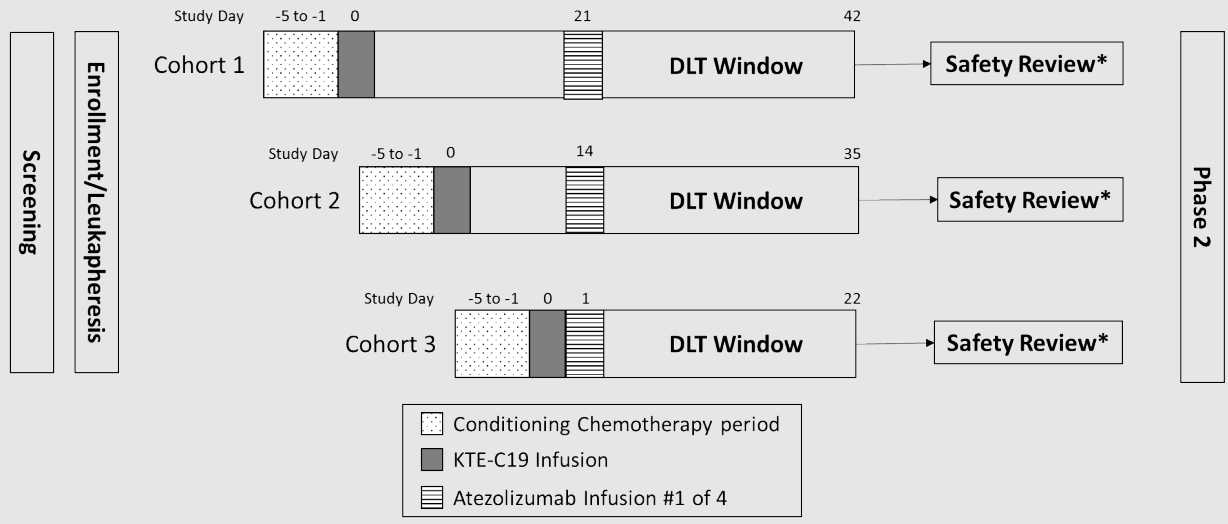
- Screening
- Enrollment/Leukapheresis
- Conditioning chemotherapy
- Combination treatment (axicabtagene ciloleucel and atezolizumab)
- Post treatment assessment
- Long term follow-up

The SRT will also meet 1 time during the Phase 2 portion of the study when 6 subjects have had the opportunity to complete their 1-month disease assessment. The SRT will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. The SRT may meet more often as needed. Refer to Section 9.6.

For study requirements assigned to each study period, please refer to the schedule of assessments (SOA) and Section 7 for details.

A study schema is drawn out and described in Figure 1.

Figure 3. Study Schema



*During phase 1, cohorts will be enrolled sequentially, beginning with cohort 1. After each phase 1 cohort has completed enrollment and all subjects have cleared the DLT window, the SRT will meet and review the overall benefit/risk profile of the dosing schedule tested in that cohort. SRT recommendations for further study conduct may include addition of patients to a cohort prior to opening a subsequent cohort, advancement to a subsequent cohort, exploration of alternative conditioning chemotherapy or KTE-C19 doses, advancement to phase 2, or study termination.

3.2. Participating Sites

Approximately 5-10 centers located in North America will participate in this study. During the conduct of the study, additional sites, regions, or countries may be added as necessary.

3.3. Number of Subjects

Participants in this trial will be referred to as "subjects". It is anticipated that approximately 3-31 subjects will be enrolled into this study as defined below:

Phase 1: approximately 3-9 subjects

Phase 2: approximately 22 subjects

It should be noted that the study sponsor may choose to close enrollment at any time. Please refer to the statistical considerations section of the protocol for sample size estimations.

3.4. Replacement of Subjects

Subjects will be replaced and continue to be enrolled until the specified number of subjects are attained in the DLT evaluable (Phase 1) and mITT sets (Phase 2). See Section 10.4 for additional information. Subjects who receive between 1.0 and 2.4 x 10^6 anti-CD19 CAR T cells/kg and who receive at least one dose of atezolizumab will be considered evaluable in the efficacy set. Subjects who have not received a axicabtagene ciloleucel cell dose in this range or have not received at least one dose of atezolizumab will be retained in the analyses of disposition and safety, where appropriate (Section 10.4).

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and, if applicable, timing of transition to the separate Long-term Follow-up (LTFU) study, KT-US-982-5968 (discussed in Section 3.5.3).

3.5.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes at least the Month 12 assessment. The end-of-study for each subject is defined as the last visit on this study, or when a subject is considered lost to follow-up, withdraws consent, or dies. The primary analyses will be conducted when all subjects for the overall study population have completed the 6-month disease response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first.

3.5.3. Long-term Follow-up

If the study is terminated prior to completion of 15 years of follow-up for all subjects, those who received an infusion of KTE-C19 will be provided an opportunity to transition to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to KTE-C19 as defined in KT-US-982-5968, presence of replication-competent retrovirus (RCR), and/or insertional mutagenesis for up to 15 years from the time of KTE-C19 infusion (also refer to Section 7.12.7).

For each subject, the subject's final visit on this study may be combined with the subject's first visit on the LTFU study. The timing of the subject's final visit/first LTFU study visit will depend upon the timing of the collection of all the subject's data that are required for the planned analysis for this study. In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

In some circumstances, subjects may be eligible to receive a second course of treatment after enrolling in the LTFU rollover study. Retreatment eligibility criteria are described in the KT-US-982-5968 protocol.

4. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the IRB/IEC approved consent form before initiating any study specific procedures or activities that are not part of a subject's routine care. Refer to Section 7 for details.

Each subject who enters the screening period will receive a unique subject identification number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened or retreated.

Subjects are considered enrolled in the study once the leukapheresis procedure is initiated.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

101) Histologically proven DLBCL including the following types defined by WHO 2008:

a) DLBCL not otherwise specified; T cell/histiocyte rich large B cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly.

102) Chemotherapy-refractory disease, defined as one or more of the following:

a) No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy chemotherapy are excluded

i) PD as best response to first-line therapy

ii) SD as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy

OR

b) No response to second or greater lines of therapy

i) PD as best response to most recent therapy regimen

ii) SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy

OR

c) Refractory post-ASCT

i) Disease progression or relapsed ≤12 months after ASCT (must have biopsy proven recurrence in relapsed subjects)

ii) if salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy

103) Subjects must have received adequate prior therapy including at a minimum:

a) anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and

b) an anthracycline containing chemotherapy regimen;

104) At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

105) MRI of the brain showing no evidence of CNS lymphoma

106) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis

107) Age 18 years or older at the time of informed consent

108) Eastern cooperative oncology group (ECOG) performance status of 0 or 1

109) Adequate bone marrow, renal, hepatic, pulmonary and cardiac function defined as:

a) ANC ≥1000/uL

b) Platelet count ≥75,000/uL

c) Absolute lymphocyte count ≥100/uL

d) Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min

e) Serum ALT/AST ≤2.5 ULN

f) Total bilirubin ≤1.5 mg/dl, except in subjects with Gilbert's syndrome.

g) Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings

h) No clinically significant pleural effusion

i) Baseline oxygen saturation >92% on room air

110) Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

5.2. Exclusion Criteria

201) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) unless disease free for at least 3 years

202) History of Richter's transformation of CLL or DLBCL that has arisen (transformed) from another histology (e.g., transformed follicular lymphoma)

203) Autologous stem cell transplant within 6 weeks of planned axicabtagene ciloleucel infusion

204) History of allogeneic stem cell transplantation

205) Prior CD19 targeted therapy with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for re-treatment

206) Prior treatment with PD-L1 inhibitor, PD-1 inhibitor, anti-CTLA4, anti-CD137, anti-OX40 or other immune checkpoint blockade or activator therapy with the exception of subjects who received atezolizumab in this study and are eligible for re-treatment

207) Treatment with systemic immunostimulatory agents (including but not limited to interferon and IL-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first atezolizumab dose.

208) Prior chimeric antigen receptor therapy or other genetically modified T cell therapy

209) History of severe, immediate hypersensitivity reaction attributed to aminoglycosides

210) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment.

211) History of HIV infection or acute or chronic active hepatitis B or hepatitis C infection. Subjects with history of Hep B or Hep C infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines.

212) 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.

213) Subjects with detectable cerebrospinal fluid malignant cells or known brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases.

214) History or presence of non-malignant CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement.

215) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement.

216) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months of enrollment.

217) Expected or possible requirement for urgent therapy within 6 weeks after leukapheresis due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome).

218) History of autoimmune disease. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

219) History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest CT scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed.

220) History of deep vein thrombosis or pulmonary embolism within 6 months of enrollment

221) Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

222) History of severe immediate hypersensitivity reaction to any of the agents used in this study

223) Treatment with a live, attenuated vaccine within 6 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study

224) Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

225) Subjects of either sex who are not willing to practice birth control from the time of consent through 5 months after the last dose of completion of atezolizumab and at least 6 months since axicabtagene ciloleucel infusion

226) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

6. PROTOCOL TREATMENT

6.1. Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- The conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The investigational products for this study are named axicabtagene ciloleucel and atezolizumab.
- The term study treatment refers to all protocol required therapies.

6.2. Study Treatment

6.2.1. Conditioning Chemotherapy

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted. Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of chemotherapy agents.

6.2.1.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.2.1.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges from 3-12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

6.2.1.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$.

Mesna should be administered per institutional guidelines. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.2.2. Axicabtagene Ciloleucel

This section contains general information and is not intended to provide specific instructions. Refer to Section 6.4.3.2 and the Investigational Product Manual for details and instruction on storage, thawing, and administration of axicabtagene ciloleucel.

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing axicabtagene ciloleucel arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor Phase of liquid nitrogen and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

Axicabtagene ciloleucel is a subject-specific product and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (e.g., initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of infused, the thaw start/stop time, and axicabtagene ciloleucel administration start/stop time, will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion.

To date, over 65 subjects have received doses of anti-CD19 CAR T cells made using the vector construct used in this study at doses ranging from 1-30 x 10^6 anti-CD19 CAR T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of axicabtagene ciloleucel or any products that support the management of axicabtagene ciloleucel (e.g., cryostorage bags, subject identification labels) required in this study are identified, please log on to kitepharma.com to report the complaint.

6.2.3. Atezolizumab

Formulation, Packaging, and Handling

The atezolizumab drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly yellow, sterile, preservative-free clear liquid solution intended for dilution in 0.9% aqueous sodium chloride solution for IV infusion. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C - 8°C (36°F -46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For detailed information and instructions, see the Atezolizumab Pharmaceutical Instructions and IB.

6.2.4. Concomitant Therapy

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care except those medications listed in the excluded medication Section 6.2.5.

All concurrent therapies, including medications, intubation, dialysis, and blood products, will be recorded from the date of the informed consent through 30 days after completing the final dose of atezolizumab, or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. Once this follow up period has been completed, only targeted concomitant medication will be collected including gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations, for 24 months or until disease progression, whichever occurs first.

For subjects who are not enrolled (e.g., screen failure or not leukapheresed), only concurrent therapies related to any serious adverse event(s) will be recorded.

For subjects who are enrolled but not dosed with axicabtagene ciloleucel, concurrent therapies will only be recorded from the date of the informed consent through 30 days after last procedure (e.g., leukapheresis, conditioning chemotherapy).

For subjects who are enrolled and receive axicabtagene ciloleucel but do not receive atezolizumab, all concurrent therapies will be collected through 3 months post-treatment of axicabtagene ciloleucel. Targeted concomitant medication will be collected including gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations, until 24 months following treatment with axicabtagene ciloleucel or until disease progression, whichever occurs first.

Specific concomitant medication collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.2.5. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis, and 5 days prior to axicabtagene ciloleucel administration.

Systemic corticosteroids may not be administered as premedication to patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Such patients should undergo non-contrast CT scans instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 6 months after axicabtagene ciloleucel administration, unless used to manage axicabtagene ciloleucel related or atezolizumab toxicities. Other medications that might interfere with the evaluation of axicabtagene ciloleucel, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

Treatment for lymphoma such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroids, other than defined/allowed in this protocol, and other investigational agents are prohibited, except as needed for treatment of disease progression after axicabtagene ciloleucel and atezolizumab administration.

Denosumab (a RANKL inhibitor) is prohibited during the study because it could potentially alter the efficacy and safety of atezolizumab. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study. Any experimental products other than those being investigated in this trial are excluded.

Traditional herbal medicines are prohibited during the study because the ingredients of many herbal medicines are not fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.

If permissibility of a specific medication/treatment is in question, please contact the Kite Pharma Medical Monitor.

6.2.6. Subsequent Therapy

Subsequent therapy, such as non-study specified chemotherapy, immunotherapy, targeted agents, SCT, or radiation therapy, administered after KTE-C19 infusion that is necessary to treat the subject's DLBCL will be recorded for all subjects until one of the following happens: the subject transitions to the KT-US-982-5968 LTFU study, is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled but do not receive a KTE-C19 infusion, any additional anticancer therapy will also be collected until the subject completes their participation in the current study, is considered lost to follow-up, withdraws consent, or dies, whichever occurs first.

Regarding allogeneic stem cell transplantation following exposure to atezolizumab, treating investigators are strongly cautioned and are referred to recent data reporting higher than expected rates of severe and fatal acute toxicities in patients recently treated with PD-1 inhibitors followed by allogeneic HCST {Merryman 2015}.

6.3. Rationale for Study Treatment dosing

6.3.1. Rationale for Conditioning Chemotherapy and Axicabtagene Ciloleucel Dose

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T cell expansion and function in pre-clinical models. The depth and duration of the lymphodepletion in preclinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific CD8+ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine is a potent lymphodepleting regimen. Optimizing the doses of cyclophosphamide and fludarabine to improve the depth and duration of lymphodepletion may enhance the activity of axicabtagene ciloleucel.

