



**PROTOCOL TITLE: A PHASE 1-2 MULTI-CENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF KTE-C19 IN COMBINATION WITH ATEZOLIZUMAB IN SUBJECTS WITH REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)**

**Protocol Number:** KTE-C19-106 (ZUMA-6)

**Kite Investigational Product** Axicabtagene ciloleucel

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## Investigators Agreement

A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Combination with Atezolizumab in Subjects with Refractory Diffuse Large B-Cell Lymphoma (DLBCL) (ZUMA-6) dated 04 Aug 2021 and agree to abide by all provisions set forth therein.

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

- Me (including, if applicable, my spouse, legal partner and dependent children)
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_____ Signature
_____ Name of investigator
_____ Date

## PROTOCOL SYNOPSIS

### TITLE

A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Combination with Atezolizumab in Subjects with Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

### INDICATION

Treatment refractory DLBCL in adult subjects.

### STUDY DESIGN

This is a Phase 1-2, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with atezolizumab in subjects with refractory DLBCL. The trial will be separated into two distinct Phases designated as Phase 1 and Phase 2.

During Phase 1, approximately 3-9 subjects with refractory DLBCL will be enrolled in up to 3 cohorts to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens. A safety review team (SRT) that is internal to the study sponsor and Phase 1 investigators, will review safety data after all subjects in each Phase 1 cohort have had the opportunity complete the dose-limiting toxicities (DLT) window. The SRT will make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in [Figure 3](#) and outlined in [Section 9.6](#).

In Phase 2, approximately 22 subjects will be enrolled to receive combination treatment with axicabtagene ciloleucel and atezolizumab based on the dose and schedule selected to move forward from the Phase 1 portion of the study as recommended by the SRT.

Independent of the cohort or Phase of the study, each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Conditioning chemotherapy
- Combination treatment (axicabtagene ciloleucel and atezolizumab)
- Post treatment assessment
- Long term follow-up

For study requirements assigned to each study period, please refer to [Section 7](#) for details.

## STUDY OBJECTIVES

The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens.

The primary objective of Phase 2 is to evaluate the efficacy of axicabtagene ciloleucel and atezolizumab, as measured by complete response rate in subjects with refractory DLBCL. Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and atezolizumab and additional efficacy, biomarker, pharmacokinetic, and anti-therapeutic antibody endpoints.

## HYPOTHESIS

No formal hypothesis will be tested in this study. The Phase 2 portion of the study is designed to estimate the true CR rate in patients with refractory DLBCL treated with the axicabtagene ciloleucel followed by atezolizumab.

## PRIMARY ENDPOINT

- Phase 1: Incidence of dose-limiting toxicities (DLT)
- Phase 2: Complete response rate (complete response [CR] per the revised International Working Group [IWG] Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by study investigators.

## SECONDARY ENDPOINT(S) FOR PHASE 1 AND 2

- Objective Response Rate (CR + PR) per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}
- Duration of Response
- Progression Free Survival
- Overall Survival
- Incidence of adverse events and clinically significant changes in safety lab values
- Levels of axicabtagene ciloleucel in blood and incidence of anti-KTE-C19 antibodies
- Atezolizumab pharmacokinetics and incidence of anti- atezolizumab antibodies in serum
- Levels of cytokines and other markers in serum

CCI

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## SAMPLE SIZE

Approximately 3-31 subjects

Phase 1: approximately 3-9 subjects

Phase 2: approximately 22 subjects

## STUDY ELIGIBILITY

Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both Phases of the study.

## TREATMENT

Conditioning Chemotherapy Treatment:

- Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m<sup>2</sup>/day and cyclophosphamide 500 mg/m<sup>2</sup>/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.

Investigational Product(s):

- Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10<sup>6</sup> **anti-CD19 CAR T cells/kg**. Subjects who receive between 1.0 and 2.4 x 10<sup>6</sup> anti-CD19 CAR T cells/kg will be considered evaluable in the efficacy set. Under circumstances where subjects initially respond and subsequently relapse, subjects may be eligible for a second course of conditioning chemotherapy and axicabtagene ciloleucel. Refer to Section 6 for treatment and Section 7.12.8 for retreatment details.
- Atezolizumab treatment consists of an intravenous infusion of 1200 mg given every 21 days for 4 doses. In the Phase 1 portion of the study, the first dose of atezolizumab will be administered 21 days following axicabtagene ciloleucel infusion (Cohort 1), 14 days following axicabtagene ciloleucel infusion (Cohort 2), or 1 day following axicabtagene ciloleucel infusion (Cohort 3).

Additional axicabtagene ciloleucel and atezolizumab schedules or regimens may be explored in Phase 1.

The axicabtagene ciloleucel and atezolizumab treatment in Phase 2 will follow the dosing schedule with the best overall benefit/risk profile tested in Phase 1 as determined by the safety review team (see [Figure 3](#)).

## PROCEDURES

At specific time points as outlined in the schedule of assessments, subjects will undergo the following procedures: collection of informed consent, general medical history including previous treatments for NHL, physical exam (including neurological assessment) including vital signs and performance status. Subjects will also undergo blood draws for complete blood count (CBC), chemistry panels, cytokines, C-reactive protein, lymphocyte subsets, anti-KTE-C19 antibodies, anti-atezolizumab antibodies, replication competent retrovirus (RCR) and anti-CD19 CAR T cell analysis. Women of child-bearing potential will undergo a urine or serum pregnancy test.

Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), brain magnetic resonance image (MRI), a positron emission tomography-computed tomography (PET-CT), and leukapheresis.

Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events and will have their disease assessed.

## SAFETY REVIEW TEAM

A safety review team (SRT), internal to the study sponsor and Phase 1 investigators, will review the safety data following each Phase 1 cohort and make recommendations on further study conduct of Phase 1 and progression to Phase 2.

The SRT will also meet 1 time during the Phase 2 portion of the study when 6 subjects have had the opportunity to complete their 1-month disease assessment. The SRT will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. The SRT may meet more often as needed. Refer to Section 9.6.

## STATISTICAL CONSIDERATIONS

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

The primary endpoint for the Phase 2 portion of the study is complete response rate per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by the study investigators.

This study uses a single-arm design to estimate the true complete response rate in patients with DLBCL treated with the combination of axicabtagene ciloleucel and atezolizumab at the dosing schedule closest to concomitant administration tested in Phase 1 and deemed safe by the SRT. With a total sample size of 25 patients at a given dosing schedule, of which at least 3 will have been treated in the Phase 1 portion, an observed CR rate of 70% will yield 95% confidence that estimate of the true CR rate is between 51% and 88%. Refer to Section 10 for additional discussion.

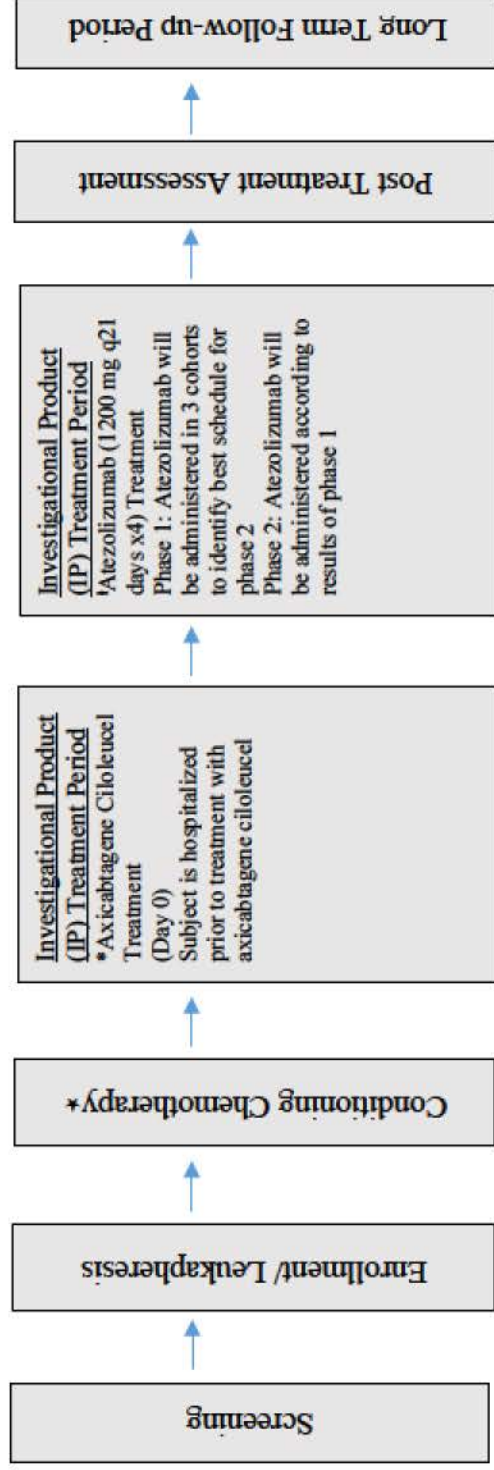
## STUDY GLOSSARY

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
ATAs	anti-therapeutic antibodies
AUC	area under the curve
<b>Axicabtagene ciloleucel / KTE-C19</b>	autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3 zeta chimeric antigen receptor
CAR	chimeric antigen receptor
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPF	central processing facility
CR	complete response / <b>Complete Remission</b>
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
eACT™	engineered autologous cell therapy
EBV	epstein-Barr virus
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	eastern cooperative oncology group
End of Study for individual subject	Defined as when the last day that protocol specified assessments are conducted for an individual subject
End of Study (primary completion)	Defined as when the last subject is assessed or received an intervention for the purposes of final collection of data for the primary endpoint at Month 6
End of Study (end of trial)	Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments
FAS	full analysis set
FL	follicular lymphoma
HAMA	human anti-mouse antibodies
HLH	hemophagocytic lymphohistiocytosis
ICF	informed consent form
ICU	intensive care unit
IP	investigational product

<b>Abbreviation or Term</b>	<b>Definition/Explanation</b>
IRB/IEC	institutional review board/independent ethics committee
IWG	International working group
LMWH	low-molecular-weight heparin
LTFU	long term follow-up
mITT	modified intend to treat
MMSE	mini mental status exam
MRI	magnetic resonance imaging
MSGV1	murine stem cell virus-based vector
NaCl	sodium chloride
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
OS	overall survival
PET-CT	positron emission tomography–computed tomography
PBMC	peripheral blood mononuclear cells
PMBCL	primary mediastinal B cell lymphoma
PD	progressive disease
PK	pharmacokinetic
PR	partial response / <b>Partial Remission</b>
RCR	replication competent retrovirus
scFv	single chain variable fragment
SOA	schedule of assessments
SD	stable disease
SRT	safety review team
SUSAR	suspected unexpected serious adverse reactions
Study day 0	Defined as the first day that axicabtagene ciloleucel is administered to the subject
TEAEs	treatment emergent adverse events
TFL	transformed follicular lymphoma
ULN	upper limit of normal



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



\* Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m<sup>2</sup>/day and cyclophosphamide 500 mg/m<sup>2</sup>/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.

\* Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously on Day 0 at a target dose of  $2 \times 10^6$  anti-CD19 CAR T cells/kg

†Atezolizumab treatment consists of an intravenous infusion of 1200 mg given every 21 days for 4 doses. In the phase 1 portion, the first dose of atezolizumab will be administered in 3 cohorts:

- Cohort 1: Beginning on day 21 following axicabtagene ciloleucel/KTE-C19 infusion
  - Cohort 2: Beginning on day 14 following axicabtagene ciloleucel/KTE-C19 infusion
  - Cohort 3: Beginning on day 1 following axicabtagene ciloleucel/KTE-C19 infusion
- Atezolizumab treatment in phase 2 will follow the dosing schedule from phase 1 agreed upon by the study sponsors and the SRT.

**Note:** After the end of KTE-C19-106, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in a separate Long-term Follow-up study, KT-US-982-5968

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## **1. OBJECTIVES**

The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens.

The primary objective of Phase 2 is to evaluate the efficacy of axicabtagene ciloleucel and atezolizumab, as measured by complete response rate in subjects with refractory diffuse large B-cell lymphoma (DLBCL). Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and atezolizumab and additional efficacy, biomarker, pharmacokinetic, and anti-therapeutic antibody endpoints.

## 2. DISEASE BACKGROUND AND RATIONALE

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes or natural killer cells. In the United States, B-cell lymphomas represent 80-85% of cases reported. In 2013, approximately 69,740 new cases of NHL and over 19,000 deaths related to the disease were estimated to occur. Non-Hodgkin lymphoma is the most prevalent hematological malignancy and is the seventh leading site of new cancers among men and women and account for 4% of all new cancer cases and 3% of deaths related to cancer {SEER 2014}.

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

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

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

Setting	Outcome to Subsequent Therapy
Refractory to 1 <sup>st</sup> line	
Phillip et al 1995 (n=28)	ORR 21%
Josting et al 2000 (n=64)	ORR 15%, median OS 6 mos
Ardeshna et al 2005 (n=5)	ORR 0%
Hitz et al 2010 (n=33)	Proceeded to ASCT 9%, 3% survived > 1 year
Telio et al 2012 (n = 111)	ORR 23%, median OS 10 mos
Matasar et al 2013 (n=10)	ORR 10%
Refractory to 2 <sup>nd</sup> line	
Moskowitz et al 1999 (n=55)	Median OS 5 mos
Ardeshna et al 2005 (n=28)	ORR 18%, median OS (aggressive NHL) <6 mos
Seshadri et al 2008 (n=73)	ORR 14%
Relapsed post ASCT	
Nagle et al 2013 (N=45)	Median OS 8 mos

These results suggest that once a patient with DLBCL has become refractory to cytotoxic chemoimmunotherapy, the likelihood of achieving a response of any significant duration with subsequent lines of chemotherapy is low. New treatment paradigms are therefore needed in these refractory patients.

Immunotherapy is an emerging category of cancer therapy that employs the patient's own immune system to combat his or her cancer. Two distinct immunotherapeutic approaches to the care of patients with chemo-refractory lymphoma, engineered T cell therapy and immune checkpoint blockade have shown promise in pilot trials {[Kochenderfer 2015](#), [Lesokhin 2014](#)}.

