CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2 Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination With Rituximab in Subjects With Refractory Large B-Cell Lymphoma (ZUMA-14)
Protocol Number:	KT-US-471-0114
Indication:	Large B-Cell Lymphoma
USAN/INN:	Axicabtagene Ciloleucel Rituximab
Kite Investigational Product:	KTE-C19
IND Number:	016278
EudraCT Number:	2019-004803-11
Clinical Trials.gov Identifier:	NCT04002401
Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404
Contact Information:	The medical monitor name and contact information is provided on the Key Study Team Contact List
Original Protocol Date:	24 January 2019
Amendment 1:	20 May 2019
Amendment 2:	18 December 2019
Amendment 3:	02 April 2020
Amendment 4:	08 July 2020
Amendment 5:	18 May 2022

SPONSOR AND INVESTIGATOR SIGNATURE PAGE

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STUDY ACKNOWLEDGMENT

A Phase 2 Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination with Rituximab in Subjects with Refractory Large B-Cell Lymphoma (ZUMA-14)

Amendment 5, 18 May 2022

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

PPD

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 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

PROTOCOL SYNOPSIS

Kite Pharma, Inc.
2400 Broadway
Santa Monica, CA 90404

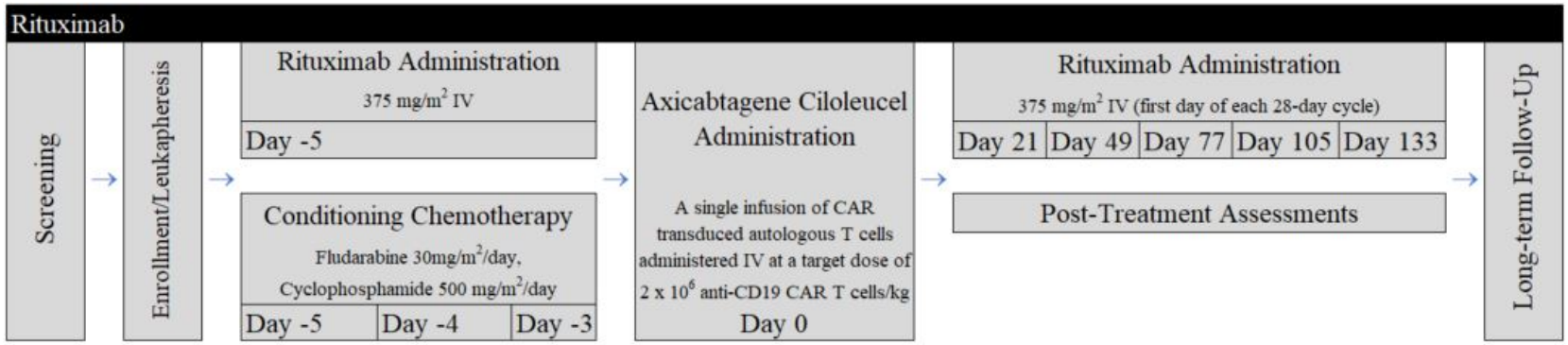
Title:	A Phase 2 Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination With Rituximab in Subjects With Refractory Large B-Cell Lymphoma (ZUMA-14)
Indication:	Refractory large B-cell lymphoma
Study Design:	This is a Phase 2 open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with rituximab in subjects with refractory large B-cell lymphoma. • Rituximab (375 mg/m^2) will be administered on Day –5, for 1 dose. Fludarabine and cyclophosphamide conditioning will be administered on Day –5, Day –4, and Day –3. • Rituximab will also then be administered on Day 21 and will be continued for a total of 5 doses after axicabtagene ciloleucel infusion at 28-day intervals, for a total of 6 doses of rituximab. • A safety review team (SRT) will review safety data after the first 6 subjects and again after the first 15 subjects have completed 28 days of follow-up after axicabtagene ciloleucel infusion. The SRT will make recommendations on further study conduct and progression to expansion. • A second dosing strategy (Dose Level −1) will be to administer rituximab only after axicabtagene ciloleucel infusion. This dose level may be explored only if the planned dosing strategy (rituximab initiation concurrent with conditioning chemotherapy) has an unacceptable rate of toxicity. For study requirements, refer to the schedule of assessments (SOAs).
Study Objectives:	Primary Objective • To estimate the efficacy of axicabtagene ciloleucel in combination with rituximab, as measured by assessment of response rates, in adult subjects with relapsed/refractory large B-cell lymphoma.

	Secondary Objectives • To estimate the safety of axicabtagene ciloleucel in combination with rituximab, as measured by assessment of adverse event (AE) rates, in adult subjects with relapsed/refractory large B-cell lymphoma. • To assess the efficacy of axicabtagene ciloleucel and rituximab, using additional efficacy endpoints. • To determine levels of axicabtagene ciloleucel expansion and persistence in blood (pharmacokinetics [PK]) using chimeric antigen receptor (CAR) T-cell polymerase chain reaction (PCR) assay, in combination with rituximab.
Hypothesis:	No formal hypothesis will be tested in this study. The study is designed to evaluate safety and efficacy in subjects with refractory large B-cell lymphoma treated with axicabtagene ciloleucel in combination with rituximab.
Primary Endpoints:	• Complete response rate; complete response (CR) per the International Working Group (IWG) Lugano Classification {Cheson 2014}, as determined by study investigators**.**
Secondary Endpoint(s):	• Incidence of AEs and clinically significant changes in safety lab values • Objective response rate (ORR; CR + partial response [PR]) per the IWG Lugano Classification {Cheson 2014}, as determined by study investigators • Duration of response (DOR) • Progression-free survival (PFS) per the IWG Lugano Classification {Cheson 2014}, as determined by study investigators • Overall survival (OS) • PK (levels of axicabtagene ciloleucel in blood)
CCI	
Sample Size:	Approximately 30 subjects
Study Eligibility:	Refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria.

Treatment:	Conditioning Chemotherapy Treatment: • A conditioning chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day will be administered for 3 days prior to axicabtagene ciloleucel infusion. Refer to Section 6 for chemotherapy treatment details. Investigational Products: • 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 and Section 7.8 for treatment details. • Rituximab treatment, as described in the Study Design.
Procedures:	As outlined in the SOAs, subjects will undergo the following procedures: collection of informed consent, medical history; physical examination; brain magnetic resonance imaging (MRI); neurological examination; Eastern Cooperative Oncology Group (ECOG) performance status; bone marrow biopsy and aspirate; disease staging, including a baseline positron emission tomography-computed tomography (PET-CT) scan; and blood draws for lactate dehydrogenase levels, complete blood count (CBC), and serum chemistries. Subjects will also undergo baseline echocardiogram (ECHO) and electrocardiogram (ECG) assessments. Females of childbearing potential (FCBP) will undergo medically supervised urine or serum pregnancy tests. Routinely throughout the conduct of the study, all subjects will be asked to report concomitant therapies, AEs, and subsequent lymphoma therapy. Subjects will undergo routine disease assessments as outlined in the SOAs. For details for all study requirements, refer to Section 7 and the SOAs.
Safety Review Team (SRT):	An internal SRT, comprising the study sponsor medical monitor, drug safety physician, study statistician, and at least 1 active investigator, will meet after 6 subjects have completed their 28-day disease assessment and again after 15 subjects have completed their 28-day disease assessment. The SRT will review ongoing safety data and will be chartered to make study conduct recommendations based on this analysis.

Statistical Considerations:	No formal hypothesis will be tested in this study. The study is designed to evaluate safety and efficacy in subjects with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel in combination with rituximab. The primary efficacy analyses will be conducted on subjects treated with axicabtagene ciloleucel and at least 1 dose of rituximab after axicabtagene ciloleucel infusion, and safety analyses will be conducted on all subjects treated with axicabtagene ciloleucel. The primary analysis will be conducted when the last subject has had the opportunity to be followed to the 6-month disease assessment. The final analysis will occur when all subjects have had the opportunity to be followed for at least 24 months. Subjects treated with axicabtagene ciloleucel will be transitioned to the KT-US-982-5968 study for the remainder of the 15-year Long-term Follow-up (LTFU) period. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

Figure 1. Study Schema



Abbreviations: CAR, chimeric antigen receptor; IV, intravenous

Note: At the end of study KT-US-471-0114, 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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LIST OF ABBREVIATIONS

ABC	Activated B-cell
ADCC	Antibody-dependent cell mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aRMMs	Additional Risk Minimization Measures
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the curve
CAR	Chimeric antigen receptor
CBC	Complete blood count
CDC	Complement-dependent cytotoxicity
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response/remission
CrCl	Creatinine clearance
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
CTEP	Cancer Therapy Evaluation Program
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DVT	Deep vein thrombosis
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FAS	Full analysis set
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FL	Follicular lymphoma

GCP	Good Clinical Practice
GCB	Germinal center B-cell
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, ears, eyes, nose, and throat
HGBCL	High-grade B-cell lymphoma
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
IC	Investigator's choice
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
ID	Identification
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IMiD	Immunomodulatory drug
IP	Investigational product
IPM	Investigational Product Manual
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IV	Intravenous
IWG	International Working Group
LTFU	Long-term follow-up
LTFU study	Long term follow study, KT-US-982-5968
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NPT	Nasopharyngeal-throat
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
PK	Pharmacokinetics
PMBCL	Primary mediastinal large B-cell lymphoma
PO	Taken orally
PR	Partial response/remission
qPCR	Quantitative polymerase chain reaction
RCR	Replication-competent retrovirus
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
SAE	Serious adverse event
scFv	Single-chain variable fragment
SCT	Stem cell transplant
SD	Stable disease
SmPC	Summary of product characteristics
SOA	Schedule of assessment
SPM	Secondary primary malignancy
SRT	Safety review team
SSAP	Supplementary statistical analysis plan
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
TNF	Tumor necrosis factor
UA	Urinalysis
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	Urinary tract infection
WBC	White blood cell

1. OBJECTIVES

1.1. Primary Objective

- To estimate the efficacy of axicabtagene ciloleucel in combination with rituximab, as measured by assessment of response rates, in adult subjects with relapsed/refractory large B-cell lymphoma

1.2. Secondary Objectives

- To estimate the safety of axicabtagene ciloleucel in combination with rituximab, as measured by assessment of adverse event (AE) rates, in adult subjects with relapsed/refractory large B-cell lymphoma

- To assess the efficacy of axicabtagene ciloleucel and rituximab, using additional efficacy endpoints

- To determine levels of axicabtagene ciloleucel expansion and persistence in blood (pharmacokinetics [PK]) using chimeric antigen receptor (CAR) T-cell polymerase chain reaction (PCR) assay, in combination with rituximab

2. DISEASE BACKGROUND

2.1. Disease Background

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes, or natural killer (NK) cells. In the United States (US), B-cell lymphomas represent 80% to 85% of NHL cases reported {American Cancer Society 2019}. In 2018, approximately 74,680 new cases of NHL and over 19,000 deaths related to the disease were estimated to occur. NHL is the most prevalent hematological malignancy and is the seventh most common new cancer among men and women. It accounts for 4.3% of all new cancer cases and approximately 3% of deaths related to cancer {Noone 2017}.