To improve the depth and duration of lymphocyte depletion, the conditioning chemotherapy dose will be cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days. Cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days has been studied and tolerated in subjects with B cell malignancies {O'Brien 2001}. This regimen has been evaluated in the NCI study (09-C-0082; IND 13871) and is the dose of conditioning chemotherapy that was chosen as the initial dose for Phase 1 of ZUMA-1 and carried forward to the Phase 2 portion of the ZUMA-1 study as recommended by the SRT.

The rationale for the axicabtagene ciloleucel dose in this study is based on aggregate safety and efficacy data compiled from the ZUMA-1 study as outlined in in the current axicabtagene ciloleucel investigator's brochure.

6.3.2. Rationale for Atezolizumab Dose and Schedule:

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) Q3W was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (Ctrough) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor interstitial concentration–to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first-in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses ranging from 0.01 to 20 mg/kg Q3W during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The MTD of atezolizumab was not

reached, and no dose-limiting toxicities were observed at any dose. ATAs to atezolizumab were associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but patients treated at 10, 15, and 20 mg/kg maintained the expected target trough levels of drug despite the detection of ATAs. To date, no relationship has been observed between the development of measurable ATAs and safety or efficacy. After review of available PK and ATA data for a range of doses, 15 mg/kg Q3W was identified as the lowest atezolizumab dosing regimen that would maintain Ctrough at ≥ 6 μg/mL while further safeguarding against interpatient variability and the potential for ATAs to lead to subtherapeutic levels of atezolizumab.

Simulations {Bai 2012} do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight-adjusted dose. Therefore, patients in this study will be treated Q3W at a fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg).

6.3.3. Rationale for Dosing schedule

PD-1 is an activation/exhaustion marker of cytolytic T cells, and its expression is upregulated on the surface of CAR T cells beginning prior to infusion and is further enhanced during *in vitro* exposure to CD19-expressing target cells {Bot 2015}. PD-1 surface expression is also increased following CAR T cell infusion {Perez 2015}. The capacity for cell division and cytolytic activity of the infused CAR T cells is therefore likely inhibited by ligation of PD-1 on the T cell surface beginning at the time of infusion. Furthermore, emerging evidence suggests that a primary biomarker of CAR T efficacy in lymphoma is the peak level of CAR T cells in peripheral circulation, which occurs in patients treated on NCI study 09-C-0082 and in ZUMA-1 at approximately day 7-15 after infusion {Kochenderfer 2015, Rossi 2015}. Thus, a core translational objective of this study is to augment the initial expansion of CAR T cells measurable in circulation.

For this reason, blocking PD-1 receptor ligation on the surface of CAR T cells using an anti-PD-L1 monoclonal antibody such as atezolizumab as early and as completely as possible is the most rational goal with the combination strategy. However, insofar as the acute toxicity following anti-CD19 CAR T cell infusion is related to the initial axicabtagene ciloleucel expansion, disinhibition of this process with PD-L1 blockade may potentiate acute toxicity. Therefore, we have adopted a 3+3 “schedule compression” Phase 1 run-in in the study design. By staggering the doses of axicabtagene ciloleucel and atezolizumab, we aim to mitigate the potential additive or synergistic toxicities related to the combination. Patients will be enrolled and treated one at a time during the Phase 1 portion of the study. The first cohort of 3 patients will be dosed with atezolizumab 21 days following infusion of axicabtagene ciloleucel at which point the great majority of patients will have passed the window of acute axicabtagene ciloleucel-related toxicities such as CRS and neurologic events. The patients will be closely monitored for recrudescence of CRS and neurologic events following administration of atezolizumab, as well as for atezolizumab-specific toxicity.

If these patients pass the DLT window and the regimen is viewed as safe by the SRT, a second cohort of 3 patients will be dosed with atezolizumab 14 days after their axicabtagene ciloleucel

infusion and monitored for DLT. At 14 days following axicabtagene ciloleucel infusion, most patients will have cleared the acute toxicity window and the majority of patients axicabtagene ciloleucel related toxicities will have resolved to Grade 1 or less; for patients that continue to experience Grade ≥ 2 CRS- or neurologic event-related adverse events, atezolizumab infusion will be delayed per Section 6.4.4. Safety review of cohorts 1 and 2 will indicate whether addition of atezolizumab can potentiate CAR T-related toxicity. If the rate and severity of immune activation is tolerable, a third and final cohort of 3 patients will be enrolled who will receive atezolizumab 1 day after axicabtagene ciloleucel, before onset of CRS.

6.3.4. Rationale for Pharmacokinetic and ATA Sample Collection

The proposed PK and ATA sampling for atezolizumab will contribute to the characterization of the pharmacokinetics of the atezolizumab when given in combination with axicabtagene ciloleucel and conditioning chemotherapy in subjects with DLBCL. The atezolizumab concentration and atezolizumab ATA results may be compared with available data from other clinical studies to assess for a potential pharmacokinetic and/or pharmacodynamic interaction between study treatments, and/or explore correlations with any clinical activity and safety events. Sparse sampling was employed to minimize inconvenience to the patient while providing a sufficient number of samples to allow characterization of atezolizumab concentrations, and ATA formation, after a single atezolizumab dose and at steady state.

6.4. Study Treatment Schedule and Administration

6.4.1. Leukapheresis

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the Cell Processing Facility (CPF) over night as described in the investigational product manual. Once a subject commences leukapheresis, the subject is considered enrolled in the study.

Mononuclear cells will be obtained by leukapheresis (12–15-liter apheresis with a goal to target approximately 5-10 x 10^9 mononuclear cells). The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the investigational product manual.

Upon arrival at the CPF, each subject's leukapheresed product will be processed to enrich for the T cell containing PBMC fraction. T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the investigational product per CPF SOPs. Once the product has passed certain release tests, it will be shipped back to the treating facility. Following completion of each subjects' conditioning chemotherapy regimen, subjects will receive their respective axicabtagene ciloleucel infusion.

6.4.2. Cyclophosphamide and Fludarabine (Days -5 through -3 before infusion of axicabtagene ciloleucel)

Subjects will receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel *in vivo*. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day -5 through Day -3 with 2 rest days before the receiving axicabtagene ciloleucel. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

The 3-day conditioning regimen of fludarabine and cyclophosphamide will be administered in accordance with the below daily dosing instructions.

- IV hydration with 1L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500mg/m^2 IV over 60 minutes followed by:
- Fludarabine 30mg/m^2 IV over 30 minutes followed by:
- An additional 1L of 0.9% NaCl at the completion of the cyclophosphamide infusion
- Add Mesna per institutional guidelines

Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours). In general subjects should be kept well-hydrated but closely monitored to prevent fluid overload.

6.4.3. Axicabtagene Ciloleucel (Day 0):

All subjects will be hospitalized to receive treatment with axicabtagene ciloleucel followed by an observation period. Subjects will remain in the hospital at a minimum through day 7 post treatment with axicabtagene ciloleucel.

Subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities return to ≤ Grade 1 or baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (e.g., renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1, or if deemed necessary by the treating investigator.

6.4.3.1. Axicabtagene Ciloleucel Premedication Dosing

The following pre axicabtagene ciloleucel infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the medical monitor.

- Tylenol 650 mg PO
- Benadryl 12.5**-25** mg IV **or PO**

6.4.3.2. Axicabtagene Ciloleucel Dosing

Central venous access such as a port or a peripherally inserted central catheter is required for the administration of axicabtagene ciloleucel and for the hospitalization treatment period. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing and administration of axicabtagene ciloleucel are outlined in the Investigational Product Manual (IPM). The IPM must be reviewed prior to administration of axicabtagene ciloleucel.

Research sites should follow institutional guidelines for the infusion of cell products.

6.4.4. Atezolizumab Dosing and Administration Instructions (Day 21, Day 14 or Day 1 after Axicabtagene Ciloleucel Administration and every 21 days thereafter for 3 additional (4 total) doses)

Atezolizumab treatment consists of an intravenous infusion of 1200 mg (as a prepared dilution in a 250 mL of 0.9% NaCL) given every 21 days for 4 doses. In the Phase 1 portion, the first dose of atezolizumab will be administered in 3 cohorts:

- Cohort 1: Beginning on day 21 following axicabtagene ciloleucel infusion
- Cohort 2: Beginning on day 14 following axicabtagene ciloleucel infusion
- Cohort 3: Beginning on day 1 following axicabtagene ciloleucel infusion

A safety review team (SRT), internal to the study sponsor and Phase 1 investigators, will review the safety data following each Phase 1 cohort and make recommendations on further study conduct of Phase 1 and progression to Phase 2.

For more detailed information regarding administration, refer to the Atezolizumab Pharmacy Instructions and IB.

Dosage, Administration, and Compliance

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For more detailed information regarding administration, refer to the IB and Pharmacy Manual.

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes and 2 hours

(±15 minutes) after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (±10 minutes) after the infusion.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for subsequent infusions at the discretion of the treating physician after consultation with the Medical Monitor. The management of infusion-related events will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.

- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event.

- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see Appendix B.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Dosage Modification

No reduction or modification of the atezolizumab dose will be allowed. Any toxicity associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an

immediate therapeutic effect, and there is no antidote for atezolizumab. In severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

See the Atezolizumab IB for the management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity, and other immune-mediated adverse events, as these have been observed with exposure to atezolizumab and are potentially immune mediated. See Appendix B for precautions for anaphylaxis

Atezolizumab may be withheld for up to 42 days. If atezolizumab has to be withheld for > 42 days due to drug-related events without appropriate resolution, despite appropriate management, then atezolizumab should be discontinued. However, if in the investigator's judgment, the patient is likely to derive benefit from resuming atezolizumab after a 42-day delay, atezolizumab may be restarted with the approval of the Medical Monitor.

Discontinuation of atezolizumab may not have immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, tocilizumab, or TNF-alpha inhibitors.

Atezolizumab dosing will be delayed for ongoing Grade ≥2 CRS or neurologic events. The delayed dose will be given upon resolution of CRS- and neurologic events to Grade 1 or less. If a dose is held greater than 7 days beyond the scheduled administration, it will not be given. Should an atezolizumab dose be delayed less than 7 days, the remaining 3 doses should be administered every 21 days from the onset date of first dose. Likewise, all protocol required procedures should follow the same schedule as outlined in the schedule of assessments beginning on the onset date of the first dose.

6.5. Axicabtagene Ciloleucel Toxicity Management

To date, the following important risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, and cytopenias. Please refer to Section 6 of the current Investigator's Brochure for details regarding these events and management guidance.

As the safety experience with axicabtagene ciloleucel increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the axicabtagene ciloleucel IB for guidance regarding managing axicabtagene ciloleucel related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with axicabtagene ciloleucel as well as possible complications associated with malignancy and cancer treatment.

6.6. Atezolizumab Toxicity Management

6.6.1. Safety Plan

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All adverse events and serious adverse events will be recorded as outlined in Section 9.

6.6.2. Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions or systemic immune activation. Adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis or elevated transaminase, pneumonitis, colitis, myositis, and myasthenia gravis have been observed in **patients treated with atezolizumab**. For further details regarding clinical safety and a more comprehensive list of observed adverse events with atezolizumab, see the Atezolizumab IB.

6.6.3. Management of Patients Who Experience Atezolizumab-Specific Adverse Events

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids or other immunosuppressive therapy.

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab.

Guidelines for management of adverse events associated with atezolizumab can be found in the Atezolizumab IB.

6.6.4. Systemic Immune Activation

Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk when given in combination with other immunomodulating agents.

Because of the significant overlap of clinical symptoms and laboratory manifestations of SIA with those of CRS and neurologic events, as described in the current axicabtagene ciloleucel investigator's brochure, investigators are advised to consider these syndromes as

pathophysiologically interrelated and possibly only distinguishable by the timing of their onset and their duration.

As such, it is recommended that the following diagnostic and management strategies be utilized for symptoms with onset after the second dose of atezolizumab. For those symptoms that occur prior to the second dose of atezolizumab, please refer to the current axicabtagene ciloleucel investigator's brochure for information regarding axicabtagene ciloleucel-related toxicities.

Recommendations regarding early identification and management of SIA are provided below. Early communication with the Medical Monitor is essential and is strongly encouraged. As for severe CRS, neurologic events, or HLH, in the event of suspected SIA, atezolizumab should be withheld and the Medical Monitor should be contacted immediately for additional guidance.

Early disease recognition is critical, and SIA should be suspected if, in the absence of an alternative etiology, the patient meets two or more of the following criteria:

- Hypotension that is refractory to aggressive IV fluid challenge
  - Vasopressor support may be required.
- Respiratory distress that requires aggressive supportive care
  - Supplemental oxygen and intubation may be required.
- Fever $> 38.5°C$
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Any of the following unexplained laboratory abnormalities (change from baseline)
  - Cytopenias (in two or more lineages)
  - Significant transaminitis
  - Coagulopathy
- For patients with suspected SIA, an initial evaluation should include the following:
  - CBC with peripheral smear
  - PT, PTT, fibrinogen, and D-dimer
  - Ferritin
  - Triglycerides

— AST, ALT, and total bilirubin

— LDH

— Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

Laboratory tests with normal results should be repeated frequently in patients for whom a high clinical suspicion of SIA exists.

If cytopenias are present (Grade ≥ 2 in two or more lineages) or ferritin is ≥ 3000 ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)
- Soluble interleukin 2 (IL-2) receptor (sCD25)
- Natural killer cell activity
- Cytomegalovirus, Epstein-Barr virus, and herpes-simplex virus evaluation (for reactivated or active disease)

Diagnostic criteria and recommended management for SIA are provided in Table 3. The diagnostic criteria apply only when alternative etiologies have been excluded.