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

### 2.1. Anti-CD19 CAR T cell Product

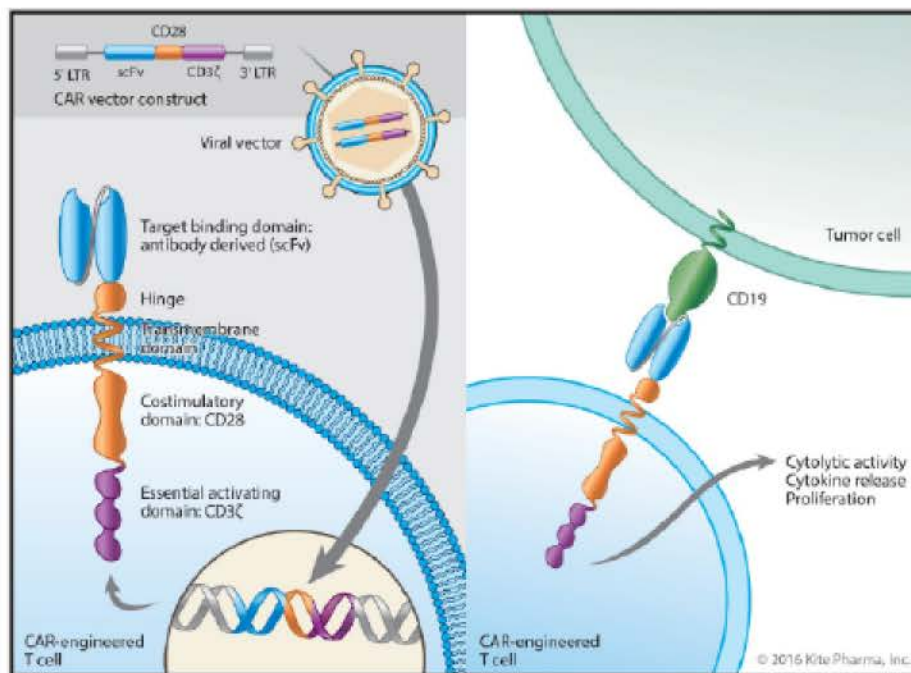
Anti-CD19 chimeric antigen receptor (CAR) T cells are autologous human T cells that have been engineered to express an extracellular single chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3 $\zeta$  (CD3-zeta)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

An anti-CD19 CAR vector construct has been designed, optimized and initially tested at the Surgery Branch of the National Cancer Institute (NCI, IND 13871) ([Figure 2](#)); {[Kochenderfer](#)

2009, Kochenderfer 2010}. The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 {Nicholson 1997}. A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and persistence of anti-CD19 CAR T cells {Kowolik 2006}. The signaling domain of the CD3-zeta chain is essential for T cell activation. These fragments were cloned into the murine stem cell virus-based (MSGV1) vector, utilized to genetically engineer the autologous T cells. Treatment with anti-CD19 CAR T cells was administered to subjects with CD19+ B cell malignancies in NCI protocol (09-C-0082; IND 13871) and in several Kite-sponsored clinical trials. The same CAR vector construct will be used in this study.

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

**Figure 2. Anti-CD19 Chimeric Antigen Receptor Construct and Mechanism of Action**



## 2.2. Anti-CD19 chimeric antigen receptor (CAR) T cells

### 2.2.1. CD19 and Expression

CD19 is a 95 kD transmembrane protein expressed only in the B cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19



expression is maintained in B cell malignancies including all subtypes of B cell NHL, chronic lymphocytic leukemia (CLL), and non-T cell acute lymphoblastic leukemia (ALL) {Blanc 2011} with the exception of multiple myeloma.

### **2.2.2. Prior experience with axicabtagene ciloleucel and other anti-CD19 CAR T cells**

The design and rationale of this study is in part derived from prior experience with axicabtagene ciloleucel on another Kite-sponsored study, ZUMA-1, and on a single-center study conducted at the National Cancer Institute. Please see the most current axicabtagene ciloleucel/KTE-C19 investigator's brochure for details.

### **2.3. Atezolizumab**

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and in cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma and for the treatment of non-small cell lung cancer.

**Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.**

#### **2.3.1. Summary of Nonclinical Studies for Atezolizumab**

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to evaluate the safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were performed with atezolizumab.

The safety, PK, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical PK and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway; heightened immune responses and the potential to increase immune-associated inflammatory lesions were identified as possible safety risks in patients.

Refer to the Atezolizumab IB for details on the nonclinical studies.

### 2.3.2. Summary of Clinical Studies for Atezolizumab

For information on the additional ongoing studies, see the latest version of the Atezolizumab IB.

#### 2.3.2.1. Clinical Safety for Atezolizumab

##### Single-Agent Clinical Safety in Study PCD4989g

Study PCD4989g, in which atezolizumab is being used as a single agent in subjects with locally advanced or metastatic solid tumors or hematologic malignancies, provides the majority of data (with 558 safety-evaluable patients as of the data extraction date of 11 May 2015) for the safety profile of atezolizumab as monotherapy.

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications. The most common cancer types for these patients include NSCLC, urothelial bladder cancer, melanoma, and renal cell carcinoma. Safety data for NSCLC are also derived from Studies GO28625 (FIR) and GO28753 (POPLAR).

##### Adverse Events

Of the 558 patients, 520 patients (93.2%) experienced at least one adverse event, including 376 patients (67.4%) who experienced one treatment-related adverse event. Commonly reported events (reported in > 10% of all patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, and cough (see Table 2).

**Table 2. Study PCD4989g: Adverse Events with Frequency > 10% of Patients for All Grades**

Preferred Term	All Grades n (%)	All Grades Related n (%)	Grade 3/4 n (%)	Grade 3/4 Related n (%)
Any adverse event	520 (93.2)	376 (67.4)	239 (42.8)	66 (11.8)
Fatigue	192 (34.4)	115 (20.6)	13 (2.3)	6 (1.1)
Decreased Appetite	142 (25.4)	62 (11.1)	4 (0.7)	0 (0.0)
Nausea	136 (24.4)	65 (11.6)	5 (0.9)	2 (0.4)

Preferred Term	All Grades n (%)	All Grades Related n (%)	Grade 3/4 n (%)	Grade 3/4 Related n (%)
Pyrexia	117 (21.0)	63 (11.3)	2 (0.4)	0 (0.0)
Constipation	116 (20.8)	8 (1.4)	2 (0.4)	0 (0.0)
Cough	113 (20.3)	11 (2.0)	1 (0.2)	1 (0.2)
Dyspnea	112 (20.1)	18 (3.2)	18 (3.2)	4 (0.7)
Diarrhea	110 (19.7)	53 (9.5)	2 (0.4)	1 (0.2)
Anemia	104 (18.6)	26 (4.7)	23 (4.1)	5 (0.9)
Vomiting	96 (17.2)	28 (5.0)	3 (0.5)	2 (0.4)
Asthenia	88 (15.8)	53 (9.5)	8 (1.4)	4 (0.7)
Back Pain	85 (15.2)	9 (1.6)	8 (1.4)	1 (0.2)
Headache	83 (14.9)	32 (5.7)	2 (0.4)	1 (0.2)
Arthralgia	79 (14.2)	35 (6.3)	2 (0.4)	0 (0.0)
Pruritus	75 (13.4)	55 (9.9)	0 (0.0)	0 (0.0)
Rash	73 (13.1)	53 (9.5)	0 (0.0)	0 (0.0)
Abdominal Pain	63 (11.3)	12 (2.2)	8 (1.4)	0 (0.0)
Insomnia	62 (11.1)	7 (1.3)	1 (0.2)	0 (0.0)
Peripheral edema	59 (10.6)	7 (1.3)	-	-
Chills	57 (10.2)	31 (5.6)	0 (0.0)	0 (0.0)

1. Note: '-' refers to missing Common Terminology Criteria Grade.

Grade 3/4 adverse events (on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) were reported in 239 patients (42.8%), of which 66 (11.8%) were considered related. Grade 3 and 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased gamma-glutamyl transferase (GGT), lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia.

Refer to the Atezolizumab IB for details on adverse events observed in patients treated with atezolizumab.

### Immune-Mediated Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, gastrointestinal, and respiratory events.

Refer to the Atezolizumab IB for details on immune-mediated adverse events that were observed in patients treated with atezolizumab. Guidelines for the management of immune-mediated adverse events are described in the Atezolizumab IB.

For additional information, refer to the Atezolizumab IB.

### **Single-Agent Clinical Safety in Patients with NSCLC in the POPLAR Study**

The Phase II POPLAR study interim analysis, as of the 30 January 2015 data cutoff, included data from 142 patients treated with atezolizumab as a fixed dose of 1200 mg IV every 3 weeks and 135 patients treated with docetaxel 75 mg/m<sup>2</sup> IV every 3 weeks. The frequency of patients in the POPLAR study who reported any adverse event regardless of attribution was 96.5% for the atezolizumab arm and 95.6% for the docetaxel arm. A higher number of Grade  $\geq 3$  adverse events were observed in the docetaxel arm (55.6% vs. 43.0%), explained primarily by the difference in adverse events due to bone marrow suppression.

For additional information, refer to the Atezolizumab IB.

### **Clinical Safety in Combination with Bevacizumab or Platinum-Based Doublet Chemotherapy**

Study GP28328 is a Phase Ib study of atezolizumab in combination with bevacizumab or cytotoxic chemotherapy in patients with multiple tumor types including NSCLC, TNBC, and colorectal cancer. As of 10 February 2015, 144 patients had been enrolled in this study: 39 in Arm A (atezolizumab, bevacizumab), 36 in Arm B (atezolizumab, bevacizumab, and FOLFOX), 14 in Arm C (atezolizumab, carboplatin, and paclitaxel), 24 in Arm D (atezolizumab + carboplatin and pemetrexed), 20 in Arm E (atezolizumab, carboplatin, and nab-paclitaxel), and 11 in Arm F (atezolizumab + nab-paclitaxel). The treatment combinations have been generally well tolerated. No DLTs have been reported during the dose-escalation stage in any study arm. Patients are being enrolled in safety and biopsy expansion cohorts in Arms A and B as well as in additional arms testing atezolizumab in combination with commonly used NSCLC chemotherapy doublets.

A total of 141 of 144 patients (97.9%) reported at least one adverse event while receiving study drug. The majority of these events were Grade 2 and 3 in severity. The five most commonly reported adverse events across the study arms (>10% of patients) included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. The adverse events were consistent with the known safety profile of each agent (atezolizumab monotherapy and chemotherapy). No additive effects were observed when atezolizumab was administered with chemotherapy.

All 39 patients who were enrolled in Arm A reported one or more adverse event. The five most frequently reported events were consistent with the overall population and included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. There were 36 patients enrolled in Arm B, and 97% of patients reported at least one adverse event. The most frequently reported adverse events (> 20% of patients) included fatigue, pyrexia, peripheral neuropathy, neutropenia, anemia, diarrhea, decreased appetite, temperature intolerance, constipation, vomiting, and nausea.

All patients who were enrolled in Arms C and D experienced an adverse event; 95% of patients who were enrolled in Arm E experienced an adverse event, and 83.3 % of patients enrolled in Arm F experienced an adverse event. The adverse events commonly reported in 2 or more patients in Arms C, D, and E included anemia, decreased appetite, hypomagnesemia, nausea,

neutropenia, constipation, vomiting, fatigue, rash, cough, and diarrhea. Adverse events commonly reported in 2 or more patients in Arm F included dermatitis, upper respiratory infection, alopecia, peripheral sensory neuropathy, fever, constipation, neutrophil count decreased, anemia, diarrhea, headache, nausea, and fatigue.

#### 2.3.2.2. Clinical Activity for Atezolizumab

As of May 10, 2015 relevant clinical data for atezolizumab are mainly available from seven clinical trials in patients with solid tumors and hematologic malignancies. For all of these studies, treatment and/or analyses are ongoing. These include:

- **Monotherapy:** One Phase Ia (Study PCD4989g) and two-Phase II studies (Studies GO28625[FIR] and GO28753 [POPLAR])
- **Combination Therapy:** Three Phase Ib studies (Studies GP28328, GP28363 and GP28384), and one Phase II (WO29074 [IMmotion150]) study.

Additional safety information is also gleaned from the entire development program from atezolizumab. Further details of all ongoing and planned studies with atezolizumab can be found in the Atezolizumab Investigator's Brochure.

#### 2.3.2.3. Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03-20 mg/kg), atezolizumab appeared to show linear PK at doses  $\geq 1$  mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent clearance (CL) and the mean volume of distribution at steady state ( $V_{ss}$ ) had a range of 3.11 to 4.14 mL/kg and 48.1 to 67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) to atezolizumab has been observed in patients in all dose cohorts and was associated with changes in PK for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and adverse events or infusion reactions has been observed.

For additional information on atezolizumab please refer to the Investigator's Brochure.

#### 2.4. Rationale for Combination Therapy

Preclinical and translational results have suggested that T cells that have been engineered to express anti-CD19 chimeric antigen receptors, such as axicabtagene ciloleucel, rapidly upregulate markers of activation, including programmed cell death-1 (PD-1) {Perez 2015}, upon target engagement. Signaling through PD-1 is known to deliver a suppressive stimulus on the activated T-cells, giving rise to a phenotype commonly referred to as T-cell "exhaustion." Exhausted T cells have diminished proliferative and cytolytic capacity {John 2013}. Therefore, PD-1 expression and signaling on CAR T cells may lead to reduced clinical activity.

Conversely, a growing body of literature suggests that PD-L1 is expressed on a variety of human cancers and tumor-infiltrating immune cells, including in DLBCL {Chen 2013, Herbst 2014, Kiyasu 2015}. Furthermore, PD-L1 expression on DLBCL tends to associate with known markers of poor prognosis including activated B cell (ABC) phenotype and has been shown in retrospective series to be associated with shortened survival {Chen 2013, Kiyasu 2015}. Early results of PD-1 blockade with a monoclonal antibody, nivolumab, suggests that inhibition of this signaling cascade yields clinical responses in lymphoma {Lesokhin 2014}, although with limited OR (36%) and CR (9%) rates. The expression of PD-L1 on tumor cells and within the tumor microenvironment coupled with the activation-dependent expression of PD-1 on engineered T cells given to patients with refractory DLBCL led to the hypothesis that blockade of PD-1 ligation would augment the activation, proliferation, and cytolytic activity of CAR T cells.

As an additional safeguard against the potential of added toxicity in patients treated with the combination of anti-CD19 CAR T cells and atezolizumab, we have adopted a 3+3 “schedule compression” Phase 1 run-in in this study design. By staggering the doses of axicabtagene ciloleucel and atezolizumab, we aim to mitigate the potential additive or synergistic toxicities related to the combination.