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for approximately 30% of NHL cases {Chaganti 2016, Morton 2006, Sehn 2015}. There are approximately 22,000 new diagnoses of DLBCL in the US each year. In the past 2 decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of chemotherapy and immunotherapy. The addition of rituximab into combination therapies for DLBCL, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), has greatly improved patient outcomes. However, first-line R-CHOP has been associated with a 10-year progression-free survival (PFS) of < 40% {Coiffier 2010}. Patients with chemotherapy-refractory DLBCL have a particularly dire prognosis {Flowers 2010}.

SCHOLAR-1, a large multicenter, patient-level, retrospective study, examined outcomes of refractory DLBCL using pooled data from 2 randomized Phase 3 clinical trials (the Lymphoma Academic Research Organization CORAL study and Canadian Cancer Trials Group study LY.12) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). For the study, refractory DLBCL was defined as progressive disease (PD) or stable disease (SD) as the best response at any point during chemotherapy (> 4 cycles of first-line or 2 cycles of later-line therapy) or relapsed within ≤ 12 months of autologous stem cell transplantation (ASCT). The study highlighted the poor prognosis of patients affected with refractory DLBCL, finding an objective response rate (ORR) to the next line of therapy of 26% (complete response [CR] rate, 7%) and a median overall survival (OS) of only 6.3 months {Crump 2017}.

These discouraging results demonstrate that new treatment options are needed for patients whose tumors have demonstrated a lack of response to chemotherapy. The recently approved anti-CD19 CAR products are a promising treatment option for patients with relapsed or refractory large B-cell lymphoma who have no other curative alternatives.

2.2. Axicabtagene Ciloleucel

Axicabtagene ciloleucel is a CD19-directed genetically modified autologous T-cell immunotherapy. For this therapy, a patient's T cells are genetically modified to produce a CAR protein, allowing the T cells to identify and eliminate CD19-expressing normal and malignant cells. CD19 is expressed by most B-cell malignancies {Leonard 2001, Olejniczak 2006, Rodriguez 1994, Uckun 1988}, as well as normal B lymphocytes in peripheral blood and spleen, but not by granulocytes, monocytes, platelets, erythrocytes, and T lymphocytes {Uckun 1988}. Briefly, the anti-CD19 CAR transgene comprises the following key domains: 1) an extracellular anti-human CD19 single-chain variable region fragment (scFv) derived from the monoclonal antibody (mAb) FMC63, 2) the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28, and 3) the cytoplasmic portion of human CD3ζ that includes the signaling domain {Nicholson 1997}. Following CAR engagement with $CD19^+$ target cells, the CD3ζ domain activates a downstream signaling cascade that leads to T-cell activation, proliferation, and acquisition of effector function.

On 18 October 2017, the US Food and Drug Administration (FDA) approved axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma (HGBCL), and DLBCL arising from follicular lymphoma (FL) {YESCARTA 2017}.

On 23 August 2018, the European Medicines Agency (EMA) approved axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory DLBCL and PMBCL after 2 or more lines of systemic therapy.

FDA and EMA approvals were based on ZUMA-1, a single-arm, multicenter study of 108 adult subjects with relapsed or refractory aggressive large B-cell NHL. The ORR among these subjects was 82%, and the CR rate was 58%. At a median follow-up of 15.4 months, 42% of subjects remained in ongoing response, highlighting the durability of responses achieved with axicabtagene ciloleucel over time. Median OS was not reached, and 56% of subjects remained alive {Neelapu 2017}. The most common Grade 3 or higher AEs (incidence of $\geq$ 10%) included febrile neutropenia, fever, cytokine release syndrome (CRS), encephalopathy, infections (pathogen unspecified), hypotension, hypoxia, and lung infections. Serious adverse reactions occurred in 52% of subjects and included, but were not limited to, encephalopathy, fever, febrile neutropenia, and serious infections. Fatal cases of CRS and neurologic toxicity occurred. FDA approved axicabtagene ciloleucel with a Risk Evaluation and Mitigation Strategy (REMS) {YESCARTA 2017}. EMA approved axicabtagene ciloleucel with additional Risk Minimization Measures (aRMMs) as part of the Risk Management Plan (RMP).

The dose of axicabtagene ciloleucel is a single intravenous (IV) infusion with a target of 2×10^6 CAR-positive viable T cells per kg body weight (maximum dose of 2×10^8 CAR T cells), preceded by cyclophosphamide and fludarabine lymphodepleting chemotherapy {Yescarta 2018, YESCARTA 2017}. Additional details regarding the mechanism of action and clinical results of axicabtagene ciloleucel can be found in the Investigator's Brochure (IB).

Despite the success of axicabtagene ciloleucel, about 60% of patients have primary or secondary resistance to axicabtagene ciloleucel therapy; therefore, additional strategies are needed to further improve outcomes for patients with relapsed or refractory DLBCL.

2.3. Prior Anti-CD19 CAR T-cell Study Designs and Results

Refer to the current axicabtagene ciloleucel IB for the most current anti-CD19 CAR T-cell non-clinical and clinical information.

2.4. Rituximab

Rituximab (RITUXAN®) is a chimeric IgG1 mAb against CD20, a receptor expressed on the surface of B cells {Perez-Callejo 2015}. Rituximab is approved in the US for the treatment of NHL, including previously untreated DLBCL; CD20-positive NHL, in combination with CHOP or other anthracycline-based chemotherapy regimens; CD20-positive chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide; rheumatoid arthritis, in combination with methotrexate; granulomatosis with polyangiitis and microscopic polyangiitis, in combination with glucocorticoids; and pemphigus vulgaris {MabThera 2019, RITUXAN 2018}. The boxed warnings for rituximab include fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy.

R-CHOP is the current standard of care for first-line treatment for DLBCL {Flowers 2010}. Although more effective than chemotherapy alone, first-line R-CHOP only results in long-term disease remission in < 40% of subjects {Coiffier 2010}. Thus, 60% or more of all subjects with large B-cell lymphoma may have relapsed or refractory disease.

In NHL, rituximab has 3 main mechanisms of action after binding to CD20: antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of apoptosis in healthy and malignant B cells {Marshall 2017, Perez-Callejo 2015, RITUXAN 2018}.

2.4.1. Rationale for Anti-CD19 CAR T Cells in Combination with Rituximab

The use of anti-CD20 rituximab in conjunction with CAR T cells has been explored preclinically to determine whether a dual-targeting approach could improve the response rate for lymphoma treatment. Mihara and colleagues studied the effect of rituximab and anti-CD19 CAR T cells on mice inoculated with HT-luciferase cells (a cell line derived from B-NHL cells) {Mihara 2010}. The study demonstrated that rituximab augmented the tumor-suppressing effect of anti-CD19 CAR T cells on B-NHL cells in vitro and in vivo with few side effects. In addition, Rufener and colleagues studied the effect of rituximab concentrations on the activity of anti-CD20 CAR T cells in vitro and in vivo and found more tumors were eradicated in mice that received rituximab plus CAR T cells versus rituximab alone or CAR T cells alone {Rufener 2016}. Thus, in adoptive tumor models in immunodeficient mice, rituximab could augment CAR T-cell antitumor activity.

The use of anti-CD20 rituximab in conjunction with CAR T cells has not been studied clinically for lymphoma treatment. To explore whether unexpected safety findings might occur with this combination, an ad hoc analysis of ZUMA-1, the pivotal study for axicabtagene ciloleucel, was performed comparing the 64 subjects with rituximab in their last prior line of therapy with the 108 subjects in the total study population. Rituximab levels in these subjects are expected to be low because the median duration from receiving rituximab in the last line of therapy to CAR T-cell infusion was approximately 9 weeks, and rituximab terminal half-life is 3 weeks; thus, levels are expected to be less than 1/8 or 1/16 of peak. Still, the proportion of subjects with Grade 3 or higher CRS and Grade 3 or higher neurological toxicities was consistent between subjects with rituximab in their last prior line of therapy (8% and 31%, respectively) compared with the subjects in the total study population (12% and 31%, respectively).

2.5. Rationale for Combination Therapy

Previous clinical trial experience with axicabtagene ciloleucel in the same patient population (ZUMA-1) demonstrated an ORR of 82% and a CR rate of 58% at the updated analysis after a median follow-up of 15.4 months {Neelapu 2017}. Ongoing responses were seen in 42% of subjects, of whom 40% were in ongoing CR. Among the 58% of subjects who were not in ongoing response at the 12-month follow-up, 18% of subjects demonstrated primary resistance to therapy (did not achieve partial response [PR] or CR), and 40% of subjects achieved an objective response and later progressed or died. Possible mechanisms of resistance to axicabtagene ciloleucel are hypothesized to be suboptimal CAR T-cell expansion {Neelapu 2017}, an exclusionary tumor microenvironment {Rossi 2018}, and CD19 target antigen loss {Neelapu 2017}.

Further, it was also observed in ZUMA-1 that 23 of 60 subjects with either a PR (11 of 35) or SD (12 of 25) at the first tumor assessment (1 month after axicabtagene ciloleucel infusion) subsequently achieved CR up to 15 months after infusion without additional therapy. In addition, peak expansion and area under the blood concentration vs time curve (AUC) from Day 0 to Day 28 ($AUC_{0\text{-}28}$) were associated with response. Therefore, combination strategies that either increase proliferation, expansion, and persistence of CAR T cells or prevent activation--induced cell death (AICD) of CAR T cells may improve clinical outcomes seen with anti-CD19 CAR T-cell therapy.

This study will utilize a combination strategy to improve the clinical efficacy of axicabtagene ciloleucel. ZUMA-14 will use a dual-targeting approach to target CD20 with rituximab and CD19 with axicabtagene ciloleucel to augment the anti-B-cell activity and potentially mitigate loss of efficacy due to loss of CD19 antigen.