Table 3. Diagnostic Criteria and Recommended Management for Systemic Immune Activation (SIA)

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)		
Major Criteria	**Minor Criteria**	
• Fever ≥ 38.5°C on more than one occasion • Ferritin ≥ 3000 ng/mL • Cytopenias (Grade ≥ 2 in two or more lineages) • Age-adjusted soluble IL-2 receptor elevated by ≥ 2 standard deviations • Severe dysfunction in two or more organs • Decreased fibrinogen	• Splenomegaly • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Elevated GGT or LFTs (AST, ALT, or total bilirubin) • Elevated triglycerides • Elevated LDH • Decreased natural killer cell activity	
Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	**Diagnosis**	**Action to Be Taken**

≥ 4 major criteria	Consistent with SIA	• Permanently discontinue atezolizumab. • Consider treatment with an immunosuppressive agent (i.e., anti-IL-6 agent, infliximab, cyclosporine A, or etoposide) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent). • Contact the Medical Monitor for additional recommendations. • Consider HLH-94 protocol if there is no clinical improvement.
3 major criteria OR 2 major plus ≥ 3 minor criteria	Probable SIA	• Depending on clinical severity, follow guidelines for "Consistent with SIA" or "Possible SIA" diagnosis. • The Medical Monitor may be contacted for recommendations.
2 major plus ≤ 2 minor criteria OR 1 major plus ≥ 4 minor criteria	Possible SIA	• Withhold atezolizumab. • Consider treatment with IV corticosteroids. • The Medical Monitor may be contacted for additional recommendations. • Follow guidelines for "Consistent with SIA" diagnosis if there is no clinical improvement or if clinical worsening occurs. • If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor. *

GGT = γ-glutamyl transpeptidase; IL-2 = interleukin-2; IV = intravenous; LFT = liver function test;
Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients {Hejblum 2014}.
Case reports and recommendations have been published for cytokine-release syndrome {Lee 2014, Maude 2014, Teachey 2013}, and, on the basis of etiologic similarities, these practices have been incorporated into the above treatment recommendations.
These recommendations do not replace clinical judgment and are intended as suggested guidance.
**Resumption of atezolizumab may be considered in patients who are deriving benefit, as assessed by the Investigator, and have fully recovered from the immune-related event. These patients can only be re-challenged with atezolizumab after approval has been documented by both the Study Chair and the Medical Monitor.*

7. STUDY PROCEDURES

Research staff should refer to the SOAs for an outline of the procedures required. The visit schedule is calculated from axicabtagene ciloleucel infusion on Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7.12. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current IRB/IEC approved ICF prior to any study specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

7.2. Demographic Data

Demographic data will be collected as per country and local regulations and guidelines. Where applicable, demographic data will include sex, date of birth, race, ethnicity**,** and country of enrollment to study their possible association with subject safety and treatment effectiveness.

7.3. Medical and Treatment History

Relevant medical history prior to the start of adverse event reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the subject's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subject's chart should be obtained.

7.4. Physical Exam, Vital Signs and Performance Status

Physical exams will be performed during screening and at times noted in the SOA. Changes noted in subsequent exams when compared to the baseline exam will be reported as an adverse event.

During IP administration/hospitalization, vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature will be monitored before and after the axicabtagene ciloleucel infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3°C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

For the first infusion of atezolizumab, the patient's vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes and 2 hours (±15 minutes) after the infusion. For subsequent atezolizumab infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (±10 minutes) after the infusion.

Performance status as measured by the ECOG scale will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

7.5. Cardiac Function

Each subject's cardiac function, as measured by Left Ventricular Ejection Fraction (LVEF), will be assessed during the screening period to confirm study eligibility. No evidence of clinically significant pericardial effusion as required by eligibility will also be confirmed. Both LVEF and pericardial effusion will be assessed prior to study entrance by ECHO. An ECHO performed following the subject's last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

A 12-lead ECG will also be performed during the screening period.

7.6. Magnetic Resonance Imaging

Each subject will undergo a screening brain MRI to rule out CNS metastasis during the screening period of the study.

7.7. Toxicity Evaluation

Following axicabtagene ciloleucel dosing, an additional lumbar puncture for collection of CSF should be performed at first appearance of Grade 2 or greater neurological symptoms or as medically indicated. Additional evaluations of the CSF should be performed per institutional standard of care. CSF samples (i.e., baseline and collected on study to assess neurological symptoms) will be submitted to the central laboratory.

7.8. Bone Marrow Biopsy

For subjects with a potential complete response to axicabtagene ciloleucel and atezolizumab, a follow-up bone marrow aspirate and biopsy will be performed in subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. To confirm a complete response, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. Refer to Section 7.9 and Appendix A for treatment response assessment requirements per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}.

7.9. Disease Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}. Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Baseline PET-CT scans of the neck, chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. Subjects will have their first post axicabtagene ciloleucel infusion planned PET-CT tumor assessment 6 weeks following the axicabtagene ciloleucel infusion and at regular intervals as highlighted in the SOA during the post treatment and long-term follow-up portion of the study.

Post axicabtagene ciloleucel administration disease assessments will be used to determine the time when progressive disease occurs. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA.

A bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR. Per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}, a bone marrow aspirate and biopsy should be performed only when the subject had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology, or if indeterminate by morphology, it must be negative by immunohistochemistry to assign a CR to treatment.

If the subject is eligible for retreatment with axicabtagene ciloleucel, the last scan prior to retreatment will be considered the baseline for the purpose of evaluating the response to retreatment.

7.10. Laboratory

The below samples will be collected at the time points indicated in the SOA. Additional samples (e.g., blood, urine, CSF, tissue, etc) may be collected as needed for further safety testing. Please refer to the Laboratory Manual for additional detail and information on collection requirements.

Local lab analysis:

- Sodium (Na), Potassium (K), Chloride (Cl), Total CO_2 (bicarbonate), Creatinine, Glucose, Blood Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LDH, Uric Acid

- C-reactive protein (CRP)

- Complete Blood Count with Differential

- A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma Medical Monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma Medical Monitor for instructions.

Central lab analysis:

- Blood draws for lymphocyte subsets, cytokine levels, RCR and tracking of anti-CD19 CAR T cells by qPCR analysis will be performed at intervals outlined in the SOA. Mid cycle assessments one week after the first cycle of atezolizumab are mandatory. Thereafter, repeated mid cycle assessments one week after doses 2-4 of atezolizumab will be at the discretion of the investigator unless the patient is admitted to the hospital in which case the assessments will be mandatory.

- For Phase 2 only, a PBMC sample will be collected and CBC with differential will be done 2 to 3 days after the first 2 doses of atezolizumab as described in the Schedule of Assessments.

- Serum samples will also be evaluated for anti-KTE-C19 antibodies and human anti-mouse antibodies

  — For serum samples that demonstrate increased anti-KTE-C19 human anti-mouse (HAMA) at the Post-Treatment Assessment Visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first.

- Serum samples for analysis of anti-atezolizumab antibodies and PK will be sent to and held at the central laboratory until distribution to a sponsor-designated bioanalytical laboratory or to the sponsor for analysis

- Archived tumor tissue and, for subjects who sign the optional portion of the informed consent, fresh tumor biopsies will be collected for central path review and evaluation of prognostic markers specific for NHL and pertaining to the tumor immune environment, including PD-1 and PD-L1 and other baseline immune and stromal

characteristics. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations), RNA, or protein markers relevant to this line of therapy.

7.11. Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for axicabtagene ciloleucel in conjunction with PD-L1 blockade. Prognostic markers specific for aggressive NHL and related to the tumor immune environment may also be evaluated.

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR T prior to and after atezolizumab treatment cells will be monitored in the blood primarily by PCR analysis, complemented by flow cytometry.

Levels of serum cytokines will also be evaluated in the blood. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines IL-6, TNFα, IL-10, IL-2, GM-CSF, IL 15, IL-17a, IFNγ, IL-12p40/p70; immune effector molecules Granzyme A, B, Perforin; correlates of acute Phase response CRP, ferritin, sIL-2Ra and chemokines MIP-1α, MIP-1β, IP-10, MCP-4.

Cerebral spinal fluid (CSF), and additional subject samples (e.g., pleural fluid), may be harvested from subjects who develop neurologic events or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable, lymphocyte populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of axicabtagene ciloleucel.

As axicabtagene ciloleucel comprises retroviral vector transduced T cells, the presence of replication-competent-retrovirus (RCR) in the blood of treated subjects will be monitored until Month 12. If there are not positive results, samples will be collected and held for up to 15 years.

In addition, baseline leukapheresis and final axicabtagene ciloleucel samples will be banked and may be analyzed by immunophenotyping, qPCR, and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of immune-related markers.

Archived tumor tissue will be collected for central path review. Additional analysis will include CD19 and PD-L1 expression (immunohistochemistry), gene expression profiling, and analysis of DNA alterations for sub-classification of DLBCL. Remaining samples may be stored for future exploratory analysis of tumor DNA, RNA, or protein markers.

For subjects who sign the optional portion of the consent form, on-study paired core biopsies of tumor or bone marrow core biopsy and aspirate (in cases where bone marrow disease involvement is suspected) will be performed at baseline and after axicabtagene ciloleucel and at least one atezolizumab infusion when we expect expansion and tumor infiltration with CAR T cells (any time between day 7 and 30). In addition, persisting, relapsing or emerging lesions could also be biopsied to help determine eligibility for re-treatment or mechanisms of tumor

resistance. Exploratory analysis of tumor or immune cell markers that correlate with response to axicabtagene ciloleucel or disease prognosis will be analyzed.

At selected sites and for subjects who sign the optional portion of the consent form, on-study paired lumbar puncture for collection of CSF samples will be performed at baseline prior to axicabtagene ciloleucel infusion and after axicabtagene ciloleucel infusion when we expect expansion, infiltration of the CAR T cells and neurologic events. Exploratory analysis of cells, analytes or immune cell markers within the CSF will be analyzed in conjunction with the clinical data to better understand the underlying pathogenesis of neurologic events. These samples and any other derivatives from these samples may be stored up to 15 years to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who in turn can contact the central laboratory. The investigator should provide the sponsor with the study and subject number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

Pharmacokinetic and Anti-Therapeutic Antibody Assays

Instruction manuals and supply kits will be provided for all samples sent to the central laboratory. The following samples will be sent to the central laboratory, and then to a sponsor-designated bioanalytical laboratory or to the sponsor for analysis:

- Serum samples will be assayed for the presence of ATAs to atezolizumab with the use of validated immunoassays.

- Serum samples will be assayed for atezolizumab concentrations with the use of a validated immunoassay.

These samples and any other derivatives from these samples may be stored up to 15 years to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who in turn can contact the central or bioanalytical laboratory. The investigator should provide the sponsor with the study and subject number so that the sample can be located and destroyed.

7.12. Description of Study Periods

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled or the reason for why the subject failed screening.

7.12.1. Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through commencement of leukapheresis **(**enrollment**)**. Informed consent must be obtained before completion of any non-standard of care study specific procedures. Procedures that are part of standard of care are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA.

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled in the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA:

- Medical history and disease assessment
- Physical examination including height and weight
  - Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.
- Vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- ECOG performance status
- Neurological examination
- ECG
- ECHO for LVEF and pericardial effusion assessment
  - An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility
- Imaging Studies
  - Brain MRI
  - Baseline PET CT of the neck, chest, abdomen and pelvis

- PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility.
- If PET CT is performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible.

- Labs
  - Chemistry panel
  - CBC with differential
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Lumbar puncture for subjects with new or suspicious neurological findings suggestive of CNS involvement.
- Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- Once eligibility confirmed, submission of archived tumor tissue to the central lab, and, for subjects who signed the optional portions of the consent, collection of fresh tumor sample.

7.12.2. Rescreening

Subjects who are unable to complete the screening assessments or do not meet the eligibility criteria during the 28-day screening period will be permitted to rescreen one time. Subjects will retain the same subject identification number assigned at the original screening. If rescreening occurs within 28 days of the initial signing of the informed consent, only the procedure(s)/assessment(s) that did not originally meet the eligibility criteria need to be repeated. All other initial screening procedures/assessments do not need to be repeated. If rescreening occurs or leukapheresis is delayed more than 28 days from the signing of the initial informed consent, subjects must be reconsented and repeat all screening procedures/assessments.

7.12.3. Enrollment/Leukapheresis

If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and results are outside the eligibility criteria listed in Section 5, contact the Kite Medical Monitor prior to proceeding with leukapheresis.

Additionally, the investigator must review the last CBC with differential and chemistry panel drawn prior to the start of leukapheresis to confirm that Inclusion 109 (eg, creatinine clearance, serum ALT/AST, total bilirubin) continues to be met (see Section 5.1).

Before leukapheresis commences, the below criteria must be met. If criteria are not met, leukapheresis, cell collection must be delayed until the event resolves. If leukapheresis is delayed beyond 5 days, baseline CBC with differential and chemistry panel must be repeated. If results are outside of the eligibility criteria listed in Section 5, contact the Kite Medical Monitor prior to proceeding with leukapheresis.

- No evidence or suspicion of an infection
- Corticosteroid therapy at a pharmacological dose (≥5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis

If leukapheresis is delayed beyond 28 days from the Screening Visit, screening procedures will be repeated to confirm that the subject remains eligible for enrollment (see Section 7.12.1).

Leukapheresis should occur within approximately 5 days of eligibility confirmation.

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

The following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA:

- Vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- Height and weight
- Labs (to be drawn prior to leukapheresis on the day of or day before leukapheresis)
  - Chemistry panel
  - CBC with differential
  - C-reactive protein (CRP)
  - Cytokine levels
  - Anti-KTE-C19
  - PBMCs including (Anti-CD19 CAR T cells and Lymphocyte subsets)
- Leukapheresis
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

7.12.4. Conditioning Chemotherapy Period

Before conditioning chemotherapy commences, the following criteria must be met. If these criteria are not met, then conditioning chemotherapy must be delayed until these events resolve.