### 3. STUDY DESIGN

#### 3.1. General Study Design

This is a Phase 1-2, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with atezolizumab in subjects with refractory DLBCL. The trial will be separated into two distinct Phases designated as Phase 1 and Phase 2.

During Phase 1, approximately 3-9 subjects with refractory DLBCL will be enrolled in up to 3 cohorts to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens. A SRT that is internal to the study sponsor and Phase 1 investigators, will review safety data after all subjects in each Phase 1 cohort have had the opportunity complete the DLT window. The SRT will make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in [Figure 3](#) and outlined in [Section 9.6](#).

In Phase 2, approximately 22 subjects will be enrolled to receive combination treatment with axicabtagene ciloleucel and atezolizumab based on the dose and schedule selected to move forward from the Phase 1 portion of the study as recommended by the SRT.

Independent of the Phase of the study, each subject will proceed through the following study periods:

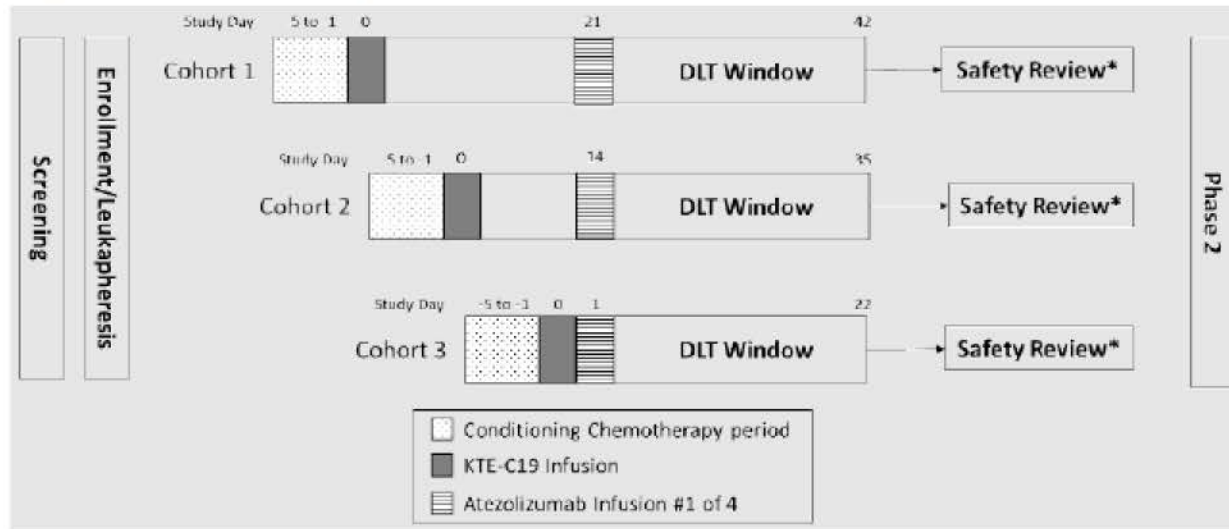
- Screening
- Enrollment/Leukapheresis
- Conditioning chemotherapy
- Combination treatment (axicabtagene ciloleucel and atezolizumab)
- Post treatment assessment
- Long term follow-up

The SRT will also meet 1 time during the Phase 2 portion of the study when 6 subjects have had the opportunity to complete their 1-month disease assessment. The SRT will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. The SRT may meet more often as needed. Refer to [Section 9.6](#).

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

A study schema is drawn out and described in [Figure 1](#).

**Figure 3. Study Schema**



\*During phase 1, cohorts will be enrolled sequentially, beginning with cohort 1. After each phase 1 cohort has completed enrollment and all subjects have cleared the DLT window, the SRT will meet and review the overall benefit/risk profile of the dosing schedule tested in that cohort. SRT recommendations for further study conduct may include addition of patients to a cohort prior to opening a subsequent cohort, advancement to a subsequent cohort, exploration of alternative conditioning chemotherapy or KTE-C19 doses, advancement to phase 2, or study termination.

### 3.2. Participating Sites

Approximately 5-10 centers located in North America will participate in this study. During the conduct of the study, additional sites, regions, or countries may be added as necessary.

### 3.3. Number of Subjects

Participants in this trial will be referred to as “subjects”. It is anticipated that approximately 3-31 subjects will be enrolled into this study as defined below:

Phase 1: approximately 3-9 subjects

Phase 2: approximately 22 subjects

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

### 3.4. Replacement of Subjects

Subjects will be replaced and continue to be enrolled until the specified number of subjects are attained in the DLT evaluable (Phase 1) and mITT sets (Phase 2). See Section 10.4 for additional information. Subjects who receive between  $1.0$  and  $2.4 \times 10^6$  anti-CD19 CAR T cells/kg and who receive at least one dose of atezolizumab will be considered evaluable in the efficacy set. Subjects who have not received a axicabtagene ciloleucel cell dose in this range or have not received at least one dose of atezolizumab will be retained in the analyses of disposition and safety, where appropriate (Section 10.4).



### **3.5. Study Duration**

#### **3.5.1. Study Duration for Individual Subjects**

The duration of the study for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and, if applicable, timing of transition to the separate Long-term Follow-up (LTFU) study, KT-US-982-5968 (discussed in Section 3.5.3).

#### **3.5.2. Completion of Study**

Completion of the study is defined as the time at which the last subject completes at least the Month 12 assessment. The end-of-study for each subject is defined as the last visit on this study, or when a subject is considered lost to follow-up, withdraws consent, or dies. The primary analyses will be conducted when all subjects for the overall study population have completed the 6-month disease response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first.

#### **3.5.3. Long-term Follow-up**

If the study is terminated prior to completion of 15 years of follow-up for all subjects, those who received an infusion of KTE-C19 will be provided an opportunity to transition to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to KTE-C19 as defined in KT-US-982-5968, presence of replication-competent retrovirus (RCR), and/or insertional mutagenesis for up to 15 years from the time of KTE-C19 infusion (also refer to Section 7.12.7).

For each subject, the subject's final visit on this study may be combined with the subject's first visit on the LTFU study. The timing of the subject's final visit/first LTFU study visit will depend upon the timing of the collection of all the subject's data that are required for the planned analysis for this study. In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

In some circumstances, subjects may be eligible to receive a second course of treatment after enrolling in the LTFU rollover study. Retreatment eligibility criteria are described in the KT-US-982-5968 protocol.

#### **4. SUBJECT SCREENING AND ENROLLMENT**

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

Each subject who enters the screening period will receive a unique subject identification number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened or retreated.

Subjects are considered enrolled in the study once the leukapheresis procedure is initiated.

## 5. SUBJECT ELIGIBILITY

### 5.1. Inclusion Criteria

- 101) Histologically proven DLBCL including the following types defined by WHO 2008:
- a) DLBCL not otherwise specified; T cell/histiocyte rich large B cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly.
- 102) Chemotherapy-refractory disease, defined as one or more of the following:
- a) No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy chemotherapy are excluded
    - i) PD as best response to first-line therapy
    - ii) SD as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy
- OR
- b) No response to second or greater lines of therapy
    - i) PD as best response to most recent therapy regimen
    - ii) SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy
- OR
- c) Refractory post-ASCT
    - i) Disease progression or relapsed  $\leq 12$  months after ASCT (must have biopsy proven recurrence in relapsed subjects)
    - ii) if salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy
- 103) Subjects must have received adequate prior therapy including at a minimum:
- a) anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and
  - b) an anthracycline containing chemotherapy regimen;
- 104) At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

- 105) MRI of the brain showing no evidence of CNS lymphoma
- 106) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis
- 107) Age 18 years or older at the time of informed consent
- 108) Eastern cooperative oncology group (ECOG) performance status of 0 or 1
- 109) Adequate bone marrow, renal, hepatic, pulmonary and cardiac function defined as:
  - a) ANC  $\geq$ 1000/uL
  - b) Platelet count  $\geq$ 75,000/uL
  - c) Absolute lymphocyte count  $\geq$ 100/uL
  - d) Creatinine clearance (as estimated by Cockcroft Gault)  $\geq$  60 mL/min
  - e) Serum ALT/AST  $\leq$ 2.5 ULN
  - f) Total bilirubin  $\leq$ 1.5 mg/dl, except in subjects with Gilbert's syndrome.
  - g) Cardiac ejection fraction  $\geq$  50%, no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings
  - h) No clinically significant pleural effusion
  - i) Baseline oxygen saturation  $>$ 92% on room air
- 110) Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

## 5.2. Exclusion Criteria

- 201) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) unless disease free for at least 3 years
- 202) History of Richter's transformation of CLL or DLBCL that has arisen (transformed) from another histology (e.g., transformed follicular lymphoma)
- 203) Autologous stem cell transplant within 6 weeks of planned axicabtagene ciloleucel infusion
- 204) History of allogeneic stem cell transplantation
- 205) Prior CD19 targeted therapy with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for re-treatment

- 206) Prior treatment with PD-L1 inhibitor, PD-1 inhibitor, anti-CTLA4, anti-CD137, anti-OX40 or other immune checkpoint blockade or activator therapy with the exception of subjects who received atezolizumab in this study and are eligible for re-treatment
- 207) Treatment with systemic immunostimulatory agents (including but not limited to interferon and IL-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first atezolizumab dose.
- 208) Prior chimeric antigen receptor therapy or other genetically modified T cell therapy
- 209) History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
- 210) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment.
- 211) History of HIV infection or acute or chronic active hepatitis B or hepatitis C infection. Subjects with history of Hep B or Hep C infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines.
- 212) Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted.
- 213) Subjects with detectable cerebrospinal fluid malignant cells or known brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases.
- 214) History or presence of non-malignant CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement.
- 215) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement.
- 216) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months of enrollment.
- 217) Expected or possible requirement for urgent therapy within 6 weeks after leukapheresis due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome).
- 218) History of autoimmune disease. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

- 219) History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest CT scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed.
- 220) History of deep vein thrombosis or pulmonary embolism within 6 months of enrollment
- 221) Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
- 222) History of severe immediate hypersensitivity reaction to any of the agents used in this study
- 223) Treatment with a live, attenuated vaccine within 6 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study
- 224) Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential
- 225) Subjects of either sex who are not willing to practice birth control from the time of consent through 5 months after the last dose of completion of atezolizumab and at least 6 months since axicabtagene ciloleucel infusion
- 226) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

## 6. PROTOCOL TREATMENT

### 6.1. Treatment Terminology

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

- The conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The investigational products for this study are named axicabtagene ciloleucel and atezolizumab.
- The term study treatment refers to all protocol required therapies.

### 6.2. Study Treatment

#### 6.2.1. Conditioning Chemotherapy

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

##### 6.2.1.1. Fludarabine

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

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

##### 6.2.1.2. Cyclophosphamide

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

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

##### 6.2.1.3. Mesna

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

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

### **6.2.2. Axicabtagene Ciloleucel**

This section contains general information and is not intended to provide specific instructions. Refer to Section 6.4.3.2 and the Investigational Product Manual for details and instruction on storage, thawing, and administration of axicabtagene ciloleucel.

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

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

To date, over 65 subjects have received doses of anti-CD19 CAR T cells made using the vector construct used in this study at doses ranging from 1-30 x 10<sup>6</sup> anti-CD19 CAR T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

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

### **6.2.3. Atezolizumab**

#### **Formulation, Packaging, and Handling**

The atezolizumab drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly yellow, sterile, preservative-free clear liquid solution intended for dilution in 0.9% aqueous sodium chloride solution for IV infusion. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.



Atezolizumab must be refrigerated at 2°C - 8°C (36°F -46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For detailed information and instructions, see the Atezolizumab Pharmaceutical Instructions and IB.

#### **6.2.4. Concomitant Therapy**

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care except those medications listed in the excluded medication Section 6.2.5.

All concurrent therapies, including medications, intubation, dialysis, and blood products, will be recorded from the date of the informed consent through 30 days after completing the final dose of atezolizumab, or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. Once this follow up period has been completed, only targeted concomitant medication will be collected including gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations, for 24 months or until disease progression, whichever occurs first.

For subjects who are not enrolled (e.g., screen failure or not leukapheresed), only concurrent therapies related to any serious adverse event(s) will be recorded.

For subjects who are enrolled but not dosed with axicabtagene ciloleucel, concurrent therapies will only be recorded from the date of the informed consent through 30 days after last procedure (e.g., leukapheresis, conditioning chemotherapy).

For subjects who are enrolled and receive axicabtagene ciloleucel but do not receive atezolizumab, all concurrent therapies will be collected through 3 months post-treatment of axicabtagene ciloleucel. Targeted concomitant medication will be collected including gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations, until 24 months following treatment with axicabtagene ciloleucel or until disease progression, whichever occurs first.

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

#### **6.2.5. Excluded Medications**

Corticosteroid therapy at a pharmacologic dose ( $\geq 5$  mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis, and 5 days prior to axicabtagene ciloleucel administration.

Systemic corticosteroids may not be administered as premedication to patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Such patients should undergo non-contrast CT scans instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 6 months after axicabtagene ciloleucel administration, unless used to manage axicabtagene ciloleucel related or atezolizumab toxicities. Other medications that might interfere with the evaluation of axicabtagene ciloleucel, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

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

Denosumab (a RANKL inhibitor) is prohibited during the study because it could potentially alter the efficacy and safety of atezolizumab. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study. Any experimental products other than those being investigated in this trial are excluded.

Traditional herbal medicines are prohibited during the study because the ingredients of many herbal medicines are not fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.

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

#### **6.2.6. Subsequent Therapy**

Subsequent therapy, such as non-study specified chemotherapy, immunotherapy, targeted agents, SCT, or radiation therapy, administered after KTE-C19 infusion that is necessary to treat the subject's DLBCL will be recorded for all subjects until one of the following happens: the subject transitions to the KT-US-982-5968 LTFU study, is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled but do not receive a KTE-C19 infusion, any additional anticancer therapy will also be collected until the subject completes their participation in the current study, is considered lost to follow-up, withdraws consent, or dies, whichever occurs first.

Regarding allogeneic stem cell transplantation following exposure to atezolizumab, treating investigators are strongly cautioned and are referred to recent data reporting higher than expected rates of severe and fatal acute toxicities in patients recently treated with PD-1 inhibitors followed by allogeneic HCST {Merryman 2015}.