3. STUDY DESIGN AND RATIONALE

3.1. General Study Design

Study KT-US-471-0114 (ZUMA-14) is a Phase 2, open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with rituximab in subjects with relapsed/refractory large B-cell lymphoma.

Study candidates will be adults with recurrent large B-cell lymphoma who are refractory to prior chemotherapy or have had ASCT. They must have at least 1 measurable lesion and meet multiple organ function criteria. Approximately 30 subjects will be enrolled and treated using an interactive response technology (IRT) system to dispense rituximab. Six subjects will be enrolled for an initial safety evaluation, followed by safety review team (SRT) review, prior to expansion.

At the end of ZUMA-14, 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.

3.1.1. Rituximab Dosing

Subjects will receive a planned dose of rituximab on Day –5 and conditioning chemotherapy with fludarabine and cyclophosphamide on Day –5, Day –4, and Day –3. After 2 days of rest on Day –2 and Day –1, subjects will receive axicabtagene ciloleucel, administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg on Day 0. Subjects will also receive rituximab for 5 additional doses at 28-day intervals beginning on Day 21 after axicabtagene ciloleucel infusion.

A second dosing strategy (Dose Level −1) will be to administer rituximab only after axicabtagene ciloleucel infusion. This dose level may be explored only if the planned dosing strategy (rituximab initiation concurrent with conditioning chemotherapy) has an unacceptable rate of toxicity.

An internal SRT, comprising the study sponsor medical monitor, drug safety physician, study statistician, and at least 1 active investigator, will meet after 6 subjects have completed their 28-day disease assessment and then again after 15 subjects have completed their 28-day disease assessment. The SRT will review safety data and will be chartered to make study conduct recommendations based on this analysis.

For study requirements assigned to each study period, refer to the schedule of assessments (SOAs) in Table 2 and Table 3.

A study schema is described in Figure 1.

3.2. Dosing Rationale

3.2.1. Rationale for Conditioning Chemotherapy

Increasing levels of lymphodepleting 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 preclinical models, which demonstrate that the depth and duration of lymphodepletion correlate with antitumor 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 combination is a potent lymphodepleting regimen. Cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) are both given for 3 consecutive days. This combination has been studied in subjects with B-cell malignancies and was tolerated by this population {Kochenderfer 2017, O'Brien 2001}. Cyclophosphamide and fludarabine combination treatment was also used in the ZUMA-1 study {Locke 2017, Neelapu 2017}.

3.2.2. Rationale for Axicabtagene Ciloleucel Dose

The rationale for the axicabtagene ciloleucel dose in this study is based on the aggregate safety and efficacy data compiled from ZUMA-1, as outlined in the IB**,** US Prescribing Information (USPI)**,** and summary of product characteristics (SmPC). Based on the favorable benefit/risk ratio seen in ZUMA-1, axicabtagene ciloleucel will be administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg, but subjects may be dosed at a minimum of 1 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing > 100 kg, a maximum flat dose of axicabtagene ciloleucel at 2 x 10^8 anti-CD19 CAR T cells will be administered.

3.2.3. Rationale for Rituximab Dose

Standard lymphoma dose rituximab will be used per rituximab package insert: 375 mg/m^2 IV. The schedule will be every 28 days for a total of 6 doses. The first dose will be given on the day conditioning chemotherapy starts (Day –5).

3.3. Participating Sites

Approximately 15 centers located in the US will participate in this study. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

3.4. Number of Subjects

Participants in this study will be referred to as “subjects.” It is anticipated that up to approximately 30 subjects will be enrolled and treated in this study.

3.5. Replacement of Subjects

Subjects may continue to be enrolled until the specified approximate number of subjects are dosed with axicabtagene ciloleucel and at least 1 dose of rituximab after axicabtagene ciloleucel infusion. Subjects who have not received the target dose of axicabtagene ciloleucel will be retained in the analyses of disposition and safety, where appropriate (see Section 10.6).

3.6. Study Duration

3.6.1. 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 timing of transition to the separate LTFU study, KT-US-982-5968 (discussed in Sections 3.6.2. and 7.11.).

For a subject who completes participation in this study and also completes the LTFU period in the separate LTFU study, the entire duration of a subject's participation in both studies will be up to approximately 15 years from the time of the initial infusion of axicabtagene ciloleucel. The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects, and need to understand and mitigate the potential risks of delayed onset AEs that could be the potential consequence of this emerging technology.

3.6.2. Completion of Study

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

4. SUBJECT IDENTIFICATION ASSIGNMENT

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. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. The subject ID number will never be changed even if the subject is rescreened.

After study eligibility has been confirmed, subjects will receive axicabtagene ciloleucel in combination with rituximab.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

101) Histologically proven large B-cell lymphoma, including the following types defined by {Swerdlow 2016}:

- DLBCL not otherwise specified (germinal center B-cell [GCB]/activated B-cell [ABC] types)
- PMBCL
- DLBCL arising from FL
- HGBCL with or without MYC and BCL2 and/or BCL6 rearrangements
- Intravascular large B-cell lymphoma
- T-cell/histiocyte rich large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Primary cutaneous DLBCL, leg type
- Epstein-Barr virus (EBV) + DLBCL

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

- No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy are excluded
  - — PD as best response to first-line therapy
  - — SD as best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy
- No response to second or greater lines of therapy
  - — PD as best response to most recent therapy regimen
  - — 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

- Refractory after ASCT

  — Disease progression or relapsed ≤ 12 months after ASCT (must have biopsy-proven recurrence in relapsed subjects)

  — If salvage therapy is given after ASCT, the subject must have had no response to or relapsed after the last line of therapy.

103) At least 1 measurable lesion according to the International Working Group (IWG) Lugano Classification {Cheson 2014}. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy.

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

- Anti-CD20 mAb
- An anthracycline-containing chemotherapy regimen

105) No evidence, suspicion, and/or history of central nervous system (CNS) involvement of lymphoma or detectable cerebrospinal fluid (CSF) malignant cells or brain metastases

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

108) Age 18 or older

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

110) Absolute neutrophil count (ANC) ≥ 1000/μL. Growth factor 7 days prior to screening is not allowed to meet ANC eligibility criteria.

111) Platelet count ≥ 75,000/μL. Transfusion 7 days prior to screening is not allowed to meet platelet eligibility criteria.

112) Absolute lymphocyte count ≥ 100/μL

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

- Creatinine clearance (CrCl; as estimated by Cockcroft Gault) ≥ 60 mL/min
- Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 upper limit of normal (ULN)
- Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's syndrome

- Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air

114) Females of childbearing potential (FCBP)* must have medically supervised negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL**.**
A female is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

115) FCBP must agree to practice highly effective forms of birth control until at least 6 months after lymphodepleting chemotherapy, 6 months after axicabtagene ciloleucel, or 12 months after rituximab dosing, whichever is longer, and must also agree to routine pregnancy testing as described in the schedule of assessments. Methods of highly effective birth control are defined in Appendix 2.

5.2. Exclusion Criteria

201) Known CD19 negative or CD20 negative tumor

202) History of Richter's transformation of CLL

203) Prior CAR therapy or other genetically modified T-cell therapy

204) Hypersensitivity to rituximab or any excipients of rituximab

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

206) Presence or suspicion 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 and after consultation with the sponsor's medical monitor.

207) History of human immunodeficiency virus (HIV) infection or acute or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) 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.

208) Presence of any in-dwelling line or drain (eg, percutaneous nephrostomy tube, in-dwelling 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.

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

210) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

211) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, heart failure requiring use of digoxin or other drug for rate control, or other clinically significant cardiac disease within 12 months of enrollment

212) Requirement for urgent therapy due to tumor mass effects (eg, blood vessel compression, bowel obstruction, or transmural gastric involvement)

213) Primary immunodeficiency

214) History of autoimmune disease (eg, Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/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.

215) History of deep vein thrombosis (DVT) or pulmonary embolism within the last 6 months

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

217) Live vaccine ≤ 6 weeks prior to planned start of conditioning chemotherapy

218) Women who are breastfeeding

219) History of malignancy other than nonmelanoma skin cancer in situ (eg, cervix, bladder, breast) or low-grade (Gleason ≤ 6) prostate cancer or surveillance without any plans for treatment, unless disease-free for at least 3 years

220) ASCT within 6 weeks of planned enrollment

221) Prior organ transplantation, including prior allogeneic stem cell transplant (SCT)

222) Prior CD19 targeted therapy

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.

6. PROTOCOL TREATMENT

6.1. Study Treatment

6.1.1. Leukapheresis

Leukapheresis refers to the procedure for collecting peripheral blood mononuclear cells (PBMCs) that are used to manufacture the subject-specific axicabtagene ciloleucel treatment.

Subjects will undergo leukapheresis to obtain T cells for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the sponsor's manufacturing facility as described in the Investigational Product Manual (IPM).

6.1.2. Conditioning Chemotherapy

Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion before administration of axicabtagene ciloleucel.

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.

6.1.2.1. 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.

6.1.2.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard derivative that acts as an alkylating agent following conversion to active metabolites in the liver and has 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 current version of the package insert for specific details associated with the administration of cyclophosphamide.

6.1.2.3. 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 current version of the package insert for specific details surrounding the administration of mesna.

6.1.3. Axicabtagene Ciloleucel

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy and cream to yellow color. The cryostorage bag containing axicabtagene ciloleucel arrives frozen in a liquid nitrogen dry shipper. The bag must be stored in a vapor phase of liquid nitrogen and remain frozen until the subject is ready for treatment to assure that 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. The product is labelled per local regulations with the subject's unique subject ID number assigned at the time of screening. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, 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 IPM for details and instructions on storage, thawing, and administration of axicabtagene ciloleucel.

There have been no instances of accidental overdose of subjects in this program to date. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity. Toxicity management guidelines are found in the current product IB and should be consulted.

If any problems related to the use of axicabtagene ciloleucel or any products that support the management of axicabtagene ciloleucel (eg, cryostorage bags, subject ID labels) are identified, research staff should report the problem per the instructions in the IPM.

6.1.4. Rituximab

6.1.4.1. Formulation, Packaging, and Handling

Rituximab drug product may be supplied in clear glass vials at a 10-mg/mL (100 mg/vial and 500 mg/vial) concentration as sterile solution for IV administration. Refer to the package insert for additional information.