- No evidence or suspicion of infection.
- No clinically evident changes in bone marrow, renal, hepatic, pulmonary or cardiac function since screening
- Creatinine clearance is at or above limits set in eligibility criteria (Section 5)
- No acute neurological toxicity > Grade 1 (with the exception of peripheral neuropathy)

In addition, if any of the following are known to occur, a delay in conditioning chemotherapy may be required. Contact the Kite Medical Monitor before conditioning chemotherapy commences for guidance.

- WBC count of ≥ 20,000/μL within 48 hours prior to conditioning chemotherapy
- CRP is ≥100 mg/L
- Temperature is ≥ 38.0° C within 48 hours prior to conditioning chemotherapy. Unexplained fever requires pan-culture, respiratory viral panel, chest CT and any additional symptom-directed workup to rule out occult infection.
- If any other screening assessments or procedures are repeated between enrollment and the start of conditioning chemotherapy and results are outside the eligibility criteria (Section 5)

The following procedures will be completed during Day -5 to Day -3 at the time points outlined in the SOA:

- Vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy)
  - Chemistry Panel
  - CBC with differential
- Fludarabine and cyclophosphamide administration
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

7.12.5. Investigational Product Treatment Period

Before axicabtagene ciloleucel infusion commences, the following criteria must be met. If these criteria are not met, then axicabtagene ciloleucel infusion must be delayed until these events resolve.

- No evidence or suspicion of infection. Subject must not be receiving systemic anti-microbials for the treatment of an active infection within 48 hours prior to axicabtagene ciloleucel infusion (prophylactic use of anti-microbials is allowed).
- No clinically evident changes in bone marrow, renal, hepatic, pulmonary or cardiac function since screening
- Creatinine clearance is at or above limits set in eligibility criteria (see Section 5)
- No acute neurological toxicity > Grade 1 (with the exception of peripheral neuropathy)

In addition, if any of the following are known to occur, the axicabtagene ciloleucel infusion may need to be delayed. Contact the Kite Medical Monitor before axicabtagene ciloleucel infusion commences for guidance:

- CRP is ≥100 mg/L
- Temperature is ≥ 38.0°C within 48 hours prior to axicabtagene ciloleucel infusion. Unexplained fever requires pan-culture, respiratory viral panel, chest CT scan and any additional symptom-directed workup to rule out occult infection.
- WBC count of ≥ 20,000/μL within 48 hours prior to axicabtagene ciloleucel infusion
- If any other screening assessments or procedures are repeated between leukapheresis and the axicabtagene ciloleucel infusion and results are outside the eligibility criteria (Section 5; with the exception of conditioning chemotherapy-induced cytopenias)

If the axicabtagene ciloleucel infusion is delayed > 2 weeks, conditioning chemotherapy must be repeated. In all cases of axicabtagene ciloleucel infusion delays, contact the Kite Medical Monitor for guidance.

Subjects will be hospitalized to receive treatment with axicabtagene ciloleucel followed by an observation period lasting through Day 7 post treatment with axicabtagene ciloleucel. Subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities return to ≤ Grade 1. Subjects may be discharged with non-critical and clinically stable or improving toxicities (e.g., renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1, or if deemed necessary by the treating investigator.

Given the possibility that a subject could develop CRS or neurologic events after discharge from the hospital or after treatment with atezolizumab, subjects and their family members/caregivers should be educated on potential symptoms such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the principal investigator or seek immediate medical attention.

During this period, the following procedures will be completed at the time points outlined in the SOA:

- Physical exam with vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- Labs (before axicabtagene ciloleucel infusion, as described in the SOA)
  - Chemistry Panel
  - CBC with differential
  - Cytokine levels
  - PBMCs including (Anti-CD19 CAR T cells, Lymphocyte subsets and RCRs)
- Infusion of axicabtagene ciloleucel
- Atezolizumab PK and ATA samples
- For Phase 2 only, CBC with differential and PBMC sample collection will be done 2 to 3 days after the first 2 doses of atezolizumab as noted in the SOA.
- Infusion of atezolizumab x 4, according to the subject's assigned cohort in Phase 1 or to the selected dosing schedule for Phase 2
- Lumbar puncture and CSF examination as deemed clinically appropriate by the investigator, in subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion
- Collection of fresh tumor sample(s) for subjects who signed the optional portion of the consent (anytime between Day 7 and Day 30)
- PET-CT +/- bone marrow biopsy and aspirate {Cheson 2007} for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated within 7 days.
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regard to CRS/neurologic event/SIA. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continuing through hospitalization.

7.12.6. Post Treatment Assessment Period

After completing study treatment all subjects will return to the clinic 30 days following the final dose of atezolizumab for post treatment assessment. The following procedure will be completed for subjects as outlined in the SOA:

- PET-CT +/- bone marrow biopsy and aspirate {Cheson 2007} for disease assessment: If the PET-CT is not of high enough resolution for accurate disease assessment, the scan must be repeated within 7 days.
- Physical exam with vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- Labs
  - Chemistry Panel
  - CBC with differential
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Anti-KTE-C19
  - Cytokine levels
  - PBMCs including (Anti-CD19 CAR T cells, Lymphocyte subsets and RCRs)
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is subsequently re-admitted to the hospital with any axicabtagene ciloleucel or atezolizumab-related adverse events, the following procedures will be performed as outlined in the SOA:

- The labs below will be collected on the day of hospital re-admission then weekly through and including the day of discharge.
  - PBMCs (Anti-CD19 CAR+ T cells)
  - Cytokines

At any time during the treatment period, if a subject did not respond to treatment (i.e., did not achieve a CR or PR) or progresses following a response, the subject will proceed directly to the post treatment assessment visit and be followed for survival and disease outcomes in the long-term follow-up period.

7.12.7. Long-term Follow-up Period

All enrolled subjects will be followed in the long-term follow-up period for survival and disease status, if applicable. Subjects will begin the long-term follow-up period beginning at Month 6 following axicabtagene ciloleucel infusion and will be given the opportunity to transition to a separate LTFU study, KT-US-982-5968, after providing signed informed consent:

- Every 3 months (± 2 weeks) beginning with Month 6 through and including Month 18
- Every 6 months (± 1 month) beginning with Month 18 through and including Month 60

The following procedures will be completed for subjects who are enrolled and receive axicabtagene ciloleucel and atezolizumab, at the time points outlined in the SOA:

- Physical exam
- PET-CT/ Disease assessment through **60** months or until disease progression, whichever occurs first.
- Survival status
- Labs
  - CBC with differential
  - Anti-KTE-C19
  - PBMCs including (Anti-CD19 CAR T cells, Lymphocyte subsets and RCRs)
- Atezolizumab PK and ATA samples.
- Targeted Adverse/Serious Adverse Event reporting (for 24 months or until disease progression whichever occurs first)
  - Including neurological, hematological, infections, autoimmune disorders, and secondary malignancies until disease progression.
- Targeted concomitant medication documentation (for 24 months or until disease progression whichever occurs first)
  - Including gammaglobulin, immunosuppressive drugs, anti-infective, and vaccinations

- Subsequent therapy for the treatment of NHL

Subjects may also be contacted by telephone to confirm survival status and report targeted concomitant medication use. Should a subject require lab collection, labs may be collected at the clinic or at an outside facility to reduce the subject burden.

Subjects who are enrolled/leukapheresed but did not receive KTE-C19 treatment will be followed only until the end of this study, and will undergo the following assessments at the time points outlined in the SOA:

- Subsequent therapy for the treatment of NHL
- Survival status
- Disease assessment per standard of care
- Adverse/Serious Adverse Event reporting until 30 days after last procedure (e.g., leukapheresis, conditioning chemotherapy).

Should the subject fail to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact the subject will be considered lost to follow-up and no additional contact will be required.

7.12.8. Retreatment

Subjects who achieve a PR or CR will have an option to receive a second course of conditioning chemotherapy, axicabtagene ciloleucel and treatment course of atezolizumab if their disease subsequently progresses greater than 3 months following the axicabtagene ciloleucel infusion, provided CD19 expression on tumor cells is confirmed locally by biopsy after disease progression and prior to re-treatment, and after consultation and agreement of the study sponsor. A discussion regarding benefits and risks of retreatment and including the potential need to undergo leukapheresis a second time for the manufacturing of axicabtagene ciloleucel should occur with the subject prior to performing any study related procedures or treatment. This conversation should also be recorded in the subject's source document.

Allowance for retreatment is based on clinical experience reported in the 2 studies conducted at the pediatric {Lee 2015} and Surgery Branch {Kochenderfer 2015} of the NCI where 6 subjects in total have been re-treated with conditioning chemotherapy, and axicabtagene ciloleucel alone upon progression. Three of the re-treated subjects, each of whom had indolent lymphoma or chronic lymphocytic leukemia, experienced durable responses to retreatment after an initial response and disease progression.

To be eligible for a second course of treatment, subjects must be re-evaluated and continue to meet the original study eligibility criteria (with the exception of prior axicabtagene ciloleucel and atezolizumab use in this study) and should not have received subsequent treatment for

lymphoma. Screening assessments may be repeated if clinically indicated, as determined by the investigator, to confirm eligibility for retreatment. Furthermore, any toxicity related to fludarabine or cyclophosphamide, with the exception of alopecia, should be resolved to ≤ Grade 1**,** or return to baseline, prior to retreatment. A maximum of 1 retreatment course may occur per subject. Subjects who are retreated will follow the same treatment schedule and procedural requirements per the initial treatment.

Subjects enrolled in Phase 2 will receive the same doses of conditioning chemotherapy, axicabtagene ciloleucel and atezolizumab as those in Phase 1. Subjects originally enrolled and treated during the Phase 1 portion of the study will receive the most recent conditioning chemotherapy, axicabtagene ciloleucel and atezolizumab regimen deemed safe by the SRT. For example, consider the retreated subject as being originally treated in cohort 1 of the Phase 1 portion, in which the first dose of atezolizumab was given 21 days after axicabtagene ciloleucel, and achieves a PR. If the subject then experiences disease progression greater than 3 months after axicabtagene ciloleucel infusion, by which point all 3 subjects scheduled to enroll in cohort 1 of the Phase 1 portion of the study had completed the DLT window without experiencing a DLT, and the SRT had deemed this dosing schema safe, the retreatment regimen would be given according to the schedule in cohort 2. Similarly, if by the time a subject originally treated under a Phase 1 experiences disease progression the study has entered Phase 2 enrollment, the retreatment regimen will follow the Phase 2 dosing schema. Retreated patients will follow the schedule of assessments associated with the retreatment dosing schedule, including all disease assessments, clinic visits, biomarker assessments, etc. Remaining visits and study assessments associated with their first study enrollment will cease.

Subjects who experience a DLT in Phase 1 or a comparable toxicity in Phase 2 will not be eligible for retreatment. Furthermore, if a subject has a known neutralizing antibody to either axicabtagene ciloleucel or atezolizumab, the subject will not be eligible for retreatment. However, if a non-neutralizing HAMA antibody develops to either axicabtagene ciloleucel or atezolizumab, subjects may be retreated if they meet the eligibility criteria.

Table 4. Schedule of Assessments (Cohort 1) *

Procedures	**Screening**	**Enrollment/ Leukapheresis**	**Conditioning Chemotherapy Period**			**IP Treatment Period (each visit calculated from Day 0)**											**Post Tx Follow-up**
Day	Within 28 days of enrollment		-5	-4	-3	0	1 - 7	Day 14 (± 2 days)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 49 [h] (± 2 days)	Day 63 (± 2 days)	Day 70 [h] (± 2 days)	Day 84 (± 2 days)	Day 91 [h] (± 2 days)	Day 114 (± 1 week)
Medical history & disease assessment	X																
ECOG Performance Status	X																
ECG	X																
ECHO	X																
Archival/Fresh tumor to central lab [a]	X						between Day 7 & Day 30										
Brain MRI	X																
PET-CT/ disease assessment [b]	X										X						X
Physical exam	X					**X**	**X**	X	X	X	X	X[h]	X	X[h]	X	X[h]	X
Vital signs (BP, HR, RR O_2 sat, temp) [c]	X	X	X	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X[h]	X
Height & Weight	X	X															
Neurological assessment	X																
Pregnancy test (serum or urine)	X																X
Lumbar Puncture [d]	X						with new onset Grade ≥ 2 neurologic symptoms as clinically indicated [d]										
Blood draw for Chemistry panel	X	X	X	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X[h]	X
Blood draw for CBC w/differential	X	X	X	X	X	X	X	X	X[l]	X	X[l]	X[h]	X	X[h]	X	X[h]	X
Blood draw for C-reactive protein		X															
Blood draw for Anti-KTE-C19 [e]		X															X
Blood draw for Atezolizumab PK									X [i]		X [j]		X [j]		X [k]		
Blood draw for Atezolizumab ATA									X [k]		X [j]		X [j]		X [k]		
Blood draw for Cytokines [f]		X				X	Q3D [f]	X	X	X	X	X[h]		X[h]		X[h]	X
Blood draw for PBMCs [g]		X				X	Day 7	X	X[l]	X	X[l]	X[h]	X	X[h]	X	X[h]	X
Leukapheresis		X															
Fludarabine/Cyclophosphamide			X	X	X												
Axicabtagene ciloleucel IV infusion						X											
Atezolizumab IV infusion									X		X		X		X		
Adverse events/ Concomitant	X	→															

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period	IP Treatment Period (each visit calculated from Day 0)	Post Tx Follow-up
medication					

Schedule of Assessments (Footnotes Cohort 1)

*If cohort 1 is selected to serve as the dosing model for Phase 2 of the study, then this schedule of assessments will apply for all patients enrolled in Phase 2

[a] Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. Fresh tumor sample for subjects who sign the optional portion of consent, refer to Section 7.11. Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. Optional Post treatment fresh tumor samples (if applicable) will be collected/submitted anytime between Day 7 and Day 30.