### 6.3. Rationale for Study Treatment dosing

#### 6.3.1. Rationale for Conditioning Chemotherapy and Axicabtagene Ciloleucel Dose

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

To improve the depth and duration of lymphocyte depletion, the conditioning chemotherapy dose will be cyclophosphamide (500 mg/m<sup>2</sup>) and fludarabine (30 mg/m<sup>2</sup>) both given for 3 concurrent days. Cyclophosphamide (500 mg/m<sup>2</sup>) and fludarabine (30 mg/m<sup>2</sup>) both given for 3 concurrent days has been studied and tolerated in subjects with B cell malignancies {O'Brien 2001}. This regimen has been evaluated in the NCI study (09-C-0082; IND 13871) and is the dose of conditioning chemotherapy that was chosen as the initial dose for Phase 1 of ZUMA-1 and carried forward to the Phase 2 portion of the ZUMA-1 study as recommended by the SRT.

The rationale for the axicabtagene ciloleucel dose in this study is based on aggregate safety and efficacy data compiled from the ZUMA-1 study as outlined in in the current axicabtagene ciloleucel investigator's brochure.

#### 6.3.2. Rationale for Atezolizumab Dose and Schedule:

The fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) Q3W was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C<sub>trough</sub>) was projected to be 6 µg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor interstitial concentration-to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first-in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses ranging from 0.01 to 20 mg/kg Q3W during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The MTD of atezolizumab was not

reached, and no dose-limiting toxicities were observed at any dose. ATAs to atezolizumab were associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but patients treated at 10, 15, and 20 mg/kg maintained the expected target trough levels of drug despite the detection of ATAs. To date, no relationship has been observed between the development of measurable ATAs and safety or efficacy. After review of available PK and ATA data for a range of doses, 15 mg/kg Q3W was identified as the lowest atezolizumab dosing regimen that would maintain C<sub>trough</sub> at  $\geq 6 \mu\text{g/mL}$  while further safeguarding against interpatient variability and the potential for ATAs to lead to subtherapeutic levels of atezolizumab.

Simulations {Bai 2012} do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight-adjusted dose. Therefore, patients in this study will be treated Q3W at a fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg).

### 6.3.3. Rationale for Dosing schedule

PD-1 is an activation/exhaustion marker of cytolytic T cells, and its expression is upregulated on the surface of CAR T cells beginning prior to infusion and is further enhanced during *in vitro* exposure to CD19-expressing target cells {Bot 2015}. PD-1 surface expression is also increased following CAR T cell infusion {Perez 2015}. The capacity for cell division and cytolytic activity of the infused CAR T cells is therefore likely inhibited by ligation of PD-1 on the T cell surface beginning at the time of infusion. Furthermore, emerging evidence suggests that a primary biomarker of CAR T efficacy in lymphoma is the peak level of CAR T cells in peripheral circulation, which occurs in patients treated on NCI study 09-C-0082 and in ZUMA-1 at approximately day 7-15 after infusion {Kochenderfer 2015, Rossi 2015}. Thus, a core translational objective of this study is to augment the initial expansion of CAR T cells measurable in circulation.

For this reason, blocking PD-1 receptor ligation on the surface of CAR T cells using an anti-PD-L1 monoclonal antibody such as atezolizumab as early and as completely as possible is the most rational goal with the combination strategy. However, insofar as the acute toxicity following anti-CD19 CAR T cell infusion is related to the initial axicabtagene ciloleucel expansion, disinhibition of this process with PD-L1 blockade may potentiate acute toxicity. Therefore, we have adopted a 3+3 “schedule compression” Phase 1 run-in in the study design. By staggering the doses of axicabtagene ciloleucel and atezolizumab, we aim to mitigate the potential additive or synergistic toxicities related to the combination. Patients will be enrolled and treated one at a time during the Phase 1 portion of the study. The first cohort of 3 patients will be dosed with atezolizumab 21 days following infusion of axicabtagene ciloleucel at which point the great majority of patients will have passed the window of acute axicabtagene ciloleucel-related toxicities such as CRS and neurologic events. The patients will be closely monitored for recrudescence of CRS and neurologic events following administration of atezolizumab, as well as for atezolizumab-specific toxicity.

If these patients pass the DLT window and the regimen is viewed as safe by the SRT, a second cohort of 3 patients will be dosed with atezolizumab 14 days after their axicabtagene ciloleucel

infusion and monitored for DLT. At 14 days following axicabtagene ciloleucel infusion, most patients will have cleared the acute toxicity window and the majority of patients axicabtagene ciloleucel related toxicities will have resolved to Grade 1 or less; for patients that continue to experience Grade  $\geq 2$  CRS- or neurologic event-related adverse events, atezolizumab infusion will be delayed per Section 6.4.4. Safety review of cohorts 1 and 2 will indicate whether addition of atezolizumab can potentiate CAR T-related toxicity. If the rate and severity of immune activation is tolerable, a third and final cohort of 3 patients will be enrolled who will receive atezolizumab 1 day after axicabtagene ciloleucel, before onset of CRS.

#### **6.3.4. Rationale for Pharmacokinetic and ATA Sample Collection**

The proposed PK and ATA sampling for atezolizumab will contribute to the characterization of the pharmacokinetics of the atezolizumab when given in combination with axicabtagene ciloleucel and conditioning chemotherapy in subjects with DLBCL. The atezolizumab concentration and atezolizumab ATA results may be compared with available data from other clinical studies to assess for a potential pharmacokinetic and/or pharmacodynamic interaction between study treatments, and/or explore correlations with any clinical activity and safety events. Sparse sampling was employed to minimize inconvenience to the patient while providing a sufficient number of samples to allow characterization of atezolizumab concentrations, and ATA formation, after a single atezolizumab dose and at steady state.

#### **6.4. Study Treatment Schedule and Administration**

##### **6.4.1. Leukapheresis**

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the Cell Processing Facility (CPF) over night as described in the investigational product manual. Once a subject commences leukapheresis, the subject is considered enrolled in the study.

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

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

#### **6.4.2. Cyclophosphamide and Fludarabine (Days -5 through -3 before infusion of axicabtagene ciloleucel)**

Subjects will receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel *in vivo*. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day -5 through Day -3 with 2 rest days before the receiving axicabtagene ciloleucel. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

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

- IV hydration with 1L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500mg/m<sup>2</sup> IV over 60 minutes followed by:
- Fludarabine 30mg/m<sup>2</sup> IV over 30 minutes followed by:
- An additional 1L of 0.9% NaCl at the completion of the cyclophosphamide infusion
- Add Mesna per institutional guidelines

Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours). In general subjects should be kept well-hydrated but closely monitored to prevent fluid overload.

#### **6.4.3. Axicabtagene Ciloleucel (Day 0):**

All subjects will be hospitalized to receive treatment with axicabtagene ciloleucel followed by an observation period. Subjects will remain in the hospital at a minimum through day 7 post treatment with axicabtagene ciloleucel.

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

##### **6.4.3.1. Axicabtagene Ciloleucel Premedication Dosing**

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

- Tylenol 650 mg PO
- Benadryl 12.5-25 mg IV or PO

#### 6.4.3.2. Axicabtagene Ciloleucel Dosing

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

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

#### 6.4.4. Atezolizumab Dosing and Administration Instructions (Day 21, Day 14 or Day 1 after Axicabtagene Ciloleucel Administration and every 21 days thereafter for 3 additional (4 total) doses)

Atezolizumab treatment consists of an intravenous infusion of 1200 mg (as a prepared dilution in a 250 mL of 0.9% NaCL) given every 21 days for 4 doses. In the Phase 1 portion, the first dose of atezolizumab will be administered in 3 cohorts:

- Cohort 1: Beginning on day 21 following axicabtagene ciloleucel infusion
- Cohort 2: Beginning on day 14 following axicabtagene ciloleucel infusion
- Cohort 3: Beginning on day 1 following axicabtagene ciloleucel infusion

A safety review team (SRT), internal to the study sponsor and Phase 1 investigators, will review the safety data following each Phase 1 cohort and make recommendations on further study conduct of Phase 1 and progression to Phase 2.

For more detailed information regarding administration, refer to the Atezolizumab Pharmacy Instructions and IB.

#### Dosage, Administration, and Compliance

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For more detailed information regarding administration, refer to the IB and Pharmacy Manual.

The initial dose of atezolizumab will be delivered over 60 ( $\pm 15$ ) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 ( $\pm 10$ ) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ( $\pm 10$ ) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature) should be determined within 60 minutes before, during (every 15 [ $\pm 5$ ] minutes), and 30 ( $\pm 10$ ) minutes and 2 hours

(±15 minutes) after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (±10 minutes) after the infusion.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for subsequent infusions at the discretion of the treating physician after consultation with the Medical Monitor. The management of infusion-related events will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event.
- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see [Appendix B](#).

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

### **Dosage Modification**

No reduction or modification of the atezolizumab dose will be allowed. Any toxicity associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an



immediate therapeutic effect, and there is no antidote for atezolizumab. In severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

See the Atezolizumab IB for the management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity, and other immune-mediated adverse events, as these have been observed with exposure to atezolizumab and are potentially immune mediated. See [Appendix B](#) for precautions for anaphylaxis

Atezolizumab may be withheld for up to 42 days. If atezolizumab has to be withheld for > 42 days due to drug-related events without appropriate resolution, despite appropriate management, then atezolizumab should be discontinued. However, if in the investigator's judgment, the patient is likely to derive benefit from resuming atezolizumab after a 42-day delay, atezolizumab may be restarted with the approval of the Medical Monitor.

Discontinuation of atezolizumab may not have immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, tocilizumab, or TNF-alpha inhibitors.

Atezolizumab dosing will be delayed for ongoing Grade  $\geq 2$  CRS or neurologic events. The delayed dose will be given upon resolution of CRS- and neurologic events to Grade 1 or less. If a dose is held greater than 7 days beyond the scheduled administration, it will not be given. Should an atezolizumab dose be delayed less than 7 days, the remaining 3 doses should be administered every 21 days from the onset date of first dose. Likewise, all protocol required procedures should follow the same schedule as outlined in the schedule of assessments beginning on the onset date of the first dose.

## 6.5. Axicabtagene Ciloleucel Toxicity Management

To date, the following important risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, and cytopenias. Please refer to Section 6 of the current Investigator's Brochure for details regarding these events and management guidance.

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

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

## **6.6. Atezolizumab Toxicity Management**

### **6.6.1. Safety Plan**

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All adverse events and serious adverse events will be recorded as outlined in Section 9.

### **6.6.2. Risks Associated with Atezolizumab**

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions or systemic immune activation. Adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis or elevated transaminase, pneumonitis, colitis, myositis, and myasthenia gravis have been observed in patients treated with atezolizumab. For further details regarding clinical safety and a more comprehensive list of observed adverse events with atezolizumab, see the Atezolizumab IB.

### **6.6.3. Management of Patients Who Experience Atezolizumab-Specific Adverse Events**

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids or other immunosuppressive therapy.

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab.

Guidelines for management of adverse events associated with atezolizumab can be found in the Atezolizumab IB.

### **6.6.4. Systemic Immune Activation**

Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk when given in combination with other immunomodulating agents.

Because of the significant overlap of clinical symptoms and laboratory manifestations of SIA with those of CRS and neurologic events, as described in the current axicabtagene ciloleucel investigator's brochure, investigators are advised to consider these syndromes as

pathophysiologically interrelated and possibly only distinguishable by the timing of their onset and their duration.

As such, it is recommended that the following diagnostic and management strategies be utilized for symptoms with onset after the second dose of atezolizumab. For those symptoms that occur prior to the second dose of atezolizumab, please refer to the current axicabtagene ciloleucel investigator's brochure for information regarding axicabtagene ciloleucel-related toxicities.

Recommendations regarding early identification and management of SIA are provided below. Early communication with the Medical Monitor is essential and is strongly encouraged. As for severe CRS, neurologic events, or HLH, in the event of suspected SIA, atezolizumab should be withheld and the Medical Monitor should be contacted immediately for additional guidance.

Early disease recognition is critical, and SIA should be suspected if, in the absence of an alternative etiology, the patient meets two or more of the following criteria:

- Hypotension that is refractory to aggressive IV fluid challenge
  - Vasopressor support may be required.
- Respiratory distress that requires aggressive supportive care
  - Supplemental oxygen and intubation may be required.
- Fever > 38.5°C
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Any of the following unexplained laboratory abnormalities (change from baseline)
  - Cytopenias (in two or more lineages)
  - Significant transaminitis
  - Coagulopathy
- For patients with suspected SIA, an initial evaluation should include the following:
  - CBC with peripheral smear
  - PT, PTT, fibrinogen, and D-dimer
  - Ferritin
  - Triglycerides

- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

Laboratory tests with normal results should be repeated frequently in patients for whom a high clinical suspicion of SIA exists.

If cytopenias are present (Grade  $\geq 2$  in two or more lineages) or ferritin is  $\geq 3000$  ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)
- Soluble interleukin 2 (IL-2) receptor (sCD25)
- Natural killer cell activity
- Cytomegalovirus, Epstein-Barr virus, and herpes-simplex virus evaluation (for reactivated or active disease)

Diagnostic criteria and recommended management for SIA are provided in [Table 3](#). The diagnostic criteria apply only when alternative etiologies have been excluded.