6.1.4.2. Dosage and Administration

Rituximab dosage is 375 mg/m^2, the standard approved dose for NHL. Rituximab will be administered as an IV infusion per institutional guidelines. Refer to the package insert for additional information.

6.1.5. Concomitant Therapy

Concomitant therapy refers to treatment that subjects receive during the conduct of the study.

During the course of the study, investigators may prescribe any concomitant therapies deemed necessary to provide adequate supportive care except those medications listed in Section 6.1.6.

All concomitant therapies, including medications, intubation, dialysis, oxygen, and blood products, will be recorded.

For subjects who receive axicabtagene ciloleucel treatment:

- Concomitant therapies will be recorded from the date of the informed consent until 30 days after the final rituximab infusion, or for 3 months after completing treatment with axicabtagene ciloleucel (whichever is longer).
- After the post-treatment follow-up, targeted concomitant therapies will be recorded for either 24 months after axicabtagene ciloleucel infusion or until disease progression, whichever occurs first. Targeted concomitant therapies include immunoglobulins (eg, gammaglobulin**)**, immunosuppressive drugs, anti-infective drugs, and vaccinations.

For subjects who are enrolled but not dosed with axicabtagene ciloleucel, concomitant therapies will be recorded from the date of the informed consent until 30 days after the last study-specific procedure has occurred (eg, leukapheresis, conditioning chemotherapy) or until the initiation of new anticancer therapy, whichever occurs first.

For subjects who are not enrolled (eg, screen failure), concomitant therapies related to any SAE(s) will be recorded.

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

6.1.6. Excluded Medications

Excluded medications refer to treatment that is not to be administered, unless otherwise specified, during the conduct of the study.

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 before leukapheresis and 5 days before 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 noncontrast 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 toxicities. Other medications, such as nonsteroidal anti-inflammatory agents, that might interfere with the evaluation of axicabtagene ciloleucel should also be avoided for the same period unless medically necessary.

Therapeutic doses of systemic anticoagulants, such as unfractionated heparin and low-molecular weight heparin, should be avoided, when possible, anytime subjects are at risk of bleeding due to thrombocytopenia.

Treatments for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation, and high-dose corticosteroids (other than those defined/allowed in this protocol) and other investigational agents, are prohibited, except those outlined in the protocol (rituximab) and as needed for treatment of disease progression after axicabtagene ciloleucel infusion.

If permissibility of a specific medication/treatment is in question, contact the sponsor's medical monitor (contact information located on title page of this protocol).

6.1.7. Subsequent Therapy

Subsequent therapy refers to treatment administered after axicabtagene ciloleucel infusion that is necessary to treat a subject's disease.

Subsequent therapy, such as non-study specified chemotherapy, immunotherapy, targeted agents, SCT, or radiation therapy, administered after axicabtagene ciloleucel infusion that is necessary to treat a subject's disease will be recorded for all subjects until one of the following happens: the subject transitions to the LTFU study, KT-US-982-5968, is considered lost to follow-up, withdraws consent, or dies.

If a subject achieves a CR as best response and subsequently progresses, sites are strongly encouraged to collect a biopsy confirming disease progression.

For subjects who are enrolled but do not receive axicabtagene ciloleucel infusion, any additional anticancer therapy will also be collected until subject completes the LTFU period, is considered lost to follow-up, withdraws consent, or dies.

6.1.8. Axicabtagene Ciloleucel Toxicity Management

To date, the following risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, hypogammaglobulinemia, and cytopenias. Refer to the current axicabtagene ciloleucel 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 regarding important potential risks associated with axicabtagene ciloleucel, as well as possible complications associated with malignancy and cancer treatment, can also be found in the IB.

6.1.9. Rituximab Toxicity Management

While rituximab is widely used and most subjects will have been treated with rituximab multiple times, it may still cause AEs. Rituximab has warnings for infusion reactions, severe mucocutaneous reactions, hepatitis B reactivation, progressive multifocal leukoencephalopathy, tumor lysis syndrome (TLS), infection, cardiovascular adverse reactions, renal toxicity, bowel obstruction and perforation, and embryo-fetal toxicity.

Refer to the current rituximab package insert for details regarding toxicity management guidance.

7. STUDY PROCEDURES

Research staff should refer to the SOA Table 2 and Table 3 for an outline of the procedures required.

The visit schedule is calculated from axicabtagene ciloleucel infusion on study Day 0.

An overview of study assessments/procedures is outlined in the following sections. Refer to the CRF completion guidelines for data collection requirements and best practices for documentation of study procedures.

7.1. Informed Consent

Before a subject participates in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequately explaining the study design, anticipated benefits, and potential risks. Subjects should sign the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved ICF before any study-specific activity or procedure is performed.

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

7.2. Screening

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected in 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.

The screening period begins on the date the subject signs the IRB/IEC-approved ICF and continues through confirmation of eligibility into the study. 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 and, therefore, may be performed before obtaining consent and used to confirm eligibility provided they occur within the time allowance outlined below and in the SOA.

After written informed consent has been obtained, Kite Pharma will assign a screening number to the subject, as described in Section 4.

Refer to Section 7.2.1 for the study procedures for subjects who rescreen into the study. Only subjects who meet the eligibility criteria listed in Section 5 will be enrolled into the study. If at any time before enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure, and the reasons for failing screening should also be recorded.

Refer to the SOA (Table 2) for a list of study procedures to be completed during the screening period.

7.2.1. 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 ID number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, it is only necessary to perform the procedure(s)/assessment(s) that did not originally meet the eligibility criteria; 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.

7.3. Demographic Data

Demographic data will be collected for each subject as per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity, and country of enrollment with the intent to assess the possible association of demographics with subject safety and treatment effectiveness.

7.4. Medical and Treatment History

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

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

7.5. Physical Exam, Vital Signs, and Performance Status

Physical exams will be performed during screening and at times noted in the SOA. All physical exam changes noted in subsequent exams when compared to the baseline exam will be reported as AEs.

Vital signs, including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature, will be monitored and recorded at screening and at times outlined in the SOA. In addition to the time points outlined in the SOA, it is recommended that vital signs are monitored during and after study treatment 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.

7.5.1. 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. Absence of pericardial effusion will also be confirmed, per study eligibility criteria. Both LVEF and pericardial effusion will be assessed by echocardiogram (ECHO) before study entrance. An ECHO that was performed after the subject's last chemotherapy treatment may also be used to confirm eligibility, provided that it occurred ≤ 28 days before signing the consent.

To establish a baseline, a 12-lead electrocardiogram (ECG) will also be performed during the screening period.

7.6. Neurological Examination

A neurological examination will be performed, and any of the following abnormalities will be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, and neuropsychological findings (eg, speech, cognition, and emotion).

A neurological examination should be done before axicabtagene ciloleucel infusion on treatment Day 0, on treatment Day 1, and on every other day during the observation period, which must last a minimum of 7 days unless otherwise required by country regulatory agencies.

Subjects will be specifically asked about changes in neurological status since the previous neurological examination, as noted in the SOA (see Table 2).

7.7. Disease 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 IWG Lugano Classification {Cheson 2014}; refer to Appendix 1. Flow cytometric, molecular, or cytogenetic studies will not be used to determine response.

7.7.1. Imaging

7.7.1.1. Imaging at Baseline

Each subject will undergo a screening brain magnetic resonance imaging (MRI) during the screening period of the study to rule out CNS metastasis. If an MRI is contraindicated, then a brain CT scan may be performed instead.

To confirm eligibility and/or to establish a 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 at screening. PET-CT performed after the subject's last line of therapy and prior to signing the consent may be used for confirmation of eligibility if within 28 days prior to enrollment and no other anticancer treatment has been administered. If PET-CT is performed > 28 days prior to enrollment, the PET-CT scan must be repeated to establish a new baseline. PET-CT should be performed as close to enrollment as possible.

7.7.1.2. Post-treatment Response Assessment

The first planned post-treatment PET-CT tumor assessment will occur at Day 28.

PET-CTs will continue at time points outlined in the SOA through Month 24 or until disease progression, whichever comes first. If the subject's disease has not progressed by Month 24, disease assessments will continue to be performed per standard of care for imaging assessment of large B-cell lymphoma. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if this requires an unscheduled visit. If the subject has started subsequent anticancer therapy, then imaging assessments will no longer be required per protocol.

7.7.2. Determination of Bone Marrow Involvement

A subject's bone marrow involvement should be confirmed by the baseline PET-CT or bone marrow biopsy and aspirate prior to the start of conditioning chemotherapy.

If there is evidence of baseline bone marrow involvement and follow-up PET-CT is not available, if there are unexplained cytopenias, or if there is any other suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR to confirm 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 (IHC). Refer to Appendix 1 for treatment response assessment requirements per the IWG Lugano Classification {Cheson 2014}.

Bone marrow aspirate/biopsy should also be considered to evaluate hemophagocytic lymphohistiocytosis (HLH) as indicated. Refer to the current axicabtagene ciloleucel IB (section on "Hemophagocytic Lymphohistiocytosis in the Setting of CRS") for additional information.

7.8. Cell Collection and Axicabtagene Ciloleucel Study Treatment Schedule and Administration

7.8.1. Leukapheresis

The leukapheresis visit should occur within approximately 5 days of eligibility confirmation. Subjects must remain eligible per the eligibility criteria outlined in Section 5 prior to the start of 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 sponsor's medical monitor (contact information located on title page of this protocol) prior to proceeding with leukapheresis.

Before leukapheresis commences, the below criteria must be met:

- 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 criteria are not met, leukapheresis must be delayed until the event resolves. If leukapheresis is delayed more than 5 days after eligibility confirmation, baseline complete blood count (CBC) with differential and chemistry panel must be repeated. If results are outside the eligibility criteria listed in Section 5, contact the medical monitor (contact information located on title page of this protocol) prior to proceeding with leukapheresis.

After a subject commences leukapheresis and is entered in the IRT system, the subject will be considered enrolled into the study.

After the above criteria are met, mononuclear cells will be obtained by leukapheresis (12 to 15 L apheresis with a goal to target approximately 5 x 10^9 to 10 x 10^9 mononuclear cells**)**. The leukapheresed cells are then packaged for expedited shipment to the manufacturing facility as described in the IPM.

Refer to the SOA Table 2 for a list of study procedures to be completed on the leukapheresis collection day and as outlined in the SOA.

7.8.1.1. Pregnancy Testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP This requirement includes FCBP who practice absolute and continuous abstinence.