[b] PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility. If PET CT is performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the scans must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible. Patients with known bone marrow involvement will undergo bone marrow biopsy and aspirate as part of restaging {Cheson 2007}.

[c] Refer to Section 7.4 for the frequency of vital sign collection following axicabtagene ciloleucel and atezolizumab infusions

[d] Lumbar Puncture: subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade ≥ 2 neurologic symptoms post axicabtagene ciloleucel infusion will have lumbar puncture performed to assess cerebral spinal fluid as clinically appropriate. In addition, subjects who sign the optional portion of the consent, will have lumbar puncture for the collection of CSF performed at baseline prior to KTE-C19/axicabtagene ciloleucel infusion and post infusion (Day 5 +/- 2 days)

[e] Blood draw for Anti-KTE-C19: Baseline antibody samples to be collected prior to start of leukapheresis. Refer to Section 7.10 for further details.

[f] Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1 and then every third day through hospitalization

[g] PBMCs Blood draw for PBMCs include the analysis of lymphocytes prior to axicabtagene ciloleucel infusion and lymphocytes, anti KTE-C19 CAR T cells, and RCR after axicabtagene ciloleucel infusion.

[h] Optional visits and/or procedure(s). Additional procedures and blood draws at discretion of investigator if worsening of axicabtagene ciloleucel- or atezolizumab-related toxicity is suspected or if patient is admitted to the hospital

[i] Take a sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable). For the initial course of treatment only, take a sample at 30 min +/- 10 min after the end of the atezolizumab infusion

[j] Take sample prior to the atezolizumab infusion. This sample is NOT required during the retreatment period.

[k] Take sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable).

[l] For Phase 2 only, CBC with differential and blood draw for PBMCs will be done 2 to 3 days after each of the first 2 doses of atezolizumab.

Table 5. Schedule of Assessments (Cohort 2) *

Procedures	**Screening**	**Enrollment/ Leukapheresis**	**Conditioning Chemotherapy Period**			**IP Treatment Period (each visit calculated from Day 0)**											**Post Tx**
Day	Within 28 days of enrollment		-5	-4	-3	0	1 - 7	Day 14 (± 2 days)	**Ph 1:** Day 17 **Ph 2: Day 16** [m] (± 2 days)	**Ph 1:** Day 21 **Ph 2: Day 28** [m] (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 63 [h] (± 2 days)	Day 77 (± 2 days)	Day 84 [h] (± 2 days)	Day 107 (± 1 week)
Medical history & disease assessment	X																
ECOG Performance Status	X																
ECG	X																
ECHO	X																
Archival/Fresh tumor to central lab [a]	X							between Day 7 & Day 30									
Brain MRI	X																
PET-CT/ disease assessment [b]	X											X					X
Physical exam	X					**X**	**X**	X	X	X	X	X[h]	X	X[h]	X	X[h]	X
Vital signs (BP, HR, RR O_2 sat, temp) [c]	X	X	X	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X[h]	X
Height & Weight	X	X															
Neurological assessment	X																
Pregnancy test (serum or urine)	X																X
Lumbar Puncture [d]	X							with new onset Grade ≥ 2 neurologic symptoms as clinically indicated [d]									
Blood draw for Chemistry panel	X	X	X	X	X	X	X	X		X	X	X[h]	X	X[h]	X	X[h]	X
Blood draw for CBC w/differential	X	X	X	X	X	X	X	X	**X**[l]	X	X[l]	X[h]	X	X[h]	X	X[h]	X
Blood draw for C-reactive protein (CRP)		X															
Blood draw for Anti-KTE-C19 [e]		X															X
Blood draw for Atezolizumab PK								X[i]			X[j]		X[j]		X[k]		
Blood draw for Atezolizumab ATA								X[k]			X[j]		X[j]		X[k]		
Blood draw for Cytokines [f]		X				X	Q3D [f]	X		X	X	X[h]		X[h]		X[h]	X
Blood draw for PBMCs [g]		X				X	Day 7	X	**X**[l]	X	X[l]	X[h]	X	X[h]	X	X[h]	X
Leukapheresis		X															
Fludarabine/Cyclophosphamide			X	X	X												
Axicabtagene ciloleucel IV infusion						X											
Atezolizumab IV infusion								X			X		X		X		

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period			IP Treatment Period (each visit calculated from Day 0)										Post Tx
Day	Within 28 days of enrollment		-5	-4	-3	0	1 - 7	Day 14 (± 2 days)	**Ph 1:** Day 17 **Ph 2: Day 16 [m]** (± 2 days)	**Ph 1:** Day 21 **Ph 2: Day 28[m]** (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 63 [h] (± 2 days)	Day 77 (± 2 days)	Day 84 [h] (± 2 days)	Day 107 (± 1 week)
Adverse events/ Concomitant medication	X		→														

Schedule of Assessments (Footnotes Cohort 2) *

*If cohort 2 is selected to serve as the dosing model for Phase 2 of the study, then this schedule of assessments will apply for all patients enrolled in Phase 2

[a] Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. Fresh tumor sample for subjects who sign the optional portion of consent, refer to Section 7.11. Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. Optional Post treatment fresh tumor samples (if applicable) will be collected/submitted anytime between Day 7 and Day 30.

[b] PET-CT (Neck-Chest-Abdomen-Pelvis): If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. Patients with known bone marrow involvement will undergo bone marrow biopsy and aspirate as part of restaging (Cheson 2007).

[c] Refer to Section 7.4 for the frequency of vital sign collection following axicabtagene ciloleucel and atezolizumab infusions.

[d] Lumbar Puncture: subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade ≥ 2 neurologic symptoms post axicabtagene ciloleucel infusion will have lumbar puncture performed to assess cerebral spinal fluid as clinically appropriate. In addition, subjects who sign the optional portion of the consent, will have lumbar puncture for the collection of CSF performed at baseline prior to axicabtagene ciloleucel infusion and post infusion (Day 5 +/- 2 days).

[e] Blood draw for Anti-KTE-C19: Baseline antibody samples to be collected prior to start of leukapheresis. Refer to Section 7.10 for further details.

[f] Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1 and then every third day through hospitalization.

[g] PBMCs Blood draw for PBMCs include the analysis of lymphocytes prior to axicabtagene ciloleucel infusion and lymphocytes, anti KTE-C19 CAR T cells, and RCR after axicabtagene ciloleucel infusion.

[h] Optional visits and/or procedure(s). Additional blood draws at discretion of investigator if worsening of axicabtagene ciloleucel- or atezolizumab-related toxicity is suspected or if patient is admitted to the hospital

[i] Take a sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable). For the initial course of treatment only, take a sample at 30 min +/- 10 min after the end of the atezolizumab infusion.

[j] Take sample prior to the atezolizumab infusion. This sample is NOT required during the retreatment period.

[k] Take sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable).

[l] For Phase 2 only, CBC with differential and blood draw for PBMCs will be done 2 to 3 days after each of the first 2 doses of atezolizumab.

[m] For Phase 2 only If the Cohort 2 schedule is selected as the dosing model for Phase 2: Visit Day 17 will be Visit Day 16, and Visit Day 21 will be Visit Day 28 (Phase 2 only).

Table 6. Schedule of Assessments (Cohort 3) *

Procedures	**Screening**	**Enrollment/ Leukapheresis**	**Conditioning Chemotherapy Period**			**IP Administration Period (each visit calculated from Day 0)**									**Post Tx Follow-up**
Day	Within 28 days of enrollment		-5	-4	-3	0	1 – 7	Day 14 (± 2 days)	Day 22 (± 2 days)	**Ph 1**: Day 35[h] **Ph 2: Day 28**[m] (± 2 days)	Day 43 (± 2 days)	Day 49[h] (± 2 days)	Day 64 (± 2 days)	Day 69[h] (± 2 days)	Day 94 (± 1 week)
Medical history & disease assessment	X														
ECOG Performance Status	X														
ECG	X														
ECHO	X														
Archival/Fresh tumor to central lab [a]	X						between Day 7 & Day 30								
Brain MRI	X														
PET-CT/ disease assessment [b]	X										X				X
Physical exam	X					**X**	**X**	X	X	X[h]	X	X[h]	X	X[h]	X
Vital signs (BP, HR, RR, O_2 sat, temp) [c]	X	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X[h]	X
Height & Weight	X	X													
Neurological assessment	X														
Pregnancy test (serum or urine)	X														X
Lumbar Puncture [d]	X						with new onset Grade ≥ 2 neurologic symptoms as clinically indicated [d]								
Blood draw for Chemistry panel	X	X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X[h]	X
Blood draw for CBC w/differential	X	X	X	X	X	X	X[l]	X	X[l]	X[h]	X	X[h]	X	X[h]	X
Blood draw for C-reactive protein (CRP)		X													
Blood draw for Anti-KTE-C19 [e]		X													X
Blood draw for Atezolizumab PK							X[i]		X[j]		X[j]		X[k]		
Blood draw for Atezolizumab ATA							X[k]		X[j]		X[j]		X[k]		
Blood draw for Cytokines [f]		X				X	Q3D [f]	X	X	**X[h]**		X[h]		X[h]	X
Blood draw for PBMCs [g]		X				X	Day 7[l]	X	X[l]	X[h]	X	X[h]	X	X[h]	X
Leukapheresis		X													
Fludarabine/Cyclophosphamide			X	X	X										
Axicabtagene ciloleucel IV infusion						X									
Atezolizumab IV infusion							X		X		X		X		
Adverse events/ Concomitant medication		→													

Schedule of Assessments (Footnotes Cohort 3)

*If cohort 3 is selected to serve as the dosing model for Phase 2 of the study, then this schedule of assessments will apply for all patients enrolled in Phase 2

[a] Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. Fresh tumor sample for subjects who sign the optional portion of consent, refer to Section 7.11. Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. Optional Post treatment fresh tumor samples (if applicable) will be collected/submitted anytime between Day 7 and Day 30.

[b] PET-CT (Neck-Chest-Abdomen-Pelvis): If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. Patients with known bone marrow involvement will undergo bone marrow biopsy and aspirate as part of restaging {Cheson 2007}.

[c] Refer to Section 7.4 for the frequency of vital sign collection following axicabtagene ciloleucel and atezolizumab infusions.

[d] Lumbar Puncture: subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade ≥ 2 neurologic symptoms post axicabtagene ciloleucel infusion will have lumbar puncture performed to assess cerebral spinal fluid as clinically appropriate. In addition, subjects who sign the optional portion of the consent, will have lumbar puncture for the collection of CSF performed at baseline prior to KTE-C19/axicabtagene ciloleucel infusion and post infusion (Day 5 +/- 2 days).

[e] Blood draw for Anti-KTE-C19: Baseline antibody samples to be collected prior to start of leukapheresis. Refer to Section 7.10 for further details.

[f] Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1 and then every third day through hospitalization.

[g] PBMCs Blood draw for PBMCs include the analysis of lymphocytes prior to axicabtagene ciloleucel infusion and lymphocytes, anti KTE-C19 CAR T cells, and RCR after axicabtagene ciloleucel infusion.

[h] Optional visits and/or procedure(s). Additional blood draws at discretion of investigator if worsening of axicabtagene ciloleucel- or atezolizumab-related toxicity is suspected or if patient is admitted to the hospital

[i] Take a sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable). For the initial course of treatment only, take a sample at 30 min +/- 10 min after the end of the atezolizumab infusion.

[j] Take sample prior to the atezolizumab infusion. This sample is NOT required during the retreatment period.

[k] Take sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable).

[l] For Phase 2 only. CBC with differential and blood draw for PBMCs will be done 2 to 3 days after each of the first 2 doses of atezolizumab.

[m] If the Cohort 3 schedule is selected as the dosing model for Phase 2, Visit Day 35 will be Visit Day 28 (Phase 2 only) .

Table 7. Schedule of Assessments (Long-term Follow-up Period)

Procedure	Long-term Follow-up Period (Each visit calculated from Day 0)												
Visit Frequency	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	Month 72 and annually until Year 15 [j]
Physical exam[a]	X	X	X	X	X	X		**X**		**X**		**X**	
PET-CT (Neck-Chest-Abdomen-Pelvis)[b]	X	X	X		X	X		**X**		**X**		**X**	**X**
Disease assessment	X	X	X		X	X		X		X		X	X
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for CBC w/differential [c]	X	X	X	X	X	X							
Blood draw for Anti-KTE-C19 [d]													
Blood draw for Atezolizumab PK	≥90 days after the last dose of atezolizumab [i]												
Blood draw for Atezolizumab ATA	≥90 days after the last dose of atezolizumab [i]												
Blood draw for PBMCs [c, e]	X	X	X	X	X	X		X		X		X	X
Targeted AE/SAEs [f]	X	X	X	X	X	X							
Targeted concomitant medication [g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for NHL[h]	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Physical exams will continue through Month 24

[b] PET Scans CTs will continue through Month 60 or until disease progression, whichever comes first

[c] Subjects will continue to provide samples for CBC w/diffs, lymphocyte subsets and anti-CD19 CAR T cells through Month 24

[d] Anti-KTE-C19 antibody samples, refer to Section 7.10

[e] RCR samples, harvest and measured at the Post Treatment Assessment Visit, 6 and 12; then collect yearly for up to 15 years and measure only if positive at the Post Treatment Assessment, Visit, 6, or 12.

[f] Targeted AEs/SAEs will be collected for 24 months or until disease progression (whichever occurs first)

[g] Targeted concomitant medications will be collected for 24 months or until disease progression, whichever occurs first

[h] Subsequent therapy administered after axicabtagene ciloleucel infusion for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy must be collected until subject completes the long term follow up period, is considered lost to follow up, withdraws consent, or dies.

[i] Take a single time point sample ≥ 90 days after the last atezolizumab infusion for the initial course of therapy and another single time point sample after the retreatment period (if applicable).