**Table 3. Diagnostic Criteria and Recommended Management for Systemic Immune Activation (SIA)**

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)		
Major Criteria		Minor Criteria
<ul style="list-style-type: none"> <li>• Fever <math>\geq 38.5^{\circ}\text{C}</math> on more than one occasion</li> <li>• Ferritin <math>\geq 3000</math> ng/mL</li> <li>• Cytopenias (Grade <math>\geq 2</math> in two or more lineages)</li> <li>• Age-adjusted soluble IL-2 receptor elevated by <math>\geq 2</math> standard deviations</li> <li>• Severe dysfunction in two or more organs</li> <li>• Decreased fibrinogen</li> </ul>		<ul style="list-style-type: none"> <li>• Splenomegaly</li> <li>• Hemophagocytosis in bone marrow, spleen, or lymph nodes</li> <li>• Elevated GGT or LFTs (AST, ALT, or total bilirubin)</li> <li>• Elevated triglycerides</li> <li>• Elevated LDH</li> <li>• Decreased natural killer cell activity</li> </ul>
Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken

<p>≥ 4 major criteria</p>	<p>Consistent with SIA</p>	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab.</li> <li>• Consider treatment with an immunosuppressive agent (i.e., anti-IL-6 agent, infliximab, cyclosporine A, or etoposide) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent).</li> <li>• Contact the Medical Monitor for additional recommendations.</li> <li>• Consider HLH-94 protocol if there is no clinical improvement.</li> </ul>
<p>3 major criteria          OR          2 major plus ≥ 3 minor criteria</p>	<p>Probable SIA</p>	<ul style="list-style-type: none"> <li>• Depending on clinical severity, follow guidelines for “Consistent with SIA” or “Possible SIA” diagnosis.</li> <li>• The Medical Monitor may be contacted for recommendations.</li> </ul>
<p>2 major plus ≤ 2 minor criteria          OR          1 major plus ≥ 4 minor criteria</p>	<p>Possible SIA</p>	<ul style="list-style-type: none"> <li>• Withhold atezolizumab.</li> <li>• Consider treatment with IV corticosteroids.</li> <li>• The Medical Monitor may be contacted for additional recommendations.</li> <li>• Follow guidelines for “Consistent with SIA” diagnosis if there is no clinical improvement or if clinical worsening occurs.</li> <li>• If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor. *</li> </ul>
<p>GGT = <math>\gamma</math>-glutamyl transpeptidase; IL-2 = interleukin-2; IV = intravenous; LFT = liver function test;          Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients {Hejblum 2014}.          Case reports and recommendations have been published for cytokine-release syndrome {Lee 2014, Maude 2014, Teachey 2013}, and, on the basis of etiologic similarities, these practices have been incorporated into the above treatment recommendations.          These recommendations do not replace clinical judgment and are intended as suggested guidance.          *Resumption of atezolizumab may be considered in patients who are deriving benefit, as assessed by the Investigator, and have fully recovered from the immune-related event. These patients can only be re-challenged with atezolizumab after approval has been documented by both the Study Chair and the Medical Monitor.</p>		

## 7. STUDY PROCEDURES

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

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7.12. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

### 7.1. Informed Consent

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

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

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

### 7.2. Demographic Data

Demographic data will be collected as per country and local regulations and guidelines. Where applicable, demographic data will include sex, date of birth, race, ethnicity, and country of enrollment to study their possible association with subject safety and treatment effectiveness.

### 7.3. Medical and Treatment History

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

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

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

#### **7.4. Physical Exam, Vital Signs and Performance Status**

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

During IP administration/hospitalization, vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature will be monitored before and after the axicabtagene ciloleucel infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3°C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

For the first infusion of atezolizumab, the patient's vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) should be determined within 60 minutes before, during (every 15 [ $\pm$ 5] minutes), and 30 ( $\pm$ 10) minutes and 2 hours ( $\pm$ 15 minutes) after the infusion. For subsequent atezolizumab infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour ( $\pm$ 10 minutes) after the infusion.

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

#### **7.5. Cardiac Function**

Each subject's cardiac function, as measured by Left Ventricular Ejection Fraction (LVEF), will be assessed during the screening period to confirm study eligibility. No evidence of clinically significant pericardial effusion as required by eligibility will also be confirmed. Both LVEF and pericardial effusion will be assessed prior to study entrance by ECHO. An ECHO performed following the subject's last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

A 12-lead ECG will also be performed during the screening period.

#### **7.6. Magnetic Resonance Imaging**

Each subject will undergo a screening brain MRI to rule out CNS metastasis during the screening period of the study.

#### **7.7. Toxicity Evaluation**

Following axicabtagene ciloleucel dosing, an additional lumbar puncture for collection of CSF should be performed at first appearance of Grade 2 or greater neurological symptoms or as medically indicated. Additional evaluations of the CSF should be performed per institutional standard of care. CSF samples (i.e., baseline and collected on study to assess neurological symptoms) will be submitted to the central laboratory.

## 7.8. Bone Marrow Biopsy

For subjects with a potential complete response to axicabtagene ciloleucel and atezolizumab, a follow-up bone marrow aspirate and biopsy will be performed in subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. To confirm a complete response, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. Refer to Section 7.9 and Appendix A for treatment response assessment requirements per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}.

## 7.9. Disease Response Assessment

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

Baseline PET-CT scans of the neck, chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. Subjects will have their first post axicabtagene ciloleucel infusion planned PET-CT tumor assessment 6 weeks following the axicabtagene ciloleucel infusion and at regular intervals as highlighted in the SOA during the post treatment and long-term follow-up portion of the study.

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

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

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

## 7.10. Laboratory

The below samples will be collected at the time points indicated in the SOA. Additional samples (e.g., blood, urine, CSF, tissue, etc) may be collected as needed for further safety testing. Please refer to the Laboratory Manual for additional detail and information on collection requirements.



**Local lab analysis:**

- Sodium (Na), Potassium (K), Chloride (Cl), Total CO<sub>2</sub> (bicarbonate), Creatinine, Glucose, Blood Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LDH, Uric Acid
- C-reactive protein (CRP)
- Complete Blood Count with Differential
- A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma Medical Monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma Medical Monitor for instructions.

**Central lab analysis:**

- Blood draws for lymphocyte subsets, cytokine levels, RCR and tracking of anti-CD19 CAR T cells by qPCR analysis will be performed at intervals outlined in the SOA. Mid cycle assessments one week after the first cycle of atezolizumab are mandatory. Thereafter, repeated mid cycle assessments one week after doses 2-4 of atezolizumab will be at the discretion of the investigator unless the patient is admitted to the hospital in which case the assessments will be mandatory.
- For Phase 2 only, a PBMC sample will be collected and CBC with differential will be done 2 to 3 days after the first 2 doses of atezolizumab as described in the Schedule of Assessments.
- Serum samples will also be evaluated for anti-KTE-C19 antibodies and human anti-mouse antibodies
  - For serum samples that demonstrate increased anti-KTE-C19 human anti-mouse (HAMA) at the Post-Treatment Assessment Visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first.
- Serum samples for analysis of anti-atezolizumab antibodies and PK will be sent to and held at the central laboratory until distribution to a sponsor-designated bioanalytical laboratory or to the sponsor for analysis

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### 7.11. Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for axicabtagene ciloleucel in conjunction with PD-L1 blockade. Prognostic markers specific for aggressive NHL and related to the tumor immune environment may also be evaluated.

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR T prior to and after atezolizumab treatment cells will be monitored in the blood primarily by PCR analysis, complemented by flow cytometry.

Levels of serum cytokines will also be evaluated in the blood. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines IL-6, TNF $\alpha$ , IL-10, IL-2, GM-CSF, IL 15, IL-17a, IFN $\gamma$ , IL-12p40/p70; immune effector molecules Granzyme A, B, Perforin; correlates of acute Phase response CRP, ferritin, sIL-2Ra and chemokines MIP-1 $\alpha$ , MIP-1 $\beta$ , IP-10, MCP-4.

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

As axicabtagene ciloleucel comprises retroviral vector transduced T cells, the presence of replication-competent-retrovirus (RCR) in the blood of treated subjects will be monitored until Month 12. If there are not positive results, samples will be collected and held for up to 15 years.

In addition, baseline leukapheresis and final axicabtagene ciloleucel samples will be banked and may be analyzed by immunophenotyping, qPCR, and/or gene expression profiling. CCI

Archived tumor tissue will be collected for central path review. Additional analysis will include CD19 and PD-L1 expression (immunohistochemistry), gene expression profiling, and analysis of DNA alterations for sub-classification of DLBCL. CCI

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### **Pharmacokinetic and Anti-Therapeutic Antibody Assays**

Instruction manuals and supply kits will be provided for all samples sent to the central laboratory. The following samples will be sent to the central laboratory, and then to a sponsor-designated bioanalytical laboratory or to the sponsor for analysis:

- Serum samples will be assayed for the presence of ATAs to atezolizumab with the use of validated immunoassays.
- Serum samples will be assayed for atezolizumab concentrations with the use of a validated immunoassay.

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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 can contact the central or bioanalytical laboratory. The investigator should provide the sponsor with the study and subject number so that the sample can be located and destroyed.

### **7.12. Description of Study Periods**

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

### 7.12.1. Screening

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

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

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

- Medical history and disease assessment
- Physical examination including height and weight
  - Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.
- Vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- ECOG performance status
- Neurological examination
- ECG
- ECHO for LVEF and pericardial effusion assessment
  - An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility
- Imaging Studies
  - Brain MRI
  - Baseline PET CT of the neck, chest, abdomen and pelvis

- PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility.
  - If PET CT is performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible.
- Labs
    - Chemistry panel
    - CBC with differential
    - $\beta$ -HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Lumbar puncture for subjects with new or suspicious neurological findings suggestive of CNS involvement.
  - Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
  - Concomitant medications documentation and previous cancer treatment history



### 7.12.2. Rescreening

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

### 7.12.3. Enrollment/Leukapheresis

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

Additionally, the investigator must review the last CBC with differential and chemistry panel drawn prior to the start of leukapheresis to confirm that Inclusion 109 (eg, creatinine clearance, serum ALT/AST, total bilirubin) continues to be met (see Section 5.1).

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

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

If leukapheresis is delayed beyond 28 days from the Screening Visit, screening procedures will be repeated to confirm that the subject remains eligible for enrollment (see Section 7.12.1).

Leukapheresis should occur within approximately 5 days of eligibility confirmation.

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

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

- Vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- Height and weight
- Labs (to be drawn prior to leukapheresis on the day of or day before leukapheresis)
  - Chemistry panel
  - CBC with differential
  - C-reactive protein (CRP)
  - Cytokine levels
  - Anti-KTE-C19
  - PBMCs including (Anti-CD19 CAR T cells and Lymphocyte subsets)
- Leukapheresis
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

#### 7.12.4. Conditioning Chemotherapy Period

Before conditioning chemotherapy commences, the following criteria must be met. If these criteria are not met, then conditioning chemotherapy must be delayed until these events resolve.

- No evidence or suspicion of infection.
- No clinically evident changes in bone marrow, renal, hepatic, pulmonary or cardiac function since screening
- Creatinine clearance is at or above limits set in eligibility criteria (Section 5)
- No acute neurological toxicity > Grade 1 (with the exception of peripheral neuropathy)

In addition, if any of the following are known to occur, a delay in conditioning chemotherapy may be required. Contact the Kite Medical Monitor before conditioning chemotherapy commences for guidance.

- WBC count of  $\geq 20,000/\mu\text{L}$  within 48 hours prior to conditioning chemotherapy
- CRP is  $\geq 100$  mg/L
- Temperature is  $\geq 38.0^\circ\text{C}$  within 48 hours prior to conditioning chemotherapy. Unexplained fever requires pan-culture, respiratory viral panel, chest CT and any additional symptom-directed workup to rule out occult infection.
- If any other screening assessments or procedures are repeated between enrollment and the start of conditioning chemotherapy and results are outside the eligibility criteria (Section 5)

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

- Vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy)
  - Chemistry Panel
  - CBC with differential
- Fludarabine and cyclophosphamide administration
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

#### 7.12.5. Investigational Product Treatment Period

Before axicabtagene ciloleucel infusion commences, the following criteria must be met. If these criteria are not met, then axicabtagene ciloleucel infusion must be delayed until these events resolve.

- No evidence or suspicion of infection. Subject must not be receiving systemic anti-microbials for the treatment of an active infection within 48 hours prior to axicabtagene ciloleucel infusion (prophylactic use of anti-microbials is allowed).
- No clinically evident changes in bone marrow, renal, hepatic, pulmonary or cardiac function since screening
- Creatinine clearance is at or above limits set in eligibility criteria (see Section 5)
- No acute neurological toxicity > Grade 1 (with the exception of peripheral neuropathy)

In addition, if any of the following are known to occur, the axicabtagene ciloleucel infusion may need to be delayed. Contact the Kite Medical Monitor before axicabtagene ciloleucel infusion commences for guidance:

- CRP is  $\geq 100$  mg/L
- Temperature is  $\geq 38.0^{\circ}\text{C}$  within 48 hours prior to axicabtagene ciloleucel infusion. Unexplained fever requires pan-culture, respiratory viral panel, chest CT scan and any additional symptom-directed workup to rule out occult infection.
- WBC count of  $\geq 20,000/\mu\text{L}$  within 48 hours prior to axicabtagene ciloleucel infusion
- If any other screening assessments or procedures are repeated between leukapheresis and the axicabtagene ciloleucel infusion and results are outside the eligibility criteria (Section 5; with the exception of conditioning chemotherapy-induced cytopenias)

If the axicabtagene ciloleucel infusion is delayed > 2 weeks, conditioning chemotherapy must be repeated. In all cases of axicabtagene ciloleucel infusion delays, contact the Kite Medical Monitor for guidance.

Subjects will be hospitalized to receive treatment with axicabtagene ciloleucel followed by an observation period lasting through Day 7 post treatment with axicabtagene ciloleucel. Subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities return to  $\leq$  Grade 1. Subjects may be discharged with non-critical and clinically stable or improving toxicities (e.g., renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1, or if deemed necessary by the treating investigator.



Given the possibility that a subject could develop CRS or neurologic events after discharge from the hospital or after treatment with atezolizumab, subjects and their family members/caregivers should be educated on potential symptoms such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the principal investigator or seek immediate medical attention.

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

- Physical exam with vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- Labs (before axicabtagene ciloleucel infusion, as described in the SOA)
  - Chemistry Panel
  - CBC with differential
  - Cytokine levels
  - PBMCs including (Anti-CD19 CAR T cells, Lymphocyte subsets and RCRs)
- Infusion of axicabtagene ciloleucel
- Atezolizumab PK and ATA samples
- For Phase 2 only, CBC with differential and PBMC sample collection will be done 2 to 3 days after the first 2 doses of atezolizumab as noted in the SOA.
- Infusion of atezolizumab x 4, according to the subject's assigned cohort in Phase 1 or to the selected dosing schedule for Phase 2
- Lumbar puncture and CSF examination as deemed clinically appropriate by the investigator, in subjects with new onset Grade  $\geq 2$  neurologic symptoms after axicabtagene ciloleucel infusion



- PET-CT +/- bone marrow biopsy and aspirate {Cheson 2007} for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated within 7 days.
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regard to CRS/neurologic event/SIA. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continuing through hospitalization.