7.8.2. Rituximab Administration Prior to Axicabtagene Ciloleucel Infusion

Rituximab (375 mg/m^2) will be administered via IV on Day –5.

7.8.3. 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 C-reactive protein [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 7.8.3.3 for work-up requirements for potential infectious and/or inflammatory states.

7.8.3.1. Requirements for Initiating Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, the workup listed in Section 7.8.3.3 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 and start of conditioning chemotherapy
- White blood cell (WBC) count or WBC differential concerning for infectious process between enrollment and start 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 before proceeding with conditioning chemotherapy.
- Complete history and physical exam, including head, ears, eyes, 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 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, viral serologies, PCR, stool studies, imaging studies) must be negative. If there is clinical suspicion 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.

7.8.3.2. Requirements for Initiating Axicabtagene Ciloleucel Infusion

If any of the following criteria are met prior to the initiation of axicabtagene ciloleucel infusion, then the workup listed in Section 7.8.3.3 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 and start of axicabtagene ciloleucel infusion
- WBC count or WBC differential concerning for infectious process between enrollment and start of axicabtagene ciloleucel infusion (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 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 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 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 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 the 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 there is clinical suspicion 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.

If the axicabtagene ciloleucel infusion is delayed > 2 weeks, protocol-specified conditioning chemotherapy must be repeated.

7.8.3.3. Requirements to 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 before administration of conditioning chemotherapy and/or axicabtagene ciloleucel consists of:

- Call Kite medical monitor
- Infectious disease service consult
- 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 (before the initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x 2 bottles each) and urinalysis (UA) and urine culture. Deep/induced sputum culture if clinically indicated.
  - All in-dwelling 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 (NPT) 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 PCR should be performed.
- Any additional sign- or symptom-directed investigation should be performed as clinically indicated.

Before proceeding with conditioning chemotherapy or axicabtagene ciloleucel infusion, the above workup must not suggest the presence of an active infection, and all requirements for conditioning chemotherapy and axicabtagene ciloleucel infusion must be satisfied.

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

7.8.3.4. Conditioning Chemotherapy Administration (Day –5 through Day –3 Prior to Axicabtagene Ciloleucel Infusion)

Subjects will receive a conditioning chemotherapy regimen consisting of cyclophosphamide and fludarabine. The first dose of conditioning chemotherapy will be designated as Day –5. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day –5 and through Day –3, with 2 rest days (Day –2 and Day –1) before receiving axicabtagene ciloleucel. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

The 3-day conditioning chemotherapy regimen of cyclophosphamide and fludarabine will be administered in accordance with the following daily dosing instructions:

- IV hydration with a balanced crystalloid, according to institutional guidelines, prior to administration of cyclophosphamide on the day of infusion
- 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
- Additional IV hydration with a balanced crystalloid, according to institutional guidelines, to be administered upon completion of infusion
- Mesna should be administered per institutional guidelines.

Subjects should be instructed to drink plenty of liquids (approximately 2 L/24 hours) during chemotherapy and throughout the 24-hour period after chemotherapy. In general, subjects should be kept well-hydrated but closely monitored to prevent fluid overload.

Refer to the SOA Table 2 for a listing of study procedures to be completed during the conditioning chemotherapy period.

7.8.4. Axicabtagene Ciloleucel Treatment Period

7.8.4.1. Axicabtagene Ciloleucel Premedication Dosing

Prior to axicabtagene ciloleucel infusion, the following medications should be administered approximately 1 hour before infusion. Alternatives to the following recommendations should be discussed with the medical monitor.

- Acetaminophen (paracetamol) 500 to 1,000 mg PO or equivalent
- Diphenhydramine 12.5 to 25 mg administered either orally or via IV or equivalent

7.8.4.2. Axicabtagene Ciloleucel Administration Day 0

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, 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 resolve 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 neurologic events > Grade 1, or if deemed necessary by the investigator.

If a subject is discharged from the hospital or healthcare facility between Days 8 and 13, the subject's next scheduled assessments are on Day 14**.** Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following axicabtagene ciloleucel infusion. Subjects should be advised to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 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.

Refer to the SOA (Table 2) for a list of study procedures to be completed during the axicabtagene ciloleucel treatment period.

Central venous access, such as a port or a peripherally inserted 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 administration of axicabtagene ciloleucel are outlined in the IPM. Vital signs should be measured during and after axicabtagene ciloleucel treatment (see Section 7.5).

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

7.8.5. Rituximab Administration After Axicabtagene Ciloleucel Infusion

Rituximab (375 mg/m^2) will be administered via IV on Day 21 and will be continued at 28-day intervals for a total of 5 doses after axicabtagene ciloleucel infusion.

7.9. Laboratory

7.9.1. Local Laboratory Analysis

Assessments listed in Table 1 will be performed at the local laboratory at the time points indicated in the SOA. Additional samples (eg, blood, urine, CSF, tissue) may be collected as needed for further safety testing.

Table 1. Clinical Laboratory Parameters

Serum Chemistries	Hematology	Other
Albumin ALT/GPT ALP AST/GOP Bicarbonate total (if applicable) Bilirubin direct Bilirubin total BUN or urea[a] Calcium total Chloride Creatinine Creatinine clearance Glucose Inorganic phosphorus LDH Magnesium total Potassium Sodium Uric acid[b]	CBC with differential[b]	CRP Ferritin Pregnancy test

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; GOP, serum glutamic-oxaloacetic transaminase; GPT, serum glutamic-pyruvic transaminase; LDH, lactate dehydrogenase.
a If BUN test cannot be analyzed by the Local Laboratory, urea should be analyzed.
b Per institutional guidelines.

7.9.2. Central Laboratory Analyses

Biomarker analysis will be performed on blood, CSF, and tumor samples to evaluate PK and pharmacodynamics markers for axicabtagene ciloleucel in combination with rituximab. Prognostic markers for aggressive NHL and related to the tumor immune environment may also be evaluated.

Clinical biospecimens (eg, tumor tissue, bone marrow, complete blood, CSF, or other bodily fluids) will be sent from clinical study centers to the central laboratory for sample processing, accessioning, and distribution to specialty laboratories or Kite. Samples will be obtained at the time points indicated in the SOA. Additional samples (eg, complete blood, urine, CSF, tissue) may be collected as needed for further safety testing.

Apheresis and product retains are provided to the central lab or are stored at a Kite-sponsored central laboratory. Complete instructions regarding sample submission to central laboratories are provided in the Central Laboratory Manual.

Samples to be collected by study sites include the following:

- Tumor tissue
  - Tumor tissue at screening: archival formalin-fixed paraffin-embedded (FFPE) block or 30 unstained slides. If archival tissue is not available or insufficient, a fresh tumor biopsy is required to be collected and submitted prior to leukapheresis.

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- Blood for central CBC with differential, PK (levels of anti-CD19 CAR T cells and of rituximab), replication-competent retrovirus (RCR) testing, and assessment of B-cell aplasia and immune reconstitution
- Serum for pharmacodynamics (cytokine levels)
- CSF for determination of PK, pharmacodynamics, presence of CAR T cells, and other immune cell subsets

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Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who, in turn, will contact the sponsor. The investigator should provide the sponsor with the study number 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 from these samples will be entered in the study database. Complete details concerning these analyses will be provided in separate documents regarding bioanalytical analyses.

Multiple specialty laboratories may be employed for specific analyses. Refer to the Central Laboratory Manual for instructions regarding submitting such samples to the appropriate laboratory.

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7.9.2.2. PK and Pharmacodynamics

PK and pharmacodynamics analyses will be performed on blood (levels of anti-CD19 CAR T cells) or serum (cytokines and rituximab PK) at the intervals outlined in the SOA to evaluate predictive markers for the efficacy and safety of axicabtagene ciloleucel. The following cytokines and chemokines may be included in the panel: homeostatic, pro-inflammatory and immune modulating cytokines IL-2, IL-6, IL-10, IL-12p40/p70, IL-15, IL-17a, TNF-α, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF); acute phase reactants, such as CRP; chemokines IL-8, monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein (MIP)-1α, and interferon-inducible protein (IP)-10; and HLH-related markers ferritin and interleukin-2 receptor alpha **(**IL-2Rα**)**.

CSF samples and additional subject samples (eg, pleural fluid) will be collected at baseline and at time points after infusion as outlined in the SOA to enable evaluation of inflammatory cytokines and chemokine levels for determination of PK, pharmacodynamics, and presence of CAR T cells and other immune cell subsets. CSF draws and additional subject samples will be obtained from subjects who develop Grade 2 or higher neurologic events for evaluation of inflammatory cytokine and chemokine levels and presence of anti-CD19 CAR T cells. 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.

7.9.2.3. Product Characteristics

In addition, baseline leukapheresis and final axicabtagene ciloleucel samples will be banked and may be analyzed by immunophenotyping, quantitative polymerase chain reaction (qPCR), and/or gene expression profiling CCI

Samples of apheresis material or final product will be retained and tested by the sponsor or specialty laboratory for the purpose of understanding the mechanism of action and safety profile of axicabtagene ciloleucel.

7.9.2.4. RCR Testing

Axicabtagene ciloleucel comprises T cells transduced with a γ-retroviral vector; hence, there is a theoretical risk for RCR developing in exposed subjects. RCR testing will occur at the following time points: baseline, Day 105, Day 180, and Month 12. Thereafter, samples will be collected yearly and held for up to 15 years from the last patient dosed. If a subject tests positive for RCR at any time point within the first year, samples will continue to be collected and tested yearly for

up to 15 years from the last patient dosed or as clinically indicated. If secondary malignancies emerge, RCR testing will also be performed following diagnosis. Additional information is provided in the current axicabtagene ciloleucel IB.

7.10. Post-treatment Assessment Period

After completing study treatment, all subjects will return to the clinic for post-treatment follow-up visits.

If a subject does not respond to treatment at any time during the post-treatment assessment period, then the subject will continue to undergo the post-treatment follow-up procedures per the SOA and then be followed for survival and disease outcomes in the LTFU portion of the study starting with the Month 9 visit (see Table 3).

Refer to the SOA (Table 2) for a list of study procedures and disease assessments to be completed during the post-treatment follow-up period.

7.11. Long-term Follow-up Period

All enrolled and treated subjects will be followed in the LTFU period for safety analysis, survival, and disease status, if applicable. Subjects will begin the LTFU period at the Month 9 visit. Subjects who did not respond to axicabtagene ciloleucel treatment may receive off-protocol therapy but will continue to be followed for disease assessments (if progression was not documented), subsequent anti-cancer therapy, and survival. If the subject has started a subsequent anti-cancer therapy, then imaging assessments will no longer be required per protocol.