[j] In the event this study is terminated prior to the completion of the 15-year follow up for all subjects, subjects who received an infusion of KTE-C19 will be provided the opportunity to transition to a LTFU study (KT-US-982-5968) after providing signed informed consent. The subject's final on-study visit for this study may be combined with the first visit on the LTFU study. The timing of the final on-study visit/first LTFU study visit will depend on the timing of the collection of all the subject's data that are required for the planned analysis for this study.

8. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product, study treatment or other protocol required therapies and must discuss options for continued participation, completion of procedures and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and where permitted, publically available data (death records) can be included after withdrawal of consent {U. S. Department of Health and Human Services (DHHS) 2008}. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study, investigative sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Investigative sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole or at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol required investigational products or procedures include any of the following:

- Adverse Event
- Subject request/non-compliance
- Product not available
- Lost to Follow-up

- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9. SAFETY REPORTING

9.1. Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered adverse events. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered adverse events.

The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (e.g., DLBCL).

For situations when an adverse event or serious adverse event is due to the disease under investigation report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as adverse events in the appropriate section of the CRF.

The investigators clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject request to withdraw from protocol required therapies or the study due to an adverse event, the subject should undergo the procedures outlined in the post-treatment follow up visit of the SOA.

If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started.

9.2. Reporting of Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from enrollment (i.e., commencement of leukapheresis) through 30 days after completing the final dose of Atezolizumab, or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. Once this follow up period has been completed, only targeted adverse events including neurological, hematological, infections, autoimmune disorders, and secondary malignancies for 24 months or until disease progression, whichever occurs first.

For subjects who are enrolled but do not receive axicabtagene ciloleucel and/or atezolizumab, the reporting period ends 30 days after the last procedure (e.g., leukapheresis, conditioning chemotherapy, investigational product).

The investigator must address the below for adverse events:

- Adverse event diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, conditioning chemotherapy or study procedures
- Action taken

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov). Cytokine Release Syndrome events will also be reported using the grading scale outlined in the most recent version of the KTE-C19 / axicabtagene ciloleucel IB.

In reviewing adverse events, investigators must assess whether the adverse event is possibly related to 1) the investigational product (axicabtagene ciloleucel or atezolizumab), 2) conditioning chemotherapy or 3) any protocol required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the adverse event. Additional relevant data with respect to describing the adverse event will be collected in the CRFs.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. Abnormal laboratory findings without clinical significance (based on investigators assessment) are not to be recorded as adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or resolution.

9.3. Definition of Serious Adverse Events

The investigator is responsible for reporting all serious adverse events observed by the investigator or reported by the subject that occur after signing of the consent through 30 days after completing the final dose of atezolizumab, or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. Once this follow up period has been completed, only serious targeted adverse events (e.g., neurological, hematological, infections, autoimmune disorders, and secondary malignancies) observed by the investigator or reported by the subject will be reported

for 24 months or until disease progression, whichever occurs first. For subjects who screen fail or are enrolled but do not receive axicabtagene ciloleucel and/or atezolizumab, the reporting period ends 30 days after the last procedure (e.g., screen procedure, leukapheresis, conditioning chemotherapy, investigational product).

Serious events which the Investigator assesses as related to axicabtagene ciloleucel or atezolizumab should be reported regardless of the time period.

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An adverse event would meet the criterion of "requires hospitalization" if the event necessitated an admission to a health care facility (e.g., overnight stay).

Events that require an escalation of care when the subject is already hospitalized should be recorded as a serious adverse event. Examples of such events include movement from routine care in the hospital to the ICU or if that event resulted in a prolongation of the existing planned hospitalization.

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event with the criterion of "other medically important serious event."

9.4. Reporting of Serious Adverse Events and Non-Serious CRS Events Grade ≥ 3

All serious adverse events and non-serious CRS events Grade ≥ 3 (Lee 2014) must be submitted to Kite within 24 hours following the investigator's knowledge of the event. SAEs and non-serious CRS events Grade ≥ 3 will be reported through the electronic data capture (EDC) system. This is called eSAE reporting. If the eSAE system is unavailable, reports will be submitted by email to Kite_PV@ubc.com (UBC safety mailbox).

Following completion of KTE-C19-106, any relevant information on ongoing SAEs must be submitted to Kite Pharma within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via e-mail to the SAE Reporting mailbox: safety_FC@gilead.com.

Subsequently, all serious adverse events will be reported to the FDA per 21 CFR312.32.

Progression of the malignancy during the study should not be reported as a serious adverse event. Adverse events associated with disease progression may be reported as serious adverse event. If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy, axicabtagene ciloleucel or atezolizumab infusion then the event leading to death must be recorded as a serious adverse event with CTC Grade 5.

Death must be reported if it occurs during the serious adverse event reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 30 days following the final dose of atezolizumab or 3 months following the axicabtagene ciloleucel infusion, whichever is longer, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring greater than 30 days following the final dose of atezolizumab or 3 months following the axicabtagene ciloleucel infusion, whichever is longer, requires expedited reporting within 24 hours only if it is considered related to treatment.

9.5. Pregnancy and Lactation

There is no relevant clinical experience with axicabtagene ciloleucel in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

If a pregnancy occurs in a female subject enrolled into the study, or a female partner of a male subject within 6 months of completing the axicabtagene ciloleucel infusion, the pregnancy must be reported to the sponsor contact**.** If a pregnancy occurs in a female subject enrolled into the study or in a female partner of a male subject within 5 months of the last dose of atezolizumab, the pregnancy must be reported to the sponsor. Information regarding the pregnancy and/or the outcome may be requested by the sponsor.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur through 6 months after the last dose of axicabtagene ciloleucel and through 5 months after the last dose of atezolizumab

The pregnancy should be reported to the sponsor within 24 hours of the investigator's knowledge of the pregnancy event.

If a lactation case occurs while the female subject is taking protocol required therapies report the lactation case to the key sponsor contact.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol required therapies through 6 months.

Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

9.6. Safety Review Team and Dose-Limiting Toxicity

The SRT will be specifically chartered to review safety data during Phase 1 of the study and make recommendations on further study conduct in Phase 1 and progression to Phase 2 based on the incidence of axicabtagene ciloleucel DLT and review of serious adverse events.

Dose-limiting toxicity is defined as the following axicabtagene ciloleucel or atezolizumab related events with an onset from immediately after and through 21 days following the first atezolizumab infusion:

- Grade 4 hematologic toxicity lasting more than 30 days (except lymphopenia or B-cell aplasia)
- All axicabtagene ciloleucel- or atezolizumab-related Grade 3 non-hematologic toxicities lasting for > 7 days and all axicabtagene ciloleucel- or atezolizumab-related Grade 4 non-hematologic toxicities regardless of duration are considered DLTs, with the exception of the following which are not considered DLTs:
  - Aphasia/dysphasia or confusion/cognitive disturbance which resolves to at worst Grade 2 within 2 weeks, to Grade 1 within 4 weeks, and baseline within 6 weeks.
  - Fever
  - Immediate IP-related hypersensitivity reactions occurring within 2 hours of cell or atezolizumab infusion that are reversible to a Grade 2 or less within 24 hours of administration with standard therapy
  - Renal toxicity which requires dialysis for ≤ 7 days
  - Intubation for airway protection if ≤ 7 days
  - Tumor lysis syndrome (TLS) including associated manifestations attributable to TLS (e.g., electrolyte abnormalities, renal function, hyperuricemia)
  - Grade 3 transaminase, alkaline phosphatase, bilirubin, or other liver function test elevation, provided there is resolution to ≤ Grade 2 within 14 days
  - Grade 4 transient serum hepatic enzyme abnormalities provided there is resolution to ≤ Grade 3 within < 72 hours
  - Hypogammaglobulinemia Grade 3 or 4
  - Grade 3 nausea and/or anorexia

CRS will be graded according to a revised grading system (Lee 2014) as described in the current axicabtagene ciloleucel investigator's brochure. Adverse events attributed to CRS will be

mapped to the overall CRS grading assessment for the determination of DLT. If Grade 3 or 4 CRS per Lee is due to one of the exceptions above, the event will not be considered a DLT.

During Phase 1, approximately 3-9 subjects with DLBCL will be enrolled to evaluate the safety of axicabtagene ciloleucel and atezolizumab schedules/regimens.

Subjects in each cohort will be evaluated for DLTs within the first 21 days following the completion of their first dose of atezolizumab. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.5. The SRT will make recommendations based on the incidence of DLT and overall safety profile of the axicabtagene ciloleucel and atezolizumab regimen. If the subject incidence of DLT is ≤ 1 of 3 subjects, the study will proceed to the next cohort, or if specific to cohort 3, proceeding to Phase 2 of the trial. This decision will be based on overall benefit/risk and available biomarker data.

However, if ≥ 2 of the 3 enrolled subjects within any cohort present with a protocol defined DLT during Phase 1, the SRT may recommend enrolling an additional set of 3 subjects (up to 6 subjects in total) at the same dose and schedule that was administered in the first 3 subjects in that cohort. In this scenario, progression to the next cohort or to Phase 2 of the study will proceed if ≤2 of the first 6 subjects present with a DLT.

If the subject incidence of DLT is > 2/6, other axicabtagene ciloleucel regimens, including reduced cell dose of axicabtagene ciloleucel and/or reduced conditioning chemotherapy may be explored in collaboration with the SRT in an additional 3-6 subjects (Figure 3). The same DLT rules apply as above.

9.7. Criteria to Pause Enrollment

As part of its oversight of the study, the SRT also will assess criteria to pause enrollment after 6 subjects have been treated with axicabtagene ciloleucel and atezolizumab in the Phase 2 portion of the study and have had the opportunity to be followed for 30 days from the first atezolizumab dose. Enrollment will be paused if any of the following criteria is met:

1) Subject incidence of Grade 5 axicabtagene ciloleucel or atezolizumab related adverse events within 30 days from atezolizumab infusion is ≥ 20%.

   OR

2) Subject incidence of the following Grade 4 axicabtagene ciloleucel-related adverse events lasting more than 7 days is ≥40%:

   a) Neurologic Events

   b) CRS (per Lee 2014 criteria)

   c) Other non-hematological serious adverse event

   d) Infection (treatment-related)

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

No formal hypothesis will be tested in this study. The Phase 2 portion of the study is designed to estimate the true CR rate in patients with refractory DLBCL treated with the combination of axicabtagene ciloleucel and atezolizumab.

10.2. Study Endpoints

10.2.1. Primary Endpoints

- Phase 1: Incidence of dose-limiting toxicities (DLT)
- Phase 2: Complete response rate (complete response [CR] per the revised International Working Group [IWG]) Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by study investigators.

10.2.2. Secondary Endpoints

Phase 1 and 2:

- Objective Response Rate (CR + PR) per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}
- Duration of Response
- Progression Free Survival
- Overall Survival
- Incidence of adverse events and clinically significant changes in safety lab values
- Levels of axicabtagene ciloleucel in blood and Incidence of anti-KTE-C19 antibodies
- Atezolizumab pharmacokinetics and incidence of anti- atezolizumab antibodies in serum
- Levels of cytokines and other markers in serum

Objective Response Rate: ORR is defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by the study investigators. All subjects that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders.

Duration of Response: DOR for subjects who experience an objective response is defined as the date of their first objective response (which is subsequently confirmed) to disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} or death

regardless of cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing.

Progression Free Survival: PFS is defined as the time from the KTE-C19 infusion date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

Overall Survival: OS is defined as the time from KTE-C19 infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

Incidence of adverse events and clinical significant changes in safety lab values.

Incidence of anti-KTE-C19 antibodies and levels of anti-CD19 CAR T cells in blood and levels of cytokines and other markers in serum will be summarized.

Incidence of anti-atezolizumab antibodies and levels of atezolizumab in serum will be analyzed as described in Section 7.10.

10.2.3. Exploratory Endpoints

Phase 1 and 2:

- Objective response rate based on PD-L1 expression on tumor cells or infiltrating immune cells
- Investigation of potential biomarker development based on assessment of product cells, blood cells, tumor tissue at baseline and post-treatment, and the proposed actions of the investigational product
- Frequency of atezolizumab dose delays for ongoing acute toxicities following axicabtagene ciloleucel

10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 3-31 subjects.

Phase 1 will enroll approximately 3-9 subjects. If the study proceeds to Phase 2, total of up to 22 additional subjects would be enrolled.

This study uses a single-arm design to estimate the true complete response rate in patients with DLBCL treated with the combination of atezolizumab and axicabtagene ciloleucel at the dosing schedule closest to concomitant administration tested in Phase 1 and deemed safe by the SRT. With a total sample size of 25 patients at a given dosing schedule, of which at least 3 will have

been treated in the Phase 1 portion, an observed CR rate of 70% will yield 95% confidence that estimate of the true CR rate is between 51% and 88%.

Additional assumptions and corresponding two-sided 95% and 80% exact confidence intervals are seen in Table 8.

Table 8. 95% and 80% exact confidence intervals corresponding to observed CR rate following treatment of 25 patients with axicabtagene ciloleucel and atezolizumab

Observed CR Rate	95% Confidence Interval	80% Confidence Interval
40%	[21%, 61%]	[27%, 55%]
45%	[28%, 69%]	[34%, 62%]
50%	[31%, 72%]	[38%, 66%]
55%	[35%, 76%]	[41%, 70%]
60%	[39%, 79%]	[45%, 73%]
65%	[47%, 85%]	[53%, 80%]
70%	[51%, 88%]	[57%, 84%]
75%	[55%, 91%]	[62%, 87%]
80%	[59%, 93%]	[66%, 90%]

10.4. Analysis Subsets

Full Analysis Set: the full analysis set will consist of all enrolled subjects and will be used for summaries of subject disposition.