#### 7.12.6. Post Treatment Assessment Period

After completing study treatment all subjects will return to the clinic 30 days following the final dose of atezolizumab for post treatment assessment. The following procedure will be completed for subjects as outlined in the SOA:

- PET-CT +/- bone marrow biopsy and aspirate {Cheson 2007} for disease assessment: If the PET-CT is not of high enough resolution for accurate disease assessment, the scan must be repeated within 7 days.
- Physical exam with vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
- Labs
  - Chemistry Panel
  - CBC with differential
  - $\beta$ -HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Anti-KTE-C19
  - Cytokine levels
  - PBMCs including (Anti-CD19 CAR T cells, Lymphocyte subsets and RCRs)
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is subsequently re-admitted to the hospital with any axicabtagene ciloleucel or atezolizumab-related adverse events, the following procedures will be performed as outlined in the SOA:

- The labs below will be collected on the day of hospital re-admission then weekly through and including the day of discharge.
  - PBMCs (Anti-CD19 CAR+ T cells)
  - Cytokines

At any time during the treatment period, if a subject did not respond to treatment (i.e., did not achieve a CR or PR) or progresses following a response, the subject will proceed directly to the post treatment assessment visit and be followed for survival and disease outcomes in the long-term follow-up period.

#### **7.12.7. Long-term Follow-up Period**

All enrolled subjects will be followed in the long-term follow-up period for survival and disease status, if applicable. Subjects will begin the long-term follow-up period beginning at Month 6 following axicabtagene ciloleucel infusion and will be given the opportunity to transition to a separate LTFU study, KT-US-982-5968, after providing signed informed consent:

- Every 3 months ( $\pm$  2 weeks) beginning with Month 6 through and including Month 18
- Every 6 months ( $\pm$  1 month) beginning with Month 18 through and including Month 60

The following procedures will be completed for subjects who are enrolled and receive axicabtagene ciloleucel and atezolizumab, at the time points outlined in the SOA:

- Physical exam
- PET-CT/ Disease assessment through 60 months or until disease progression, whichever occurs first.
- Survival status
- Labs
  - CBC with differential
  - Anti-KTE-C19
  - PBMCs including (Anti-CD19 CAR T cells, Lymphocyte subsets and RCRs)
- Atezolizumab PK and ATA samples.
- Targeted Adverse/Serious Adverse Event reporting (for 24 months or until disease progression whichever occurs first)
  - Including neurological, hematological, infections, autoimmune disorders, and secondary malignancies until disease progression.
- Targeted concomitant medication documentation (for 24 months or until disease progression whichever occurs first)
  - Including gammaglobulin, immunosuppressive drugs, anti-infective, and vaccinations

- Subsequent therapy for the treatment of NHL

Subjects may also be contacted by telephone to confirm survival status and report targeted concomitant medication use. Should a subject require lab collection, labs may be collected at the clinic or at an outside facility to reduce the subject burden.

Subjects who are enrolled/leukapheresed but did not receive KTE-C19 treatment will be followed only until the end of this study, and will undergo the following assessments at the time points outlined in the SOA:

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

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

#### 7.12.8. Retreatment

Subjects who achieve a PR or CR will have an option to receive a second course of conditioning chemotherapy, axicabtagene ciloleucel and treatment course of atezolizumab if their disease subsequently progresses greater than 3 months following the axicabtagene ciloleucel infusion, provided CD19 expression on tumor cells is confirmed locally by biopsy after disease progression and prior to re-treatment, and after consultation and agreement of the study sponsor. A discussion regarding benefits and risks of retreatment and including the potential need to undergo leukapheresis a second time for the manufacturing of axicabtagene ciloleucel should occur with the subject prior to performing any study related procedures or treatment. This conversation should also be recorded in the subject's source document.

Allowance for retreatment is based on clinical experience reported in the 2 studies conducted at the pediatric {Lee 2015} and Surgery Branch {Kochenderfer 2015} of the NCI where 6 subjects in total have been re-treated with conditioning chemotherapy, and axicabtagene ciloleucel alone upon progression. Three of the re-treated subjects, each of whom had indolent lymphoma or chronic lymphocytic leukemia, experienced durable responses to retreatment after an initial response and disease progression.

To be eligible for a second course of treatment, subjects must be re-evaluated and continue to meet the original study eligibility criteria (with the exception of prior axicabtagene ciloleucel and atezolizumab use in this study) and should not have received subsequent treatment for

lymphoma. Screening assessments may be repeated if clinically indicated, as determined by the investigator, to confirm eligibility for retreatment. Furthermore, any toxicity related to fludarabine or cyclophosphamide, with the exception of alopecia, should be resolved to  $\leq$  Grade 1, or return to baseline, prior to retreatment. A maximum of 1 retreatment course may occur per subject. Subjects who are retreated will follow the same treatment schedule and procedural requirements per the initial treatment.

Subjects enrolled in Phase 2 will receive the same doses of conditioning chemotherapy, axicabtagene ciloleucel and atezolizumab as those in Phase 1. Subjects originally enrolled and treated during the Phase 1 portion of the study will receive the most recent conditioning chemotherapy, axicabtagene ciloleucel and atezolizumab regimen deemed safe by the SRT. For example, consider the retreated subject as being originally treated in cohort 1 of the Phase 1 portion, in which the first dose of atezolizumab was given 21 days after axicabtagene ciloleucel, and achieves a PR. If the subject then experiences disease progression greater than 3 months after axicabtagene ciloleucel infusion, by which point all 3 subjects scheduled to enroll in cohort 1 of the Phase 1 portion of the study had completed the DLT window without experiencing a DLT, and the SRT had deemed this dosing schema safe, the retreatment regimen would be given according to the schedule in cohort 2. Similarly, if by the time a subject originally treated under a Phase 1 experiences disease progression the study has entered Phase 2 enrollment, the retreatment regimen will follow the Phase 2 dosing schema. Retreated patients will follow the schedule of assessments associated with the retreatment dosing schedule, including all disease assessments, clinic visits, biomarker assessments, etc. Remaining visits and study assessments associated with their first study enrollment will cease.

Subjects who experience a DLT in Phase 1 or a comparable toxicity in Phase 2 will not be eligible for retreatment. Furthermore, if a subject has a known neutralizing antibody to either axicabtagene ciloleucel or atezolizumab, the subject will not be eligible for retreatment. However, if a non-neutralizing HAMA antibody develops to either axicabtagene ciloleucel or atezolizumab, subjects may be retreated if they meet the eligibility criteria.

**Table 4. Schedule of Assessments (Cohort 1) \***

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period				IP Treatment Period (each visit calculated from Day 0)										Post Tx Follow- up
			-5	-4	-3	0	1 - 7	Day 14 (± 2 days)	Day 21 (± 2 days)	Day 28 (± 2 days)	Day 42 (± 2 days)	Day 49 <sup>h</sup> (± 2 days)	Day 63 (± 2 days)	Day 70 <sup>h</sup> (± 2 days)	Day 84 (± 2 days)	Day 91 <sup>h</sup> (± 2 days)	
Medical history & disease assessment	X																
ECOG Performance Status	X																
ECG	X																
ECHO	X																
<b>CCI</b>																	
Brain MRI	X																
PET-CT/ disease assessment <sup>b</sup>	X										X						X
Physical exam	X				X	X	X	X	X	X	X	X <sup>b</sup>	X	X <sup>b</sup>	X	X <sup>b</sup>	X
Vital signs (BP, HR, RR O <sub>2</sub> sat, temp) <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X <sup>b</sup>	X	X <sup>b</sup>	X	X <sup>b</sup>	X
Height & Weight	X	X															
Neurological assessment	X																
Pregnancy test (serum or urine)	X																X
Lumbar Puncture <sup>d</sup>	X						with new onset Grade ≥ 2 neurologic symptoms as clinically indicated <sup>d</sup>										
Blood draw for Chemistry panel	X	X	X	X	X	X	X	X	X	X	X	X <sup>b</sup>	X	X <sup>b</sup>	X	X <sup>b</sup>	X
Blood draw for CBC w/differential	X	X	X	X	X	X	X	X	X <sup>b</sup>	X	X <sup>b</sup>	X <sup>b</sup>	X	X <sup>b</sup>	X	X <sup>b</sup>	X
Blood draw for C-reactive protein		X															
Blood draw for Anti-KTE-C19 <sup>e</sup>		X															X
Blood draw for Atezolizumab PK									X <sup>i</sup>		X <sup>j</sup>		X <sup>j</sup>		X <sup>k</sup>		
Blood draw for Atezolizumab ATA									X <sup>k</sup>		X <sup>j</sup>		X <sup>j</sup>		X <sup>k</sup>		
Blood draw for Cytokines <sup>f</sup>		X			X	Q3D <sup>f</sup>	X	X	X	X	X <sup>b</sup>		X <sup>b</sup>		X <sup>b</sup>		X
Blood draw for PBMCs <sup>g</sup>		X			X	Day 7	X	X <sup>l</sup>	X	X <sup>l</sup>	X <sup>b</sup>	X	X <sup>b</sup>	X	X <sup>b</sup>	X	X
Leukapheresis		X															
Fludarabine/Cyclophosphamide			X	X	X												
Axicabtagene ciloleucel IV infusion						X											
Atezolizumab IV infusion									X		X		X		X		
Adverse events/ Concomitant	X																

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period	IP Treatment Period (each visit calculated from Day 0)	Post Tx Follow- up
medication					

**Schedule of Assessments (Footnotes Cohort 1)**

- \*If cohort 1 is selected to serve as the dosing model for Phase 2 of the study, then this schedule of assessments will apply for all patients enrolled in Phase 2
- <sup>a</sup> Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. CCI  
 Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. CCI
- <sup>b</sup> PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility. If PET CT is performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the scans must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible. Patients with known bone marrow involvement will undergo bone marrow biopsy and aspirate as part of restaging {Cheson 2007}.
- <sup>c</sup> Refer to Section 7.4 for the frequency of vital sign collection following axicabtagene ciloleucel and atezolizumab infusions
- <sup>d</sup> Lumbar Puncture: subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade ≥ 2 neurologic symptoms post axicabtagene ciloleucel infusion will have lumbar puncture performed to assess cerebral spinal fluid as clinically appropriate. CCI
- <sup>e</sup> Blood draw for Anti-KTE-C19: Baseline antibody samples to be collected prior to start of leukapheresis. Refer to Section 7.10 for further details.
- <sup>f</sup> Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1 and then every third day through hospitalization
- <sup>g</sup> PBMCs Blood draw for PBMCs include the analysis of lymphocytes prior to axicabtagene ciloleucel infusion and lymphocytes, anti KTE-C19 CAR T cells, and RCR after axicabtagene ciloleucel infusion.
- <sup>h</sup> [Redacted]
- <sup>i</sup> Take a sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable). For the initial course of treatment only, take a sample at 30 min +/- 10 min after the end of the atezolizumab infusion
- <sup>j</sup> Take sample prior to the atezolizumab infusion. This sample is NOT required during the retreatment period.
- <sup>k</sup> Take sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable).
- <sup>l</sup> For Phase 2 only, CBC with differential and blood draw for PBMCs will be done 2 to 3 days after each of the first 2 doses of atezolizumab.

**Table 5. Schedule of Assessments (Cohort 2) \***

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period			IP Treatment Period (each visit calculated from Day 0)											Post Tx
			-5	-4	-3	0	1 - 7	Day 14 (± 2 days)	Ph 1: Day 17 Ph 2: Day 16 <sup>m</sup> (± 2 days)	Ph 1: Day 21 Ph 2: Day 28 <sup>m</sup> (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 63 <sup>h</sup> (± 2 days)	Day 77 (± 2 days)	Day 84 <sup>h</sup> (± 2 days)	
Medical history & disease assessment	X																
ECOG Performance Status	X																
ECG	X																
ECHO	X																
<b>CCI</b>																	
Brain MRI	X																
PET-CT/ disease assessment <sup>b</sup>	X											X					X
Physical exam	X					X	X	X	X	X	X	X <sup>h</sup>	X	X <sup>h</sup>	X	X <sup>h</sup>	X
Vital signs (BP, HR, RR O <sub>2</sub> sat, temp) <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X <sup>h</sup>	X	X <sup>h</sup>	X	X <sup>h</sup>	X
Height & Weight	X	X															
Neurological assessment	X																
Pregnancy test (serum or urine)	X																X
Lumbar Puncture <sup>d</sup>	X								with new onset Grade ≥ 2 neurologic symptoms as clinically indicated <sup>d</sup>								
Blood draw for Chemistry panel	X	X	X	X	X	X	X	X		X	X	X <sup>h</sup>	X	X <sup>h</sup>	X	X <sup>h</sup>	X
Blood draw for CBC w/differential	X	X	X	X	X	X	X	X	X <sup>i</sup>	X	X <sup>i</sup>	X <sup>h</sup>	X	X <sup>h</sup>	X	X <sup>h</sup>	X
Blood draw for C-reactive protein (CRP)		X															
Blood draw for Anti-KTE-C19 <sup>e</sup>		X															X
Blood draw for Atezolizumab PK								X <sup>i</sup>			X <sup>i</sup>		X <sup>i</sup>		X <sup>h</sup>		
Blood draw for Atezolizumab ATA								X <sup>h</sup>			X <sup>i</sup>		X <sup>i</sup>		X <sup>h</sup>		
Blood draw for Cytokines <sup>f</sup>		X				X	Q3D <sup>f</sup>	X		X	X	X <sup>h</sup>		X <sup>h</sup>		X <sup>h</sup>	X
Blood draw for PBMCs <sup>g</sup>		X				X	Day 7	X	X <sup>i</sup>	X	X <sup>i</sup>	X <sup>h</sup>	X	X <sup>h</sup>	X	X <sup>h</sup>	X
Leukapheresis		X															
Fludarabine/Cyclophosphamide			X	X	X												
Axicabtagene ciloleucel IV infusion						X											
Atezolizumab IV infusion								X			X		X		X		



Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period			IP Treatment Period (each visit calculated from Day 0)										Post Tx	
			-5	-4	-3	0	1 - 7	Day 14 (± 2 days)	Ph 1: Day 17 Ph 2: Day 16 <sup>m</sup> (± 2 days)	Ph 1: Day 21 Ph 2: Day 28 <sup>m</sup> (± 2 days)	Day 35 (± 2 days)	Day 42 (± 2 days)	Day 56 (± 2 days)	Day 63 <sup>h</sup> (± 2 days)	Day 77 (± 2 days)		Day 84 <sup>h</sup> (± 2 days)
Adverse events/ Concomitant medication	X		→														

**Schedule of Assessments (Footnotes Cohort 2) \***

- \*If cohort 2 is selected to serve as the dosing model for Phase 2 of the study, then this schedule of assessments will apply for all patients enrolled in Phase 2
- <sup>a</sup> Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. **CCI**  
Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. **CCI**
- <sup>b</sup> PET-CT (Neck-Chest-Abdomen-Pelvis): If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. Patients with known bone marrow involvement will undergo bone marrow biopsy and aspirate as part of restaging (Cheson 2007).
- <sup>c</sup> Refer to Section 7.4 for the frequency of vital sign collection following axicabtagene ciloleucel and atezolizumab infusions.
- <sup>d</sup> Lumbar Puncture: subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade ≥ 2 neurologic symptoms post axicabtagene ciloleucel infusion will have lumbar puncture performed to assess cerebral spinal fluid as clinically appropriate. **CCI**
- <sup>e</sup> Blood draw for Anti-KTE-C19: Baseline antibody samples to be collected prior to start of leukapheresis. Refer to Section 7.10 for further details.
- <sup>f</sup> Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1 and then every third day through hospitalization.
- <sup>g</sup> PBMCs Blood draw for PBMCs include the analysis of lymphocytes prior to axicabtagene ciloleucel infusion and lymphocytes, anti KTE-C19 CAR T cells, and RCR after axicabtagene ciloleucel infusion.
- CCI**
- <sup>i</sup> Take a sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable). For the initial course of treatment only, take a sample at 30 min +/- 10 min after the end of the atezolizumab infusion.
- <sup>j</sup> Take sample prior to the atezolizumab infusion. This sample is NOT required during the retreatment period.
- <sup>k</sup> Take sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable).
- <sup>l</sup> For Phase 2 only, CBC with differential and blood draw for PBMCs will be done 2 to 3 days after each of the first 2 doses of atezolizumab.
- <sup>m</sup> For Phase 2 only If the Cohort 2 schedule is selected as the dosing model for Phase 2: Visit Day 17 will be Visit Day 16, and Visit Day 21 will be Visit Day 28 (Phase 2 only).