Subjects may also be contacted by telephone to confirm survival status and subsequent anticancer therapy use. If the subject fails to return to the clinic for a scheduled protocol-specific visit, sites will need to make 2 attempts, using both the telephone and either mail or email, to contact the subject. Sites must document both attempts to contact the subject. If the subject does not respond within 1 month after the second contact, then the subject will be considered lost to follow-up, and no additional contact will be required.

Refer to the SOA (Table 3) for a list of study procedures and disease assessments to be completed during the LTFU period.

Subjects who are enrolled/leukapheresed, but either did not receive axicabtagene ciloleucel treatment or received axicabtagene ciloleucel treatment and progressed, will be followed in the LTFU period and undergo the following assessments at the time points outlined in the SOA:

- Subsequent therapy for the treatment of NHL
- Survival status
- Disease assessment per protocol

- AE/SAE per Section 9

- 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 AEs/SAEs suspected to be possibly related to axicabtagene ciloleucel as defined in KT-US-982-5968, presence of RCR, and/or insertional mutagenesis for up to 15 years from the time of axicabtagene ciloleucel infusion. In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

7.12. Post-study Care

Kite will not provide additional care for study subjects after their participation in the study has ended.

Table 2. Schedule of Assessments

Procedures	Screening	Leukapheresis	Conditioning Chemotherapy					Axicabtagene Ciloleucel		Post-treatment Follow-up						
Day	**Within 28 days of enrollment**	**Within approx. 5 days after confirming eligibility**	**D-5**	**D-4**	**D-3**	**D-2**	**D-1**	**D0**	**D1 to D14[n]**	**D21 (± 3 days)**	**D28 (± 3 days)**	**D49 (± 3 days)**	**D77 (± 3 days)**	**D105 (± 14 days)**	**D133 (± 14 days)**	**D180 (± 14 days)**
Leukapheresis		X[j]														
Rituximab administration[k]			X							X		X	X	X	X	
Fludarabine/ Cyclophosphamide			X	X	X											
Axicabtagene ciloleucel IV infusion								X								
Medical history	X															
ECOG performance status	X															
ECG 12-lead	X															
ECHO	X[a]															
Brain MRI	X															
Weight (plus height at screening)	X	X														
Physical exam	X		X					X	X	X	X	X	X	X	X	X
Neurological examination	X							X[b]	Days 0, 1, 3, 5, 7[b]	X	X					
Vital signs (BP, HR, O_2 sat, temp, and RR)[c]	X	X	X	X	X			X	X	X	X	X	X	X	X	X

Procedures	Screening	Leukapheresis	Conditioning Chemotherapy					Axicabtagene Ciloleucel		Post-treatment Follow-up						
Day	**Within 28 days of enrollment**	**Within approx. 5 days after confirming eligibility**	**D-5**	**D-4**	**D-3**	**D-2**	**D-1**	**D0**	**D1 to D14[n]**	**D21 (± 3 days)**	**D28 (± 3 days)**	**D49 (± 3 days)**	**D77 (± 3 days)**	**D105 (± 14 days)**	**D133 (± 14 days)**	**D180 (± 14 days)**
Pregnancy test (serum or urine)	X	X	X											X		X
Lumbar puncture[d]	X								X[d]							
PET-CT disease assessment	X[e]										X			X		X
Tumor biopsy	X[f]								Day 5 +/- 2d[f]							
Blood draw for rituximab PK[g]			X							X		X	X	X	X	
Blood draw for chemistry panel	X	X	X	X	X			X	X	X	X			X		X
Central CBC w/differential		X							Day 7, 14	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						X	X							
Blood draw for PBMC, serum**,** plasma (central lab)[h]		X	X					X	Day 1, 3, 5, 7, 14	X	X	X		X		X
AEs/Concomitant medications[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event**;** approx., approximately; BP, blood pressure; BSA, body surface area; CAR, chimeric antigen receptor; CBC, complete blood count; CR, complete response; CRP, C-reactive protein; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; D, day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, heart rate; IRT, interactive response technology; IV, intravenous; MRD, minimal residual disease; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; PET-CT, positron emission tomography-computed tomography; PK, pharmacokinetics; QOD, every other day; RCR, replication-competent retrovirus; RR, respiratory rate; SAE, serious adverse event; sat, saturation; temp, temperature

a ECHO performed following the subject's last chemotherapy treatment and within 28 days before signing the consent may be used for confirmation of eligibility.
b As clinically indicated thereafter.
c It is recommended that vital signs are monitored during and after axicabtagene ciloleucel treatment and as clinically indicated.
d Lumbar puncture: For subjects with neurologic symptoms at screening, a lumbar puncture will be performed at screening to confirm eligibility. For subjects with new onset Grade 2 or higher neurologic symptoms after axicabtagene ciloleucel infusion, a lumbar puncture will be performed to assess cerebrospinal fluid (CSF) if there are no contraindications. If possible, opening pressure should be measured and recorded in the subject's site chart.
e PET-CT (neck-chest-abdomen-pelvis)/disease assessment: PET-CT performed following the subject's last line of therapy and prior to signing the informed consent may be used for confirmation of eligibility if within 28 days prior to enrollment, and no other anticancer treatment has been administered.
f Sites are required to submit archival samples at screening as formalin-fixed paraffin-embedded (FFPE) tumor block(s) or 30 unstained slides. Archived samples will be submitted to the central laboratory after eligibility has been confirmed and prior to leukapheresis. If archival material is unavailable or insufficient at screening, a fresh tumor sample is required to be collected and submitted prior to leukapheresis. CCI [redacted] If a subject achieves a CR as best response and subsequently progresses, sites are strongly encouraged to collect a biopsy confirming disease progression.
g Blood draw for rituximab PK should be collected immediately before each rituximab infusion and between 15 minutes and 3 hours after each rituximab infusion.
h Blood draws for PBMCs, serum, and plasma: Blood draw for PBMCs includes the analysis of anti-CD19 CAR T cells and replication-competent retrovirus (RCR); blood draw for serum includes the analysis of cytokines; blood draw for plasma includes analysis of minimal residual disease (MRD**)**. If, following discharge from initial hospitalization, the subject is subsequently re-admitted to the hospital with any axicabtagene ciloleucel-related AEs, blood samples for PBMC and serum will be collected on day of admission, then weekly, and on day of discharge. If the subject experiences a Grade 3 or higher axicabtagene ciloleucel-related toxicity, such as Grade 3 CRS or neurologic toxicities, 1 additional blood draw for serum will be taken at the time of the Grade 3 or higher axicabtagene ciloleucel-related toxicity and upon resolution of the event. If subjects develop secondary malignancies, a blood draw for PBMCs will also be scheduled and performed after diagnosis and sent to the central laboratory for RCR analysis.
i SAE and concomitant medication reporting begins after signing of the informed consent. AE reporting begins after enrollment.
j Lab draws can be performed 24 hours prior to the leukapheresis.
k Weight taken on the leukapheresis day will be used to calculate the BSA for the rituximab dosage and will be entered into IRT. This dose will remain consistent for all rituximab infusions unless a significant weight change is seen.
n. If a subject is discharged from the hospital or healthcare facility between Days 8 and 13, the subject's next scheduled assessments are on Day 14.

Table 3. Long-term Follow-up Assessments for All Subjects

Procedure	Long-term Follow-up Period[7]											
Visit Frequency	Month 9 (± 2 weeks)	Month 12 (± 2 weeks)	Month 15 (± 2 weeks)	Month 18 (± 2 weeks)	Month 24 (± 1 month)	Month 30 (± 1 month)	Month 36 (± 1 month)	Month 42 (± 1 month)	Month 48 (± 1 month)	Month 54 (± 1 month)	Month 60 (± 1 month)	Month 72 and Annually Thereafter for 15 Years[8] (± 1 month)
Physical exam[1]	X	X	X	X	X							
PET-CT/Disease assessment[2]	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
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Survival status	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for chemistry panel	X	X	X	X	X							
Blood draw for CBC w/differential	X	X	X	X	X							
Central CBC w/differential and PBMC	X	X	X	X	X		X		X		X	X
Targeted AEs/SAEs[4]	X	X	X	X	X							
Targeted concomitant medications[5]	X	X	X	X	X							
Subsequent therapy for NHL[6]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CBC, complete blood count; NHL, non-Hodgkin lymphoma; PBMC, peripheral blood mononuclear cell; PET-CT, positron emission tomography-computed tomography; SAE, serious adverse event.

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. If the subject has started subsequent anticancer therapy, then imaging assessments will no longer be required per protocol.

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4 Targeted AEs/SAEs will be collected for 15 years or until disease progression (whichever occurs first). All subjects treated with axicabtagene ciloleucel must have SPMs reported for 15 years following treatment.
5 Targeted concomitant medications will be collected for 24 months or until disease progression (whichever occurs first).
6 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 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.
7 In the event of PD, subject will begin the long-term follow-up period after completion of the post-treatment follow-up visits and be assessed for survival status, subsequent therapy for the treatment of NHL, disease assessments as indicated in footnote 2, AEs/SAEs as indicated in footnote 4, and concomitant medications as indicated in footnote 5.
8. At the end of the KT-US-471-0114 study, subjects who have received an infusion of axicabtagene ciloleucel will have the opportunity to transition to the LTFU study,KT-US-982-5968, after providing signed 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 while continuing 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 the study investigational product (IP) or other protocol-required therapies and must also 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, undergo procedures, and continue participating in study follow-up. Subject data collected up until withdrawal of consent will be retained and included in the analysis of the study. Publicly available data (death records) can be included after withdrawal of consent if local regulations permit. 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 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 before study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol-required IPs or procedures include any of the following:

- AEs
- Subject request
- Product not available
- Lost to follow-up
- Death

- Decision by sponsor
- Progressive Disease
- Pregnancy

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
- Termination of the study by the sponsor
- Other (eg. Non-compliance; refusal to consent to the KT-US-982-5968 study)

9. SAFETY REPORTING

9.1. Adverse Events

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. When recording such events, provide descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches, or blood pressure is now increased in a subject with pre-existing hypertension).

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 an AE. Death due to disease progression should be reported using the primary tumor type (eg, B-cell lymphoma).

When an AE or SAE is due to the disease under investigation, it is necessary to 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. If a subject requests to withdraw from protocol-required therapies or the study because of an AE, then the subject should undergo the procedures outlined in the Day 105 visit of the SOA.