Modified Intent to Treat Set (mITT): the modified intent to treat set will consist of all subjects enrolled and treated with the target dose of axicabtagene ciloleucel, 2 x 10^6 CAR T cells/kg (range 1 x 10^6 to 2.4 x 10^6 CAR T cells/kg) and at least one dose of atezolizumab as determined upon completion of the Phase 1 and Phase 2 portions of the study. This analysis set will be used for all efficacy analyses.

The DLT evaluable set will include all subjects in each Phase 1 cohort treated with axicabtagene ciloleucel and at least one dose of atezolizumab who either:

Received the target axicabtagene ciloleucel dose and were followed for at least 21 days after the first atezolizumab infusion; or

Received a dose of anti-CD19 CAR T cells lower than the target for that cohort and a subsequent atezolizumab infusion and experienced a DLT during the 21-day post-atezolizumab infusion period.

For the Phase 1 portion of the study and the evaluation of DLT, the target dose is defined as 2.0 x 10^6 anti-CD19 CAR T cells/kg (range 1 x 10^6 to 2.4 x 10^6 CAR T cells/kg).

If needed, more subjects will be enrolled and treated to achieve 3 DLT evaluable subjects at the target dose.

Safety analysis set: the safety set is defined as all subjects treated with any dose of axicabtagene ciloleucel.

10.5. Access to Individual Subject Treatment Assignments

This is a single arm, open-label study and subjects and investigators will be aware of treatment received. Data handling procedures for the Phase 2 portion of the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan and Trial Integrity Document.

10.6. Interim Analysis

10.6.1. Safety Interim Analysis

An SRT will be chartered to review safety during Phase 1 of the study only and make recommendations on further study conduct in Phase 1 and progression to Phase 2.

The SRT will review accumulating safety data during the Phase 2 portion of the study. Refer to Section 3.1.

10.7. Planned Method of Analysis

The primary analysis will be performed when the last treated subject in the mITT set has had the opportunity to be evaluated for response 6 months after the axicabtagene ciloleucel infusion. The final analysis will occur when all subjects have completed the study (defined in Section 3.5.3).

10.7.1. Complete Response Rate

The incidence of complete response and exact 2-sided 95% confidence intervals will be generated.

10.7.2. Progression Free Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for progression-free survival time. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided.

10.7.3. Overall Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

10.7.4. Safety

Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4 Grade 3 or higher and treatment related AEs reported throughout the conduct of the study will be tabulated by preferred term and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths though the Long-term Follow-up and treatment related SAEs will be provided.

10.7.5. Long-term Data Analysis

All subjects will be followed for survival status for up to 15 years after receiving axicabtagene ciloleucel. LTFU data analysis will be performed on subjects in this study and after transition to the KT-US-982-5968 LTFU study. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

10.7.6. Pharmacokinetic Analyses

As appropriate, serum concentrations of atezolizumab will be tabulated, summarized, and plotted after appropriate grouping. Additional PK and PK/PD analyses (e.g., population modelling, including pooled analyses across studies) may also be performed as appropriate. If done, these additional analyses may be reported separately from the Clinical Study Report and may include additional PK parameters as appropriate (e.g., AUC, time-to-maximum concentration, maximum concentration, and half-life).

10.7.7. Immunogenicity Analyses

The immunogenicity analyses will include patients with at least one pre-dose and one post-dose ATA assessment, with patients grouped as appropriate. The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized after appropriate grouping.

Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥ 0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ATA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

11. REGULATORY OBLIGATIONS

11.1. Independent Review Board /Independent Ethics Committee

A copy of the protocol, ICF and any additional subject or trial information such as subject recruitment materials must be submitted to each site respective IRB/IEC for approval. Once approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site specific and study serious adverse events (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2. Subject Confidentiality

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number
- Date of birth will be reported according with local laws and regulations
- Age at the time of enrollment

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth (as per their local reporting requirements for both initials and date of birth)

Per federal regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, CRO, IRB/IEC and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records which includes personal information.

11.3. Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the investigators agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact

Kite Pharma reserves the right to terminate the study at any time. Both Kite pharma and the investigator reserve the right to terminate the investigators participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at is sole discretion, to determine whether to manufacture axicabtagene ciloleucel and provide it to sites and subjects after the completion of the study and before treatment becomes commercially available.

13. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should outlined and included in the Delegation of Authority Form.

Source documents are original documents, data and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralize filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject identification lists
- Protocols and protocol amendments, investigator brochure, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records and experimental product related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility (ies), review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in this study will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on
  - — Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work; AND
  - — Drafting the article or revising it critically for important intellectual content; AND
  - — Final approval of the version to be published; AND
  - — Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma for review and approval. The study contract between the institution, principal investigation and Kite Pharma or its delegate will outline the requirements for publication review.

16. COMPENSATION

The study sponsor (Kite Pharma) will provide compensation for study related illness or injury pursuant to the information outlined in the injury section of the ICF.

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18. APPENDICES

Appendix A. Sponsor and Investigator Signature Page

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGMENT

A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Amendment 3.0, 03 August 2021

This protocol has been approved by Kite Pharma, Inc. The following signature documents this approval.

Ioana Kloos

Kite Medical Monitor Name (Printed)

DocuSigned by:
Ioana Kloos
Nom du signataire : Ioana Kloos
Motif de la signature : J'ai examiné ce document
Heure de signature : 18-sept.-2021 | 9:21:53 AM PDT
F29AE904961A41C396E64EE22AD53BB0

Signature

18-sept.-2021

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner and dependent children)
- Subinvestigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to one year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma, Inc.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix B. Revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007).

Complete Remission (CR): CR requires all of the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

- Typically FDG-avid lymphoma (large cell, mantle cell and follicular lymphomas are all typically FDG-avid): in subjects with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

- Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

- The spleen and/or liver, if considered to be enlarged before therapy on basis of physical exam or CT scan, must should be normal size on CT scan and not be palpable on physical examination and nodules thought to represent lymphoma must no longer be present.

- A bone marrow aspirate and biopsy is performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. The biopsy core sample must be a minimum of 20 mm in length.

Partial Remission (PR): PR requires all of the following:

- ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible and should include mediastinal and retroperitoneal nodes if possible.

- No increase in size of nodes, liver or spleen and no new sites of disease.

- If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for single nodules.

- Bone marrow is irrelevant for determination of a PR. If patient has persistent bone marrow involvement and otherwise meets criteria for CR the patient will be considered a PR.

- Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site. Note: in subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated in subjects with one or at most two residual masses that have regressed by 50% on CT scan.

Stable Disease (SD):

- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PET should be positive in typically FDG-avid lymphomas.

Progressive Disease:

Defined by at least one of the following:

- ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node.

- Appearance of a new lesion greater than 1.5 cm in any axis even if other lesions are decreasing in size

- Greater than or equal to a 50% increase in size of splenic or hepatic nodules

- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

- Lesions should be PET positive in typically FDG-avid lymphomas unless the lesion is too small to be detected by PET (<1.5 cm in its long axis by CT)

Appendix C. Atezolizumab Anaphylaxis Precautions

Equipment Needed:

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous (IV), and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

1) Stop the study drug infusion.
2) Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3) Maintain an adequate airway.
4) Administer glucocorticoids, antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5) Continue to observe the patient and document observations.

MCN: __ _____

EVENT FOLLOW-UP QUESTIONNAIRE - NEUROLOGIC EVENTS

Enter all dates in the following format: DD/MMM/YYYY

Patient			
Initials	Sex ☐ M ☐ F	DOB	Study ID (if applicable)
Product			
Name	Date dose	Indication	

Neurologic Adverse Event(s) – enter a diagnosis or signs/symptoms if a diagnosis is not available					
Neurologic Adverse Events(s)	**Start Date**	**Stop Date**	**CTCAE Grade[a]**	**Serious Criteria[b]**	**Outcome[c]**

Key:	CTCAE Grade[a]	Serious Criteria[b]	Outcome[c]
	1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant N/A = Not applicable (non-serious)	1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown

If one of the events resulted in death	Date of death:	Cause:
Was an autopsy performed?	☐ No ☐ Yes, request report	
Hospitalization	Admission date:	Discharge Date:

Diagnostic Results – enter N/A if not performed		
Diagnostic Test Date	**Brain Imaging or Other Diagnostic Results**	**Spinal Fluid Results**
Was any cerebral edema identified?	☐ Yes ☐ No	If yes, please describe how it was identified:

Additional Event Information		
In your opinion, what is the causal relationship between the neurologic adverse event and the Kite therapy? ☐ Related ☐ Not Related	If not related, what was the cause of the neurologic adverse event?	
Were alternate causes for the signs and symptoms ruled out?	☐ Yes ☐ No	If yes, please describe how these were ruled out:

Was tocilizumab administered? ☐ Yes ☐ No

Dose	Dates of Therapy	Response

Was an anti-epileptic administered? ☐ Yes ☐ No

Name of antiepileptic	Route	Dose	Therapy Dates	Response

Were corticosteroids (CS) administered? ☐ Yes ☐ No

Name of CS	Route	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ Yes ☐ No

Name of treatment	Route	Dose	Therapy Dates	Response

Relevant Medical History (list below) or ☐ No medical history **If yes, 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.**	

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**

Please provide any supplemental information on a separate page.

Signature of person completing form:	
Name of person completing form (Print):	Date Completed:
Email:	Phone:

MCN: __ _____

EVENT FOLLOW-UP QUESTIONNAIRE - CYTOKINE RELEASE SYNDROME (CRS)

Enter all dates in the following format: DD/MMM/YYYY

Patient			
Initials	Sex ☐ M ☐ F	DOB	Study ID (if applicable)
Product			
Name	Date dose	Indication	

CRS - Adverse Event (AE)			
Event	**Start Date**	**Stop Date**	**Outcome**
CRS			
CRS – associated AE (including Lab AEs) – list all below	**Start Date**	**Stop Date**	**Outcome**
CRS-associated organ specific AE (hepatic, renal, pulmonary or cardiac)- list all below			

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% FiO_2 or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
☐	Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO_2 or Hypotension requiring high-dose or multiple vasopressors or

Overall CRS Grade per Lee et al, Blood, 2014 – choose one		
		Grade 3 organ toxicity or Grade 4 transaminitis

☐	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: ☐ Required or ☐ Prolonged hospitalization

Cause of death Admission Date Discharge Date

Was autopsy performed ☐ No ☐ Yes Request report ☐ 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	If not related, what was the cause of the CRS?

Were alternate causes for he signs and symptoms ruled out? ☐ Yes ☐ No

If yes, describe how these were ruled out:

Was tocilizumab administered? ☐ Yes ☐ No

Dose	Dates of therapy	Response

Were corticosteroids (CS) administered? ☐ Yes ☐ No

Name of CS	Route	Dose	Therapy Dates	Response

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

Name of pressor	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ Yes ☐ No

Name of treatment	Route	Dose	Therapy Dates	Response

Relevant Medical History (list below) or ☐ No medical history **If yes, please specify any infection history, including treatment for infection.** **If yes, please specify any history (including severity and previous treatment) of hepatic, renal, pulmonary or cardiac disease or impairment.**	

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**

Please provide any supplemental information on a separate page.

Signature of person completing form:	
Name of person completing form (Print):	Date Completed:
Email:	Phone:

Please be aware that information provided to Gilead related to you may be used to comply with applicable laws and regulations. Gilead processes your personal or sensitive data in accordance with applicable data protection laws and the Gilead Privacy Statement. Available to you either on www.gilead.com/privacy or upon request.

MCN: __ _____

EVENT FOLLOW-UP QUESTIONNAIRE – New Malignancy

Enter all dates in the following format: DD/MMM/YYYY

Patient			
Initials	Sex ☐ M ☐ F	DOB	Study ID (if applicable)
Product			
Name	Date dose		Indication

New Malignancy- If not previously reported, please provide the information below

New Malignancy	Start Date	Stop Date	CTCAE Grade[a] (include CTCAE version)	Serious Criteria[b]	Outcome[c]

Key:	**CTCAE Grade[a]** 1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Fatal	**Serious Criteria[b]** D = Death L = Life-threatening H = Hospitalization/prolonged hospitalization S = Significant disability M = Medically significant N/A = Not applicable (non-serious)	**Outcome[c]** 1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown
If the event resulted in death	Date of death:	Cause:	Was autopsy performed? ☐ No ☐ Yes, provide report
If the event resulted in hospitalization		Admission date:	Discharge date:

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**

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**

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 the Kite therapy? ☐ Related ☐ Not Related		If not related, what was the cause of the new malignancy?				
If related, were alternate causes for the new malignancy ruled out?	Yes ☐ No ☐	If yes, please describe how these were ruled out:				
Were any treatments administered for the new malignancy?	☐ Yes ☐ No	Name of treatment:	Route:	Dose:	Therapy Dates:	Response:

Relevant Medical History ☐ Yes or ☐ No medical history or unknown **If yes, please describe below.**			
Cancer treatment received prior to Kite therapy	Please include below 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:	Dates of therapy:	Response:

Cancer treatment received after Kite therapy, but prior to new cancer diagnosis	Please include below 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:	Dates of therapy:	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**

Please provide any additional supplemental information on a separate page.

In the event that a new malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

Signature of person completing form: Click or tap here to enter text.	
Name of person completing form (Print):	Date Completed:
Email:	Phone:

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 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 administer Yescarta shall be provided with a guidance document to:

- facilitate identification of CRS and serious neurologic adverse reactions.

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

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

- 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.

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.