**Table 6. Schedule of Assessments (Cohort 3) \***

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period				IP Administration Period (each visit calculated from Day 0)									Post Tx Follow-up
			-5	-4	-3	0	1 - 7	Day 14 (± 2 days)	Day 22 (± 2 days)	Ph 1: Day 35 <sup>b</sup> Ph 2: Day 28 <sup>m</sup> (± 2 days)	Day 43 (± 2 days)	Day 49 <sup>h</sup> (± 2 days)	Day 64 (± 2 days)	Day 69 <sup>h</sup> (± 2 days)	Day 94 (± 1 week)	
Medical history & disease assessment	X															
ECOG Performance Status	X															
ECG	X															
ECHO	X															
<b>CCI</b>																
Brain MRI	X															
PET-CT/ disease assessment <sup>b</sup>	X										X				X	
Physical exam	X				X	X	X	X	X	X <sup>b</sup>	X	X <sup>a</sup>	X	X <sup>b</sup>	X	
Vital signs (BP, HR, RR, O <sub>2</sub> sat, temp) <sup>c</sup>	X	X	X	X	X	X	X	X	X	X <sup>b</sup>	X	X <sup>a</sup>	X	X <sup>b</sup>	X	
Height & Weight	X	X														
Neurological assessment	X															
Pregnancy test (serum or urine)	X														X	
Lumbar Puncture <sup>d</sup>	X					with new onset Grade ≥ 2 neurologic symptoms as clinically indicated <sup>d</sup>										
Blood draw for Chemistry panel	X	X	X	X	X	X	X	X	X	X <sup>b</sup>	X	X <sup>a</sup>	X	X <sup>b</sup>	X	
Blood draw for CBC w/differential	X	X	X	X	X	X	X <sup>b</sup>	X	X <sup>b</sup>	X <sup>b</sup>	X	X <sup>a</sup>	X	X <sup>b</sup>	X	
Blood draw for C-reactive protein (CRP)		X														
Blood draw for Anti-KTE-C19 <sup>e</sup>		X													X	
Blood draw for Atezolizumab PK						X <sup>b</sup>		X <sup>b</sup>			X <sup>b</sup>		X <sup>a</sup>			
Blood draw for Atezolizumab ATA						X <sup>a</sup>		X <sup>b</sup>			X <sup>b</sup>		X <sup>a</sup>			
Blood draw for Cytokines <sup>f</sup>		X			X	Q3D <sup>f</sup>	X	X	X <sup>b</sup>		X <sup>a</sup>		X <sup>b</sup>	X		
Blood draw for PBMCs <sup>g</sup>		X			X	Day <sup>7</sup>	X	X <sup>b</sup>	X <sup>b</sup>	X	X <sup>a</sup>	X	X <sup>b</sup>	X		
Leukapheresis		X														
Fludarabine/Cyclophosphamide			X	X	X											
Axicabtagene ciloleucel IV infusion						X										
Atezolizumab IV infusion						X		X			X		X			
Adverse events/ Concomitant medication			→													

### Schedule of Assessments (Footnotes Cohort 3)

\*If cohort 3 is selected to serve as the dosing model for Phase 2 of the study, then this schedule of assessments will apply for all patients enrolled in Phase 2

- <sup>a</sup> Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. CCI  
Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. CCI
- <sup>b</sup> PET-CT (Neck-Chest-Abdomen-Pelvis): If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. Patients with known bone marrow involvement will undergo bone marrow biopsy and aspirate as part of restaging {Cheson 2007}.
- <sup>c</sup> Refer to Section 7.4 for the frequency of vital sign collection following axicabtagene ciloleucel and atezolizumab infusions.
- <sup>d</sup> Lumbar Puncture: subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade  $\geq 2$  neurologic symptoms post axicabtagene ciloleucel infusion will have lumbar puncture performed to assess cerebral spinal fluid as clinically appropriate. CCI
- <sup>e</sup> Blood draw for Anti-KTE-C19: Baseline antibody samples to be collected prior to start of leukapheresis. Refer to Section 7.10 for further details.
- <sup>f</sup> Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1 and then every third day through hospitalization.
- <sup>g</sup> PBMCs Blood draw for PBMCs include the analysis of lymphocytes prior to axicabtagene ciloleucel infusion and lymphocytes, anti KTE-C19 CAR T cells, and RCR after axicabtagene ciloleucel infusion.
- <sup>h</sup> [REDACTED]
- <sup>i</sup> Take a sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable). For the initial course of treatment only, take a sample at 30 min +/- 10 min after the end of the atezolizumab infusion.
- <sup>j</sup> Take sample prior to the atezolizumab infusion. This sample is NOT required during the retreatment period.
- <sup>k</sup> Take sample prior to the atezolizumab infusion for the initial course of treatment and during the retreatment period (if applicable).
- <sup>l</sup> For Phase 2 only. CBC with differential and blood draw for PBMCs will be done 2 to 3 days after each of the first 2 doses of atezolizumab.
- <sup>m</sup> If the Cohort 3 schedule is selected as the dosing model for Phase 2, Visit Day 35 will be Visit Day 28 (Phase 2 only) .

**Table 7. Schedule of Assessments (Long-term Follow-up Period)**

Procedure	Long-term Follow-up Period (Each visit calculated from Day 0)												Month 72 and annually until Year 15 <sup>j</sup>
	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	
Physical exam <sup>a</sup>	X	X	X	X	X	X		X		X		X	
PET-CT (Neck-Chest-Abdomen-Pelvis) <sup>b</sup>	X	X	X		X	X		X		X		X	X
Disease assessment	X	X	X		X	X		X		X		X	X
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for CBC w/differential <sup>c</sup>	X	X	X	X	X	X							
Blood draw for Anti-KTE-C19 <sup>d</sup>													
Blood draw for Atezolizumab PK	≥90 days after the last dose of atezolizumab <sup>i</sup>												
Blood draw for Atezolizumab ATA	≥90 days after the last dose of atezolizumab <sup>i</sup>												
Blood draw for PBMCs <sup>e,*</sup>	X	X	X	X	X	X		X		X		X	X
Targeted AE/SAEs <sup>f</sup>	X	X	X	X	X	X							
Targeted concomitant medication <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for NHL <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X

<sup>a</sup> Physical exams will continue through Month 24

<sup>b</sup> PET Scans CTs will continue through Month 60 or until disease progression, whichever comes first

<sup>c</sup> Subjects will continue to provide samples for CBC w/diffs, lymphocyte subsets and anti-CD19 CAR T cells through Month 24

<sup>d</sup> Anti-KTE-C19 antibody samples, refer to Section 7.10

<sup>e</sup> RCR samples, harvest and measured at the Post Treatment Assessment Visit, 6 and 12; then collect yearly for up to 15 years and measure only if positive at the Post Treatment Assessment, Visit, 6, or 12.

<sup>f</sup> Targeted AEs/SAEs will be collected for 24 months or until disease progression (whichever occurs first)

<sup>g</sup> Targeted concomitant medications will be collected for 24 months or until disease progression, whichever occurs first

<sup>h</sup> Subsequent therapy administered after axicabtagene ciloleucel infusion for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy must be collected until subject completes the long term follow up period, is considered lost to follow up, withdraws consent, or dies.

<sup>i</sup> Take a single time point sample ≥ 90 days after the last atezolizumab infusion for the initial course of therapy and another single time point sample after the retreatment period (if applicable).

<sup>j</sup> In the event this study is terminated prior to the completion of the 15-year follow up for all subjects, subjects who received an infusion of KTE-C19 will be provided the opportunity to transition to a LTFU study (KT-US-982-5968) after providing signed informed consent. The subject's final on-study visit for this study may be combined with the first visit on the LTFU study. The timing of the final on-study visit/first LTFU study visit will depend on the timing of the collection of all the subject's data that are required for the planned analysis for this study.

## 8. SUBJECT WITHDRAWAL

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

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

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

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and where permitted, publically available data (death records) can be included after withdrawal of consent {[U. S. Department of Health and Human Services \(DHHS\) 2008](#)}. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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

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

### 8.1. Reasons for Removal from Treatment

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

- Adverse Event
- Subject request/non-compliance
- Product not available
- Lost to Follow-up

- Death
- Decision by sponsor

## 8.2. Reasons for Removal from Study

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

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

## **9. SAFETY REPORTING**

### **9.1. Adverse Events**

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

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

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

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

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

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

If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started.

### **9.2. Reporting of Adverse Events**

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from enrollment (i.e., commencement of leukapheresis) through 30 days after completing the final dose of Atezolizumab, or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. Once this follow up period has been completed, only targeted adverse events including neurological, hematological, infections, autoimmune disorders, and secondary malignancies for 24 months or until disease progression, whichever occurs first.

For subjects who are enrolled but do not receive axicabtagene ciloleucel and/or atezolizumab, the reporting period ends 30 days after the last procedure (e.g., leukapheresis, conditioning chemotherapy, investigational product).

The investigator must address the below for adverse events:

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

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). Cytokine Release Syndrome events will also be reported using the grading scale outlined in the most recent version of the KTE-C19 / axicabtagene ciloleucel IB.

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

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. Abnormal laboratory findings without clinical significance (based on investigators assessment) are not to be recorded as adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

### **9.3. Definition of Serious Adverse Events**

The investigator is responsible for reporting all serious adverse events observed by the investigator or reported by the subject that occur after signing of the consent through 30 days after completing the final dose of atezolizumab, or 3 months after the axicabtagene ciloleucel infusion, whichever is longer. Once this follow up period has been completed, only serious targeted adverse events (e.g., neurological, hematological, infections, autoimmune disorders, and secondary malignancies) observed by the investigator or reported by the subject will be reported



for 24 months or until disease progression, whichever occurs first. For subjects who screen fail or are enrolled but do not receive axicabtagene ciloleucel and/or atezolizumab, the reporting period ends 30 days after the last procedure (e.g., screen procedure, leukapheresis, conditioning chemotherapy, investigational product).

Serious events which the Investigator assesses as related to axicabtagene ciloleucel or atezolizumab should be reported regardless of the time period.

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

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

An adverse event would meet the criterion of “requires hospitalization” if the event necessitated an admission to a health care facility (e.g., overnight stay).

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

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

#### **9.4. Reporting of Serious Adverse Events and Non-Serious CRS Events Grade $\geq$ 3**

All serious adverse events and non-serious CRS events Grade  $\geq$  3 (Lee 2014) must be submitted to Kite within 24 hours following the investigator’s knowledge of the event. SAEs and non-serious CRS events Grade  $\geq$  3 will be reported through the electronic data capture (EDC) system. This is called eSAE reporting. If the eSAE system is unavailable, reports will be submitted by email to PPD

Following completion of KTE-C19-106, any relevant information on ongoing SAEs must be submitted to Kite Pharma within 24 hours of the investigator’s knowledge of the event using the paper SAE Report Form and sent via e-mail to the SAE Reporting mailbox: PPD

Subsequently, all serious adverse events will be reported to the FDA per 21 CFR312.32.

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

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

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 30 days following the final dose of atezolizumab or 3 months following the axicabtagene ciloleucel infusion, whichever is longer, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring greater than 30 days following the final dose of atezolizumab or 3 months following the axicabtagene ciloleucel infusion, whichever is longer, requires expedited reporting within 24 hours only if it is considered related to treatment.