9.2. Reporting of Adverse Events

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject that occur after enrollment through 30 days after completing the final dose of rituximab or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. For subjects who are enrolled (ie, leukapheresed) but do not receive rituximab or axicabtagene ciloleucel, the AE reporting period ends 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy).

For subjects who are dosed (ie, receive rituximab or axicabtagene ciloleucel), all AEs will be recorded from the date of enrollment through 30 days after last dose of rituximab or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. If a subject has disease progression prior to Month 3 and does not receive another anticancer therapy, only related AEs will be collected through 3 months after axicabtagene ciloleucel infusion.

After Month 3, only targeted AEs will be recorded from Month 3 through 15 years after axicabtagene ciloleucel infusion or disease progression, whichever occurs first. Targeted AEs include cytopenias, infection, thromboembolic events, autoimmune disorders, hypogammaglobulinemia, and SPMs. All subjects treated with axicabtagene ciloleucel must have SPMs reported for 15 years following treatment.

The investigator is expected to follow reported AEs until stabilization or resolution.

The investigator must provide the following information 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, lymphodepleting chemotherapy, or study procedures
- Action taken

The AE grading scale used will be the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov). The severity of CRS events will be graded using a modification of the system proposed by Lee and colleagues {Lee 2014} as outlined in the axicabtagene ciloleucel IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) axicabtagene ciloleucel, 2) rituximab, 3) conditioning chemotherapy, 4) any protocol-required study procedure or treatment, 5) disease progression, 6) concurrent disease, 7) concomitant medication, or 8) other. 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 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.

9.2.1. 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 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

9.3. Definition of Serious Adverse Events

An SAE is defined as an AE (as defined in Section 9.1) that meets at least 1 of the following serious criteria:

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

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 following events must be submitted as SAEs:
  - CRS events Grade 3 or higher
  - Neurologic events Grade 3 or higher
  - All events of cerebral edema
  - All events of hemophagocytic lymphohistiocytosis/macrophage activation syndrome

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE according to NCI CTCAE version 5.0 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 eCRF.

9.4. Reporting of Serious Adverse Events

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after completing final dose of rituximab or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. After this follow-up period is completed, only targeted SAEs will be reported. Targeted SAEs are defined as and include neurological, hematological, infections, autoimmune disorders, and SPMs that occur up to 15 years or until disease progression. In addition, all subjects treated with axicabtagene ciloleucel must have SPMs reported for 15 years following treatment.

SAEs that the investigator assesses as related to axicabtagene ciloleucel or rituximab should be reported regardless of the time period.

SPMs must be reported as SAEs regardless of when they occur and regardless of their relationship to the study treatments/procedures.

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, lymphodepleting chemotherapy, administration of rituximab).

All SAEs must be submitted to Kite Pharma via the eSAE system within 24 hours of the investigator's knowledge of the event. If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the SAE Report Form and sent via email to the SAE Reporting mailbox: PPD

Following completion of ZUMA-14, 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:
PPD

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 indicated as being due to disease progression within the CRF. If the malignancy has a fatal outcome before 24 months, then the event "B-cell lymphoma" must be recorded as an SAE with the outcome being fatal.

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

Any death occurring after enrollment and before the post-treatment follow-up period, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the post-treatment follow-up period requires expedited reporting within 24 hours only if it is considered related to treatment.

9.5. Reporting Deaths

Deaths that occur during the protocol-specified AE 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. 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 AEs, 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. Instructions for Reporting Special Situations

There is no relevant clinical experience with axicabtagene ciloleucel in pregnant or lactating women, and animal reproductive studies have not been performed. FCBP must have a negative pregnancy test before leukapheresis and before conditioning chemotherapy because of the potentially dangerous effects of the preparative chemotherapy on the fetus. FCBP 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 methods of contraception (method must achieve an annual failure rate of < 1%) for at least 6 months after lymphodepleting chemotherapy, 6 months after axicabtagene ciloleucel dosing, or

12 months after rituximab dosing, whichever is longer. Male subjects are recommended not to father a child for 6 months after lymphodepleting chemotherapy or axicabtagene ciloleucel dosing, whichever is longer.

Any pregnancy in a female subject enrolled into the study must be reported, regardless of the time after axicabtagene ciloleucel infusion. If the pregnancy occurs in a female partner of a male subject within 6 months after completing lymphodepleting chemotherapy or the administration of axicabtagene ciloleucel, whichever is longer, the pregnancy must be reported. All such pregnancies must be reported to Kite Pharmacovigilance and Epidemiology (PVE) using the Pregnancy Report Form within 24 hours after becoming aware of the pregnancy. Information regarding the pregnancy and/or the outcome will be requested by the sponsor. Pregnancy report forms should be reported to Kite PVE at PPD or PPD

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported as an SAE within 24 hours. The underlying medical reason for this procedure should be recorded as the AE term. Any SAE occurring as an adverse pregnancy outcome post study must be reported to Kite PVE.

The pregnant subject or subject partner should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Kite PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite PVE.

Pregnancies of female partners of male study subjects exposed to axicabtagene ciloleucel or other study drugs must also be reported, and relevant information should be submitted within 24 hours to Kite PVE using the pregnancy and pregnancy outcome forms. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite PVE.

If a lactation case occurs in a female subject in the study, the lactation case must be reported to Kite PVE within 24 hours after the investigator's awareness of the event using the Special Situations Reporting Form. In addition to reporting a lactation case during the study, investigators should monitor for pregnancy and lactation cases throughout the long term follow up period. Report the lactation case and Special Situations report forms to Kite PVE at PPD or PPD

9.8. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE as described in Section 9.4.

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 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 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 in 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.

9.10. Safety Review Team

The internal SRT comprises the study sponsor medical monitor, drug safety physician, study statistician, and at least 1 active study investigator. As part of its oversight, the SRT will assess safety criteria to make recommendations on dosing with rituximab, determine pause of enrollment, decide when to move forward with the expansion phase, and consider any other study conduct-related changes. The SRT will meet and review the safety data after 6 subjects have completed their 28-day disease assessment and again after 15 subjects have completed their 28-day disease assessment. The details for these criteria and for the function of the SRT are found in the SRT charter.

10. STATISICAL CONSIDERATIONS

10.1. Hypothesis

No formal hypothesis will be tested in this study. The study is designed to estimate the CR rate in subjects with large B-cell lymphoma treated with axicabtagene ciloleucel in combination with rituximab.

10.2. Study Endpoints

10.2.1. Primary Endpoint

Complete response rate (CR per the IWG Lugano Classification {Cheson 2014}), as determined by the study investigators.

10.2.2. Secondary Endpoints

- Incidence of AEs and clinically significant changes in safety lab values
- ORR is defined as the incidence of either a CR or a PR per IWG Lugano Classification {Cheson 2014}, as determined by study investigators. All subjects who do not meet the criteria for an objective response by the analysis data cutoff date will be considered nonresponders.
- Duration of response (DOR): Among subjects who experience an objective response, DOR is defined as the date of their first objective response to disease progression per IWG Lugano Classification {Cheson 2014}, as determined by study investigators, or death from any 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. Subjects who receive additional anticancer therapy in the absence of documented progression will be censored at the last evaluable disease assessment prior to the additional therapy. Subjects who receive an SCT in the absence of documented progression will be censored at the last evaluable disease assessment prior to the date of the SCT. A sensitivity analysis will be conducted in which disease assessments obtained after SCT while in axicabtagene ciloleucel-induced remission are included in the derivation of DOR.
- PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per IWG Lugano Classification {Cheson 2014}, as determined by study investigators, or death from any 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. The PFS for subjects who undergo SCT while in remission will be censored at the last evaluable disease assessment prior to the date of SCT; the PFS for subjects who undergo other new anticancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anticancer therapies. A sensitivity analysis will be conducted in which disease assessments obtained after SCT while in axicabtagene ciloleucel-induced remission are included in the derivation of PFS.

- 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 date known as alive or the data cutoff date, whichever is earlier.

- PK is defined as levels of axicabtagene ciloleucel in blood.

10.3. Sample Size Considerations

This study uses a single-arm design to estimate the true CR rate in subjects with large B-cell lymphoma treated with axicabtagene ciloleucel in combination with rituximab. The anticipated enrollment in this study is approximately 30 subjects. With a total sample size of 30 subjects at a given dosing schedule, an observed CR rate of 70% will yield an 80% confidence intervals for the response rate with a maximum half-width no greater than 13%, corresponding to a lower limit of at least 57%. This target CR rate, and the lower limit of the 80% confidence interval for the CR rate, is meaningful because it would represent a significant improvement in the response rate for the subjects with large B-cell lymphoma over existing therapies.

Additional assumptions and corresponding 2-sided 95% and 80% exact confidence intervals are provided in Table 4.

Table 4. 95% and 80% Exact Confidence Intervals Corresponding to Observed CR Rate After Treatment of 30 Subjects

Subjects with CR	Observed CR Rate	95% Confidence Interval	80% Confidence Interval
15	50%	[31%, 69%]	[37%, 63%]
18	60%	[41%, 77%]	[47%, 72%]
21	70%	[51%, 85%]	[57%, 81%]
24	80%	[61%, 92%]	[68%, 89%]
27	90%	[73%, 98%]	[79%, 96%]

Abbreviations: CR, complete response.

10.4. Access to Individual Subject Treatment Assignments

This is an open-label combination study; 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 plan.

10.5. Interim Analysis and Early Stopping Guidelines

Formal interim analyses of efficacy are not planned for the early trial stopping purpose. The team will review the interim safety data per the SRT charter.

10.6. Analysis Subsets

In this study, subjects are to be dosed at a target of 2×10^6 (1.0×10^6 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 > 100 kg, a maximum flat dose of 2×10^8 anti-CD19 CAR T cells will be administered. Subjects are considered to have received the target dose if they receive at least 1×10^6 anti-CD19 CAR T cells/kg.

Full analysis set (FAS): The FAS will consist of all enrolled subjects and will be used for the summary of subject disposition.

Modified intent-to-treat (mITT) set: The mITT set will consist of all subjects enrolled and treated with axicabtagene ciloleucel and at least 1 dose of rituximab after axicabtagene ciloleucel infusion. This analysis set will be used for all efficacy analyses.

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

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 at 6 months. The final analysis will occur when all subjects have completed at least 24 months of follow-up. Additional analyses of safety and efficacy may occur at any time after the primary analysis.