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

Version	Approval date Procedure	Change
1.4	28 Jun 2018 EMEA/H/C/004480/0000	Risk minimization measures ▪ Interim supply chain strategy for tocilizumab removed as an aRMM due to tocilizumab having received approval in the EU for treatment of CAR T induced CRS. Interim supply chain strategy for tocilizumab was intended as a contingency measure in case there was a need to bridge a time period post Yescarta approval during which tocilizumab did not have EU approval for the treatment of CAR T induced CRS. However, as tocilizumab received approval for CAR T induced CRS in parallel with the initial MA for Yescarta, the conditions that would have required an interim supply chain never arose and as such this aRMM was not needed. ▪ Corrected HCP Educational Material for the management of grade-2 neurologic adverse reactions with concurrent CRSs to align with the approved SmPC text. Pharmacovigilance Plan Added prescriber survey as effectiveness measure for additional risk minimization activities: ▪ Guide to handling and method of administration ▪ Patent Alert Card The Following tables were corrected: Part III: tables 2-1, 3-1; Part IV: table 2-1; Part V: tables 2-2, 3-1; Part VI: tables 1-3, 1-6 Annexes ▪ Annex 8: Added a summary of significant changes made to the RMP.

Version	Approval date Procedure	Change
2.1	14 Jan 2019 EMEA/H/C/004480/IB/0002	Risk minimization measures ▪ HCP Educational Material: Section 6 (Guidance on managing Cytokine Release Syndrome) and section 7 (Guidance on managing Neurologic Adverse Reactions) were updated with the ZUMA-1 study 24-month data analysis based on 108 subjects (phase 1 and phase 2 combined). Management guideline for CRS (Table 3) and neurologic adverse reactions (Table 5) were updated to enhance clarity of follow-up management of CRS and neurologic adverse reactions. ▪ Guide to Handling and Method of Administration was updated to specify that leukodepleting filter should not be used for Yescarta administration. Safety Specifications ▪ The 24-month data analysis update based on 108 subjects (phase 1 and phase 2 combined) from the ZUMA-1 study was added to Safety Specification (sections 3. 4, and 7). Annexes ▪ Annex 2: Added submission dates for EU PASS protocol and Prescriber Survey protocol. ▪ Annex 3: Added Prescriber survey protocol under Part C. ▪ Annex 6: Updated HCP Educational Material and Guide to Handling and Method of Administration. ▪ Annex 8: Added a summary of significant changes made to the RMP.

Version	Approval date Procedure	Change
2.2	13 Jun 2019 EMEA/H/C/004480/IB/0009	Risk minimization measures ▪ HCP Educational Material: Modified language to clarify that 1 dose of tocilizumab per patient must be available prior to Yescarta infusion, and treatment centers should have access to an additional dose within 8 hours of each previous dose. Added dysphagia, spinal cord edema, myelitis and quadriplegia under the risk of Serious neurologic adverse reactions including cerebral edema. ▪ Guide to Handling and Method of Administration: Title of aRMM revised to "Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies", Modified language to clarify that 1 dose of tocilizumab must be available prior to Yescarta infusion, and treatment centers should have access to an additional dose within 8 hours of each previous dose. Added recommendations for additional testing in case of secondary malignancy, including advice on sampling and management to obtain relevant analyses. Additional pharmacovigilance activities ▪ Section 3 (Table 3-1): milestones updated with approval dates for non-interventional PASS protocol and Prescriber Survey protocol. Safety Specifications ▪ Section 7.3.1.1 (Table 7-6): Modified language to clarify that 1 dose of tocilizumab must be available prior to Yescarta infusion, and treatment centers should have access to an additional dose within 8 hours of each previous dose ▪ Section 7.1.2.1 (Table 7-1 and Table 7-5): added dysphagia, myelitis, quadriplegia, spinal cord edema to further characterize the risk of Serious neurologic adverse reactions including cerebral edema Annexes ▪ Annex 2: added approval dates for non-interventional PASS protocol and Prescriber Survey protocol ▪ Annex 3: added approved protocols for non-interventional PASS and Prescriber Survey ▪ Annex 6: HCP Educational Material and Guide to Handling and Method of Administration updated ▪ Annex 8: updated summary of significant changes made to the RMP

Version	Approval date Procedure	Change
3.0	28 May 2020 EMEA/H/C/004480/II/0021	Additional pharmacovigilance activities ▪ Pharmacovigilance Plan updated to remove KTE-X19 studies which are no longer part of the Yescarta development plan Safety Specifications ▪ Section 1 Epidemiology of the indication and target populations(s) updated to reflect current epidemiology data for NHL RMP Annexes ▪ Annex 2: updated to remove KTE-X19 studies which are no longer part of the Yescarta development plan ▪ Annex 6: updated HCP Educational Material to remove 3-day steroid taper from the CRS and Neurologic Adverse Reactions management guidances ▪ Annex 8: updated summary of significant changes made to the RMP
4.0	22 April 2021 EMEA/H/C/004480/II/0028	The RMP was updated to remove data from all relevant sections related to ZUMA-1 Cohort 4 and early intervention with corticosteroids Pharmacovigilance Plan: ▪ Updated to revise format of milestone due dates ▪ Updated to reflect current clinical studies in the development program Risk Minimization measures: ▪ Updated the specific clinical measures for tumor lysis syndrome in routine risk minimization activities; added study short names and final report due date Annexes ▪ Annex 2: Updated to revise format of milestone due dates ▪ Annex 6: HCP Educational Material was updated to remove data related to ZUMA-1 Cohort 4.

Version	Approval date Procedure	Change
3.4	10 June 2021 EMEA/H/C/PSUSA/00010703/202010	Safety Concerns and Risk Minimization Measures: ▪ Added three new important potential risks (CD19 negative relapse, CAR T persistence in relapsed patients, and Failure to produce a viable CAR T product) ▪ Aligned with the Tecartus EU RMP, in particular with the aRMMs, which are combining the two products into one set of materials Pharmacovigilance Plan: ▪ Routine Pharmacovigilance Activities: added new targeted questionnaire for New Malignancy for important potential risk of Secondary malignancy ▪ Additional Pharmacovigilance Activities: added 3 new important potentials risks as safety concerns addressed; and removed KTE-X19 studies which are no longer part of the Yescarta development program ▪ Summary Table of Additional Pharmacovigilance Activities: added 3 new important potentials risks as safety concerns addressed; and updated pharmacovigilance activities to reflect current clinical studies in Yescarta development program; removed KTE-X19 studies which are no longer part of the Yescarta development program Annexes: ▪ Annex 2: Removed studies which are no longer part of the Yescarta development plan ▪ Annex 4: Added new Event follow up questionnaire for New Malignancy ▪ Annex 6: HCP Educational Material, PAC and Controlled distribution program were updated as combined aRMMs with Tecartus and added Key Messages of the aRMMs ▪ Annex 8: Updated summary of significant changes made to the RMP
5.0	10 June 2021 EMEA/H/C/PSUSA/00010703/202010	Consolidated approved versions of Yescarta EU RMP v4.0 (EMEA/H/C/004480/II/0028) and v3.4 (EMEA/H/C/PSUSA/00010703/202010), as agreed by EMA within their corresponding procedures.

Version	Approval date Procedure	Change
5.1	Not applicable EMEA/H/C/004480/II/0042	Extension of indication to include adult subjects with Relapsed/Refractory follicular lymphoma. **Part II Safety Specification**: Module SI.1: Updated to include epidemiology data for follicular lymphoma. Module SIII.1: Clinical trial exposure was updated to include safety data from ZUMA-5. Module SVII.3: Important identified risks, important potential risks, and missing information were updated with the relevant safety data from ZUMA-5. **Part III Pharmacovigilance Plan**: Updated to include new targeted follow-up questionnaires of CD19 and CAR-T Levels after Recurrence Following Initial Response to Yescarta for the important potential risks of CD19 Negative Relapse and CAR-T Persistence in Relapsed Patients. Updated to include amended PASS protocol (KT-EU-471-0117; version 2.0, amendment 4). The PASS protocol was amended to add new indication of follicular lymphoma. **Part VII Annexes**: Annex 2: Updated to include summary of amended PASS protocol (KT-EU-471-0117; version 2.0, amendment 4). Annex 3: Added PASS protocol (KT-EU-471-0117; version 2.0, amendment 4). Annex 4: Added new targeted follow-up questionnaires of CD19 and CAR- T Levels after Recurrence Following Initial Response to Yescarta for the important potential risks of CD19 Negative Relapse and CAR-T Persistence in Relapsed Patients. Annex 6: Updated HCP Educational Material to include follicular lymphoma and the incidence of CRS and neurologic adverse reactions from ZUMA-5.

Version	Approval date Procedure	Change
5.2	Not applicable EMEA/H/C/004480/WS2206/0045	A recommendation of the Committee for Advanced Therapies to submit a type II variation to amend the conditions of the marketing authorisation to allow suitable alternatives to tocilizumab to be used during periods of tocilizumab shortages listed in the EU shortage catalogue – thereby facilitating continued treatment with Yescarta during such periods. **Part II Safety Specification** Section SVII.3.1.1: The 'Preventability' section of the important identified risk of CRS was updated to align with the changes in the SmPC. **Part V Risk Minimisation Measures** Section V.2: Updated HCP educational material to align with the revised SmPC. **Part VII Annexes** Annex 6: Updated HCP Educational Material. Updated Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies.
5.3	Not applicable EMEA/H/C/004480/II/0046	Extension of indication based on the results from Study KTE-C19-107 (ZUMA-7), a phase 3, randomised, open-label study evaluating the efficacy of axicabtagene ciloleucel versus standard of care therapy in subjects with relapsed/refractory DLBCL **Part I Product Overview:** The indication was updated. **Part II Safety Specification:** All the modules were updated with the extended indication and current data. **Part V Risk Minimisation Measures:** Updated HCP educational material to align with the proposed revised SmPC. **Part VI Summary of the Risk management plan:** Updated to align with the changes in the RMP. **Part VII Annexes:** Annex 6: Updated HCP Educational Material.
5.4	Not applicable EMEA/H/C/004480/WS2206/0045	Response to the PRAC preliminary assessment report regarding Tocilizumab shortages. **Part VII Annexes**: Annex 3: Updated Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan Annex 6: Updated HCP Educational Material.

Version	Approval date Procedure	Change
5.5	Not applicable EMEA/H/C/004480/II/0042	Response to the committee for advanced therapies request for supplementary information. **Part II Safety Specification**: The potential risk of CD19 negative relapse was updated with data submitted in the response to question 13. **Part III Pharmacovigilance Plan**: Any mention to the KT-EU-471-0117 amendment was removed.
6.0	16 December 2021 EMEA/H/C/004480/WS2206/0045	Upversioned following positive Committee for Medicinal Products for Human use (CHMP) opinion (16 December 2021) regarding tocilizumab shortage.
6.1	Not applicable EMEA/H/C/004480/II/0046	Response to the committee for advanced therapies request for supplementary information. **Part II: Module SI**: Updated per indication. **Part II: Module SIII**: Updated exposure tables. **Part III Pharmacovigilance Plan**: Study KT-EU-471-0116 was completed and removed. **Annexes** Annex 6: HCP educational material was updated.
7.0	22 April 2022 EMEA/H/C/004480/II/0042	Upversioned per CHMP opinion on 22 Apr 2022 for the extension of indication to include adult subjects with relapsed/refractory follicular lymphoma after 3 or more lines of systemic therapy.

Version	Approval date Procedure	Change
7.1 & 8.0	Not applicable EMEA/H/C/004480/II/0046	Consolidation of the following procedures: EMEA/H/C/004480/II/0042 (expansion of indication based on Study ZUMA-5), EMEA/H/C/004480/WS2206/0045 (Tocilizumab shortage), and EMEA/H/C/004480/II/0046 (expansion of indication based on Study ZUMA-7).
8.1	Not applicable	**5-year marketing authorization renewal** **Safety Specification**: The safety specification was revised to combine the two risk of secondary malignancy and RCR into one risk of 'Secondary hematologic malignancy (including due to RCR)'. The following potential risks were removed: Immunogenicity, Tumor lysis syndrome, Aggravation of graft versus host disease, Transmission of infectious agents via product, Decrease in the viability of the product due to inappropriate preparation of infusion, CD19 negative relapse, CAR T persistence in relapsed patients, and Failure to produce a viable CAR T cell product. The following missing information were removed: Use in non-Caucasian patient populations and New occurrence or exacerbation of an autoimmune disorder. **Pharmacovigilance plan** The targeted follow-up questionnaires of CD19 and CAR T levels after recurrence following initial response to Yescarta was removed. **Risk minimization measures** The risks and missing information were updated to align with Module SVII. The following plans to evaluate effectiveness were removed: ▪ Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification. ▪ A summary of all reported severe, life-threatening CRS and serious neurologic adverse reactions with an analysis of adverse event outcomes and treatment is provided within periodic safety reports. **Annexes** The additional minimization measures were removed and replaced with the key messages of the additional risk minimization measures. The handling guide's section 1 was removed and was renamed to have only the 'Sampling Recommendation for Secondary Malignancies' portion.

Version	Approval date Procedure	Change
v8.2/v9.0	25 May 2023 EMEA/H/C/004480/R/0056	**Safety Specification**: The following potential risks were reinstated: Immunogenicity, Tumor lysis syndrome, Aggravation of graft versus host disease. The following missing information was reinstated: New occurrence or exacerbation of an autoimmune disorder. **Annexes** Annex 6 was updated with the key messages regarding sample collection and testing following the development of a secondary malignancy of T cell origin.
9.1	Not applicable EMEA/H/C/WS2632	Aligning the RMP with the SmPC update type II variation to reduce the post-infusion recommended daily monitoring time from 10 days to 7 days.
9.2	TBD TBD	**Pharmacovigilance plan** Removal of ZUMA-1 and ZUMA-6.
9.3	TBD EMEA/H/C/WS2632	**Risk minimization measures** Reinstating collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification.
9.4/10.0	TBD EMEA/H/C/WS2632	**Risk minimization measures** The evaluation of the effectiveness of the controlled distribution program includes: • Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification.

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Rainer Heissing	QPPV eSigned	17-Apr-2024 13:13:53
[redacted]	Patient Safety eSigned	17-Apr-2024 14:01:09
[redacted]	Regulatory Affairs eSigned	17-Apr-2024 17:41:06