#### **9.5. Pregnancy and Lactation**

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

If a pregnancy occurs in a female subject enrolled into the study, or a female partner of a male subject within 6 months of completing the axicabtagene ciloleucel infusion, the pregnancy must be reported to the sponsor contact. If a pregnancy occurs in a female subject enrolled into the study or in a female partner of a male subject within 5 months of the last dose of atezolizumab, the pregnancy must be reported to the sponsor. Information regarding the pregnancy and/or the outcome may be requested by the sponsor.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur through 6 months after the last dose of axicabtagene ciloleucel and through 5 months after the last dose of atezolizumab

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

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

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

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

## 9.6. Safety Review Team and Dose-Limiting Toxicity

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

Dose-limiting toxicity is defined as the following axicabtagene ciloleucel or atezolizumab related events with an onset from immediately after and through 21 days following the first atezolizumab infusion:

- Grade 4 hematologic toxicity lasting more than 30 days (except lymphopenia or B-cell aplasia)
- All axicabtagene ciloleucel- or atezolizumab-related Grade 3 non-hematologic toxicities lasting for > 7 days and all axicabtagene ciloleucel- or atezolizumab-related Grade 4 non-hematologic toxicities regardless of duration are considered DLTs, with the exception of the following which are not considered DLTs:
  - Aphasia/dysphasia or confusion/cognitive disturbance which resolves to at worst Grade 2 within 2 weeks, to Grade 1 within 4 weeks, and baseline within 6 weeks.
  - Fever
  - Immediate IP-related hypersensitivity reactions occurring within 2 hours of cell or atezolizumab infusion that are reversible to a Grade 2 or less within 24 hours of administration with standard therapy
  - Renal toxicity which requires dialysis for  $\leq 7$  days
  - Intubation for airway protection if  $\leq 7$  days
  - Tumor lysis syndrome (TLS) including associated manifestations attributable to TLS (e.g., electrolyte abnormalities, renal function, hyperuricemia)
  - Grade 3 transaminase, alkaline phosphatase, bilirubin, or other liver function test elevation, provided there is resolution to  $\leq$  Grade 2 within 14 days
  - Grade 4 transient serum hepatic enzyme abnormalities provided there is resolution to  $\leq$  Grade 3 within < 72 hours
  - Hypogammaglobulinemia Grade 3 or 4
  - Grade 3 nausea and/or anorexia

CRS will be graded according to a revised grading system (Lee 2014) as described in the current axicabtagene ciloleucel investigator's brochure. Adverse events attributed to CRS will be

mapped to the overall CRS grading assessment for the determination of DLT. If Grade 3 or 4 CRS per Lee is due to one of the exceptions above, the event will not be considered a DLT.

During Phase 1, approximately 3-9 subjects with DLBCL will be enrolled to evaluate the safety of axicabtagene ciloleucel and atezolizumab schedules/regimens.

Subjects in each cohort will be evaluated for DLTs within the first 21 days following the completion of their first dose of atezolizumab. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.5. The SRT will make recommendations based on the incidence of DLT and overall safety profile of the axicabtagene ciloleucel and atezolizumab regimen. If the subject incidence of DLT is  $\leq 1$  of 3 subjects, the study will proceed to the next cohort, or if specific to cohort 3, proceeding to Phase 2 of the trial. This decision will be based on overall benefit/risk and available biomarker data.

However, if  $\geq 2$  of the 3 enrolled subjects within any cohort present with a protocol defined DLT during Phase 1, the SRT may recommend enrolling an additional set of 3 subjects (up to 6 subjects in total) at the same dose and schedule that was administered in the first 3 subjects in that cohort. In this scenario, progression to the next cohort or to Phase 2 of the study will proceed if  $\leq 2$  of the first 6 subjects present with a DLT.

If the subject incidence of DLT is  $> 2/6$ , other axicabtagene ciloleucel regimens, including reduced cell dose of axicabtagene ciloleucel and/or reduced conditioning chemotherapy may be explored in collaboration with the SRT in an additional 3-6 subjects (Figure 3). The same DLT rules apply as above.

#### 9.7. Criteria to Pause Enrollment

As part of its oversight of the study, the SRT also will assess criteria to pause enrollment after 6 subjects have been treated with axicabtagene ciloleucel and atezolizumab in the Phase 2 portion of the study and have had the opportunity to be followed for 30 days from the first atezolizumab dose. Enrollment will be paused if any of the following criteria is met:

- 1) Subject incidence of Grade 5 axicabtagene ciloleucel or atezolizumab related adverse events within 30 days from atezolizumab infusion is  $\geq 20\%$ .

OR

- 2) Subject incidence of the following Grade 4 axicabtagene ciloleucel-related adverse events lasting more than 7 days is  $\geq 40\%$ :
  - a) Neurologic Events
  - b) CRS (per Lee 2014 criteria)
  - c) Other non-hematological serious adverse event
  - d) Infection (treatment-related)

## 10. STATISTICAL CONSIDERATIONS

### 10.1. Hypothesis

No formal hypothesis will be tested in this study. The Phase 2 portion of the study is designed to estimate the true CR rate in patients with refractory DLBCL treated with the combination of axicabtagene ciloleucel and atezolizumab.

### 10.2. Study Endpoints

#### 10.2.1. Primary Endpoints

- Phase 1: Incidence of dose-limiting toxicities (DLT)
- Phase 2: Complete response rate (complete response [CR] per the revised International Working Group [IWG]) Response Criteria for Malignant Lymphoma {Cheson 2007} as determined by study investigators.

#### 10.2.2. Secondary Endpoints

Phase 1 and 2:

- Objective Response Rate (CR + PR) per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007}
- Duration of Response
- Progression Free Survival
- Overall Survival
- Incidence of adverse events and clinically significant changes in safety lab values
- Levels of axicabtagene ciloleucel in blood and Incidence of anti-KTE-C19 antibodies
- Atezolizumab pharmacokinetics and incidence of anti- atezolizumab antibodies in serum
- Levels of cytokines and other markers in serum

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

**Duration of Response:** DOR for subjects who experience an objective response is defined as the date of their first objective response (which is subsequently confirmed) to disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} or death

regardless of cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing.

**Progression Free Survival:** PFS is defined as the time from the KTE-C19 infusion date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

**Overall Survival:** OS is defined as the time from KTE-C19 infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

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

Incidence of anti-KTE-C19 antibodies and levels of anti-CD19 CAR T cells in blood and levels of cytokines and other markers in serum will be summarized.

Incidence of anti-atezolizumab antibodies and levels of atezolizumab in serum will be analyzed as described in Section 7.10.



### 10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 3-31 subjects.

Phase 1 will enroll approximately 3-9 subjects. If the study proceeds to Phase 2, total of up to 22 additional subjects would be enrolled.

This study uses a single-arm design to estimate the true complete response rate in patients with DLBCL treated with the combination of atezolizumab and axicabtagene ciloleucel at the dosing schedule closest to concomitant administration tested in Phase 1 and deemed safe by the SRT. With a total sample size of 25 patients at a given dosing schedule, of which at least 3 will have

been treated in the Phase 1 portion, an observed CR rate of 70% will yield 95% confidence that estimate of the true CR rate is between 51% and 88%.

Additional assumptions and corresponding two-sided 95% and 80% exact confidence intervals are seen in [Table 8](#).

**Table 8. 95% and 80% exact confidence intervals corresponding to observed CR rate following treatment of 25 patients with axicabtagene ciloleucel and atezolizumab**

Observed CR Rate	95% Confidence Interval	80% Confidence Interval
40%	[21%, 61%]	[27%, 55%]
45%	[28%, 69%]	[34%, 62%]
50%	[31%, 72%]	[38%, 66%]
55%	[35%, 76%]	[41%, 70%]
60%	[39%, 79%]	[45%, 73%]
65%	[47%, 85%]	[53%, 80%]
70%	[51%, 88%]	[57%, 84%]
75%	[55%, 91%]	[62%, 87%]
80%	[59%, 93%]	[66%, 90%]

#### 10.4. Analysis Subsets

**Full Analysis Set:** the full analysis set will consist of all enrolled subjects and will be used for summaries of subject disposition.

**Modified Intent to Treat Set (mITT):** the modified intent to treat set will consist of all subjects enrolled and treated with the target dose of axicabtagene ciloleucel,  $2 \times 10^6$  CAR T cells/kg (range  $1 \times 10^6$  to  $2.4 \times 10^6$  CAR T cells/kg) and at least one dose of atezolizumab as determined upon completion of the Phase 1 and Phase 2 portions of the study. This analysis set will be used for all efficacy analyses.

The DLT evaluable set will include all subjects in each Phase 1 cohort treated with axicabtagene ciloleucel and at least one dose of atezolizumab who either:

Received the target axicabtagene ciloleucel dose and were followed for at least 21 days after the first atezolizumab infusion; or

Received a dose of anti-CD19 CAR T cells lower than the target for that cohort and a subsequent atezolizumab infusion and experienced a DLT during the 21-day post-atezolizumab infusion period.

For the Phase 1 portion of the study and the evaluation of DLT, the target dose is defined as  $2.0 \times 10^6$  anti-CD19 CAR T cells/kg (range  $1 \times 10^6$  to  $2.4 \times 10^6$  CAR T cells/kg).

If needed, more subjects will be enrolled and treated to achieve 3 DLT evaluable subjects at the target dose.

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

#### **10.5. Access to Individual Subject Treatment Assignments**

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

#### **10.6. Interim Analysis**

##### **10.6.1. Safety Interim Analysis**

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

The SRT will review accumulating safety data during the Phase 2 portion of the study. Refer to Section 3.1.

#### **10.7. Planned Method of Analysis**

The primary analysis will be performed when the last treated subject in the mITT set has had the opportunity to be evaluated for response 6 months after the axicabtagene ciloleucel infusion. The final analysis will occur when all subjects have completed the study (defined in Section 3.5.3).

##### **10.7.1. Complete Response Rate**

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

##### **10.7.2. Progression Free Survival**

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for progression-free survival time. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided.

##### **10.7.3. Overall Survival**

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



#### **10.7.4. Safety**

Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4 Grade 3 or higher and treatment related AEs reported throughout the conduct of the study will be tabulated by preferred term and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths through the Long-term Follow-up and treatment related SAEs will be provided.

#### **10.7.5. Long-term Data Analysis**

All subjects will be followed for survival status for up to 15 years after receiving axicabtagene ciloleucel. LTFU data analysis will be performed on subjects in this study and after transition to the KT-US-982-5968 LTFU study. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

#### **10.7.6. Pharmacokinetic Analyses**

As appropriate, serum concentrations of atezolizumab will be tabulated, summarized, and plotted after appropriate grouping. Additional PK and PK/PD analyses (e.g., population modelling, including pooled analyses across studies) may also be performed as appropriate. If done, these additional analyses may be reported separately from the Clinical Study Report and may include additional PK parameters as appropriate (e.g., AUC, time-to-maximum concentration, maximum concentration, and half-life).

#### **10.7.7. Immunogenicity Analyses**

The immunogenicity analyses will include patients with at least one pre-dose and one post-dose ATA assessment, with patients grouped as appropriate. The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized after appropriate grouping.

Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e.,  $\geq 0.60$  titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ATA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

## **11. REGULATORY OBLIGATIONS**

### **11.1. Independent Review Board /Independent Ethics Committee**

A copy of the protocol, ICF and any additional subject or trial information such as subject recruitment materials must be submitted to each site respective IRB/IEC for approval. Once approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site specific and study serious adverse events (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

### **11.2. Subject Confidentiality**

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number
- Date of birth will be reported according with local laws and regulations
- Age at the time of enrollment

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth (as per their local reporting requirements for both initials and date of birth)

Per federal regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, CRO, IRB/IEC and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records which includes personal information.

### **11.3. Investigator Signatory Obligations**

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

## **12. PROTOCOL AMENDMENTS AND TERMINATION**

If the protocol is amended, the investigators agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact

Kite Pharma reserves the right to terminate the study at any time. Both Kite pharma and the investigator reserve the right to terminate the investigators participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at is sole discretion, to determine whether to manufacture axicabtagene ciloleucel and provide it to sites and subjects after the completion of the study and before treatment becomes commercially available.

### **13. STUDY DOCUMENTATION AND ARCHIVE**

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should outlined and included in the Delegation of Authority Form.

Source documents are original documents, data and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralize filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject identification lists
- Protocols and protocol amendments, investigator brochure, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records and experimental product related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

## **14. STUDY MONITORING AND DATA COLLECTION**

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentiality is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility (ies), review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

## 15. PUBLICATION

Authorship of publications from data generated in this study will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on
  - Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work; AND
  - Drafting the article or revising it critically for important intellectual content; AND
  - Final approval of the version to be published; AND
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma for review and approval. The study contract between the institution, principal investigation and Kite Pharma or its delegate will outline the requirements for publication review.

## **16. COMPENSATION**

The study sponsor (Kite Pharma) will provide compensation for study related illness or injury pursuant to the information outlined in the injury section of the ICF.

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## 18. APPENDICES

- Appendix A. Sponsor and Investigator Signature Page
- Appendix B. Revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007).
- Appendix C. Atezolizumab Anaphylaxis Precautions

**Appendix A. Sponsor and Investigator Signature Page**

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

**STUDY ACKNOWLEDGMENT**

**A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma**

**Amendment 3.0, 03 August 2021**

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

PPD

\_\_\_\_\_  
Kite Medical Monitor Name (Printed)  
18-sept.-2021

\_\_\_\_\_  
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

**Appendix B. Revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007).**

**Complete Remission (CR): CR requires all of the following:**

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- Typically FDG-avid lymphoma (large cell, mantle cell and follicular lymphomas are all typically FDG-avid): in subjects with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed to normal size ( $\leq 1.5$  cm in greatest diameter if  $> 1.5$  cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1 cm in their short axis before treatment must have decreased to  $\leq 1.0$  cm in their short axis after treatment.
- The spleen and/or liver, if considered to be enlarged before therapy on basis of physical exam or CT scan, must should be normal size on CT scan and not be palpable on physical examination and nodules thought to represent lymphoma must no longer be present.
- A bone marrow aspirate and biopsy is performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. The biopsy core sample must be a minimum of 20 mm in length.

**Partial Remission (PR): PR requires all of the following:**

- $\geq 50\%$  decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible and should include mediastinal and retroperitoneal nodes if possible.
- No increase in size of nodes, liver or spleen and no new sites of disease.
- If multiple splenic and hepatic nodules are present, they must regress by  $\geq 50\%$  in the SPD. There must be a  $> 50\%$  decrease in the greatest transverse diameter for single nodules.
- Bone marrow is irrelevant for determination of a PR. If patient has persistent bone marrow involvement and otherwise meets criteria for CR the patient will be considered a PR.

- Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site. Note: in subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated in subjects with one or at most two residual masses that have regressed by 50% on CT scan.

**Stable Disease (SD):**

- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PET should be positive in typically FDG-avid lymphomas.

**Progressive Disease:**

**Defined by at least one of the following:**

- $\geq 50\%$  increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node.
- Appearance of a new lesion greater than 1.5 cm in any axis even if other lesions are decreasing in size
- Greater than or equal to a 50% increase in size of splenic or hepatic nodules
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
- Lesions should be PET positive in typically FDG-avid lymphomas unless the lesion is too small to be detected by PET (<1.5 cm in its long axis by CT)

## **Appendix C. Atezolizumab Anaphylaxis Precautions**

### **Equipment Needed:**

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous (IV), and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

### **Procedures**

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

- 1) Stop the study drug infusion.
- 2) Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- 3) Maintain an adequate airway.
- 4) Administer glucocorticoids, antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- 5) Continue to observe the patient and document observations.