Subjects will be transitioned to the KT-US-982-5968 study for the remainder of the 15-year LTFU period. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

10.7.1. Complete Response Rate

The incidence of CR and exact 2-sided 95% confidence intervals will be generated.

10.7.2. Objective Response Rate

The incidence of ORR and exact 2-sided 95% confidence intervals will be generated.

10.7.3. Duration of Response

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for DOR. Estimates of the proportion of subjects alive and in response at 3-month intervals will be provided.

10.7.4. Progression-free Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for PFS. Estimates of the proportion of subjects alive and in response at 3-month intervals will be provided.

10.7.5. 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.

10.7.6. Safety

Subject incidence rates of AEs including all, serious, fatal, CTCAE version 5.0 Grade 3 or higher, and treatment-emergent AEs (TEAEs) reported throughout the conduct of the study will be tabulated by preferred term and system organ class. Identified and potential risks of axicabtagene ciloleucel and rituximab will be summarized. 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 through LTFU and treatment-related SAEs will be provided.

10.7.7. Pharmacokinetics

For levels of axicabtagene ciloleucel (number of CAR T cells) in blood, descriptive summary statistics over time will be provided, including the summary for peak measurement, time to peak, and AUC of these measurements. These descriptive summaries will be generated in tabular or graphical format. Descriptive statistics refers to number of subjects, mean, median, standard deviation, first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous measurements. Graphical summaries over time will include median ± quartile (Q1, Q3) plots over time and box plots of peak and AUC of CAR T-cell measurements.

CCI [redacted]

10.7.8. 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 transitioning 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

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

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'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 within all material that is 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 according to 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 country-specific regulations and 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 include personal information.

11.3. Investigator Signatory Obligations

Each Clinical Study Report (CSR) will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- Is a recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participates 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 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 regarding either the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at its sole discretion, to determine whether to manufacture axicabtagene ciloleucel and provide it to sites and subjects after the completion of the study.

13. STUDY DOCUMENTATION AND ARCHIVING

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. The individuals authorized to fulfill 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 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, the use of the CRFs as source documentation is not recommended as a routine practice.

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, health 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 Pharma and the investigator. If storage is no longer available to archive source documents or if source documents must be moved to an alternative location, the research staff should notify the key sponsor contact before 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 must also assure that subject confidentiality is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence and 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 therapies should be identified by trade names. For additional details related to the completion of CRFs, refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in KT-US-471-0114 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 that 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 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 among the institution, principal investigator, and Kite or its delegate will outline the requirements for publication review.

16. REFERENCES

American Cancer Society. Cancer Facts & Figures 2019. 2019.

Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Mueller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014;32 (27):3048-58.

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

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32 (27):3059-68.

Clinical Trials Facilitation Group (CTFG). Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials. Final Version. 15 September. 2014.

Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116 (12):2040-5.

Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130 (16):1800-8.

Dudley ME, Yang JC, Sherry R, Hughes MS, Royal R, Kammula U, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. J Clin Oncol 2008;26 (32):5233-9.

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

Gattinoni L, Finkelstein SE, Klebanoff CA, Antony PA, Palmer DC, Spiess PJ, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. J Exp Med 2005;202 (7):907-12.

Klebanoff CA, Khong HT, Antony PA, Palmer DC, Restifo NP. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. Trends Immunol 2005;26 (2):111-7.

Kochenderfer JN, Somerville RPT, Lu T, Shi V, Bot A, Rossi J, et al. Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels. J Clin Oncol 2017;35 (16):1803-13.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124 (2):188-95.

Leonard JP, Schattner EJ, Coleman M. Biology and management of mantle cell lymphoma. Curr Opin Oncol 2001;13 (5):342-7.

Locke FL, Westin JR, Miklos DB, Herrara AF, Jacobson CA, Lee J, et al. Phase 1 Results from ZUMA-6: Axicabtagene Ciloleucel (axi-cel; KTE-C19) in Combination with Atezolizumab for the Treatment of Patients with Refractory Diffuse Large B Cell Lymphoma (DLBCL). Blood 2017;130 (Suppl 1):2826-.

MabThera, Roche Products Limited. MabThera 100 mg Concentrate for Solution for Infusion. Summary of Product Characteristics. Welwyn Garden City, United Kingdom. Revised: 30 July. 2019:

Marshall MJE, Stopforth RJ, Cragg MS. Therapeutic Antibodies: What Have We Learnt from Targeting CD20 and Where Are We Going? Frontiers in immunology 2017;8:1245.

Mihara K, Yanagihara K, Takigahira M, Kitanaka A, Imai C, Bhattacharyya J, et al. Synergistic and persistent effect of T-cell immunotherapy with anti-CD19 or anti-CD38 chimeric receptor in conjunction with rituximab on B-cell non-Hodgkin lymphoma. Br J Haematol 2010;151 (1):37-46.

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

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377 (26):2531-44.

Nicholson IC, Lenton KA, Little DJ, Decorso T, Lee FT, Scott AM, et al. Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. Mol Immunol 1997;34 (16-17):1157-65.

Noone A, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2015. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. 2017.

O'Brien SM, Kantarjian HM, Cortes J, Beran M, Koller CA, Giles FJ, et al. Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. J Clin Oncol 2001;19 (5):1414-20.

Olejniczak SH, Stewart CC, Donohue K, Czuczman MS. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry. Immunol Invest 2006;35 (1):93-114.

Perez-Callejo D, Gonzalez-Rincon J, Sanchez A, Provencio M, Sanchez-Beato M. Action and Resistance of Monoclonal CD20 Antibodies Therapy in B-cell Non-Hodgkin Lymphomas. Cancer Treat Rev 2015;41:680-9.

RITUXAN, Genentech Inc. RITUXAN® (rituximab) injection, for intravenous use. US Prescribing Information. South San Francisco, CA. Revised: June. 2018:

Rodriguez J, Pugh WC, Romaguera JE, Cabanillas F. Primary mediastinal large cell lymphoma. Hematological Oncology 1994;12 (4):175-84.

Rossi JM, Galon J, Turcan S, Danan C, Locke FL, Neelapu SS, et al. Characteristics of the pretreatment tumor microenvironment may influence clinical response in patients with refractory large B cell lymphoma treated with axicabtagene ciloleucel (axi-cel) in the pivotal ZUMA-1 [Abstract LB-016/16]. American Association for Cnacer Research (AACR); 2018 14-18 April; Chicago, Illinois.

Rufener GA, Press OW, Olsen P, Lee SY, Jensen MC, Gopal AK, et al. Preserved Activity of CD20-Specific Chimeric Antigen Receptor-Expressing T Cells in the Presence of Rituximab. Cancer Immunol Res 2016;4 (6):509-19.

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

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

Uckun FM, Jaszcz W, Ambrus JL, Fauci AS, Gajl-Peczalska K, Song CW, et al. Detailed Studies on Expression and Function of CD19 Surface Determinant by Using B43 Monoclonal Antibody and the Clinical Potential of Anti-CD19 Immunotoxins. Blood 1988;71 (1):13-29.

Yescarta, Gilead Sciences Inc. YESCARTA 0.4-2 x 10^8 Cells Dispersion for Infusion. EMA Summary of Product Characteristics. Holborn, London, UK. Available at: https://www.medicines.org.uk/emc/product/9439/smpc:. Updated: 28 August. 2018:

YESCARTA, Kite Pharma Inc. YESCARTA® (axicabtagene ciloleucel) Suspension for Intravenous Infusion. U. S. Prescribing Information. Santa Monica, CA. 2017:

17. APPENDICES

Appendix 1. International Working Group Lugano Classification

Refer to the imaging manual and {Cheson 2014} for details of assessment.

Table 5. 5-Point Scale (5PS)

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

Source: {Barrington 2014}

Complete Remission

Complete Metabolic Response (CMR) for Positron Emission Tomography-Computed Tomography (PET-CT)-based Response

The designation of 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 extranodal 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 fluorodeoxyglucose (FDG)-avid disease in bone marrow

Complete Radiologic Response (CRR) for Computed Tomography (CT)-based Response

The designation of 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 extralymphatic sites of disease
- Absent nonmeasured lesion

- Organ enlargement regress to normal
- No new sites of disease should be observed.
- Bone marrow normal by morphology; if indeterminate, immunohistochemistry (IHC) negative

Partial Remission

Partial Metabolic Response (PMR) for PET-CT-based Response

The designation of 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.

Partial Radiologic Response (PRR) for CT-based Response

The designation of 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 extranodal 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 nonmeasured lesions
- Spleen must have regressed by > 50% in length beyond normal
- No new sites of disease should be observed.

Stable Disease

No Metabolic Response (NMR) for PET-CT-based Response

The designation of 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 EOT
- No new sites of disease should be observed.
- No change from baseline in bone marrow

Stable Radiologic Disease (SRD) for CT-based Response

The designation of SRD requires all of the following:

- < 50% decrease from baseline in the SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
- No increase consistent with progression in nonmeasured lesion and organ enlargement
- No new sites of disease should be observed.

Progressive Disease

Progressive Metabolic Disease (PMD) for PET-CT-based Response

The designation of 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 EOT 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

Progressive Radiologic Disease (PRD) for CT-based Response

The designation of PRD requires at least 1 of the following:

- An individual node/lesion must be abnormal with:
  - 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) 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 nonmeasured lesions
- New lesion
  - Regrowth of previously resolved lesions
  - A new node > 1.5 cm in any axis
  - A new extranodal 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

Appendix 2. Childbearing Potential and Birth Control

This study will follow the recommendations from the Clinical Trial Facilitation Group (CTFG) {Clinical Trials Facilitation Group (CTFG) 2014}, as described below.

A. Definition of Childbearing Potential

A female is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this study, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

B. Birth Control Methods That May Be Considered as Highly Effective

Birth control methods that may be considered as highly effective must achieve an annual failure rate of less than 1% when used consistently and correctly.[1]

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[2]:

  Oral

  Intravaginal

  Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation[2]:

  Oral

  Injectable

[1] 2014 clinical trial facilitation and coordination group contraception guidance.
[2] Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method.

Implantable[3]

Intrauterine device (IUD)[3]

Intrauterine hormone-releasing system (IUS)[3]

Bilateral tubal occlusion[3]

Vasectomized partner[3,4]

Sexual abstinence[5]

Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). A female condom and a male condom should not be used together.

[3] Contraception methods that in the context of this guidance are considered to have low user dependency.
[4] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
[5] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.