Protocol Title:	A Phase 2 Multicenter Study Evaluating the Efficacy of **KTE-X19** in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)
Protocol Number:	KTE-C19-102
IND Number:	016675
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INVESTIGATOR'S AGREEMENT

I have read the attached protocol titled A Phase 2 Multicenter Study Evaluating the Efficacy of **KTE-X19** in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2) dated **29 October 2018** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines.

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

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

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

_____

Signature

_____

Name of investigator

_____

Date

PROTOCOL SYNOPSIS

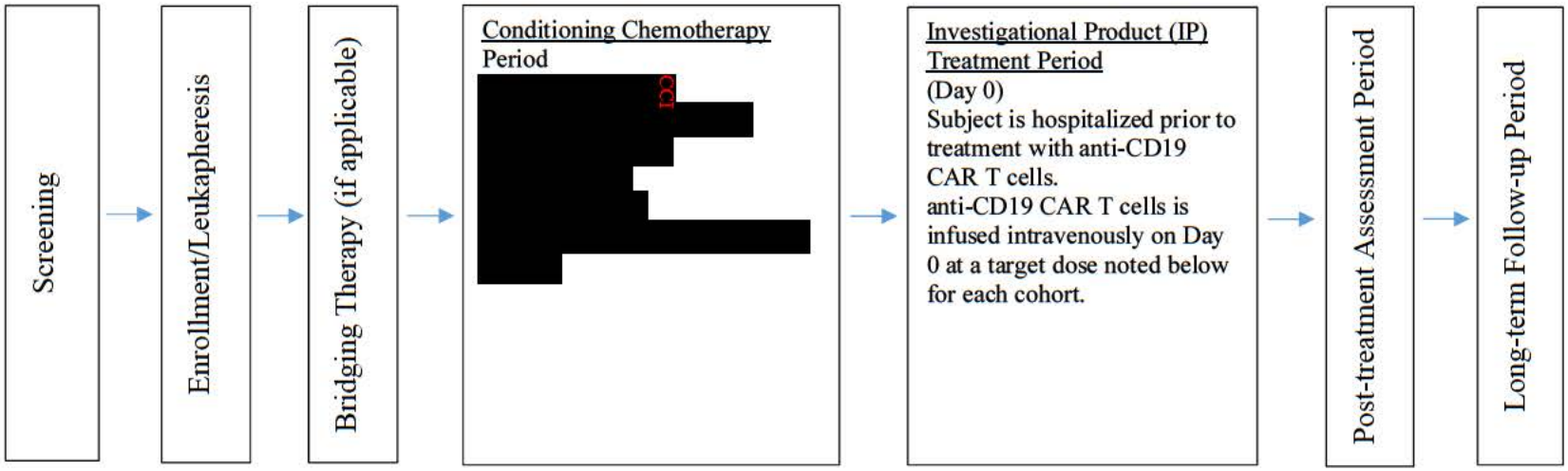
Title:	A Phase 2 Multicenter Study Evaluating the Efficacy of **KTE-X19** in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)
Indication:	The treatment of adult subjects with relapsed/refractory mantle cell lymphoma (r/r MCL).
Study Design:	Study KTE-C19-102 is a Phase 2, multicenter, open-label study evaluating the efficacy of **KTE-X19** in subjects with r/r MCL. Cohort 1 will enroll and treat up to approximately 90 subjects with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2 x 10^6 anti-CD19 CAR T cells per kg body weight. This cohort will include at least 60 but up to approximately 80 subjects treated with **KTE-X19** (referred to as **KTE-X19** subjects in this document) and 10 subjects treated with axicabtagene ciloleucel (referred to as axicabtagene ciloleucel subjects in this document). The **KTE-X19** subjects in this cohort will form the basis for hypothesis testing on the primary endpoint. Cohort 2 will enroll and treat up to 40 **KTE-X19** subjects with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 0.5 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells per kg body weight. Each subject will proceed through the following study periods: • Screening • Enrollment/Leukapheresis • Bridging therapy if applicable • Conditioning chemotherapy • Investigational product (IP) treatment • Post-treatment assessment • Long-term follow-up period For study requirements assigned to each study period, refer to Section 7 for details.
Study Objectives:	The primary objective is to evaluate the efficacy of **KTE-X19**, as measured by objective response rate (ORR), in subjects with r/r MCL. Secondary objectives will include assessing the safety and tolerability of **KTE-X19**, additional efficacy endpoints, and change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6.
Hypothesis:	This study uses an open-label 2-cohort design. Among the Cohort 1 **KTE-X19** subjects, with a target 50% response rate per independent review, an alternative hypothesis will be tested against a null hypothesis that the response rate is 25% or less. The hypothesis is that the ORR to **KTE-X19** per independent review is significantly greater than 25% in Cohort 1 **KTE-X19** subjects. No hypothesis will be tested in Cohort 1 axicabtagene ciloleucel subjects and Cohort 2 **KTE-X19** subjects. Exploratory analyses will be conducted on the data collected from these subjects.

Primary Endpoint:	ORR (complete response [CR] + partial response [PR]) per the Lugano Classification (Cheson et al, 2014) per Independent Radiology Review Committee (IRRC) review
Secondary Endpoints:	• Duration of response • Best objective response **(BOR)** • ORR as determined by study investigators • Progression-free survival • Overall survival • Incidence of adverse events (AEs) and clinically significant changes in laboratory values • Incidence of anti-**CD19 CAR** antibodies • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines in serum • Changes over time in the EQ-5D scale score and visual analogue scale score
Exploratory Endpoints:	CCI
Sample Size:	• Up to approximately 130 will be enrolled in the study: — 90 subjects in Cohort 1 (10 axicabtagene ciloleucel subjects and approximately 80 **KTE-X19** subjects) at 2 x 10^6 anti-CD19 CAR T cells per kg body weight — Up to 40 **KTE-X19** subjects in Cohort 2 at 0.5 x 10^6 anti-CD19 CAR T cells per kg body weight
Study Eligibility:	Refer to Section 5 for a detailed list of inclusion and exclusion criteria.
Treatment:	Bridging Therapy • At the discretion of the investigator, bridging therapy may be considered for subjects particularly with high disease burden at screening (eg, > 25% marrow involvement or ≥ 1000 leukemic phase mantle cells/mm^3 in the peripheral circulation). • Bridging therapy is allowed with (1) dexamethasone or other corticosteroid, (2) ibrutinib, or (3) acalabrutinib. • If prescribed, bridging therapy must be administered after leukapheresis and completed at least 5 days prior to initiating conditioning chemotherapy. • Refer to Section 6 for dosing and further details. Conditioning Chemotherapy Treatment: • **KTE-X19** or axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.

	Investigational Product: • **KTE-X19** or axicabtagene ciloleucel treatment consists of a single infusion of CAR-transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg (Cohort 1) or 0.5 x 10^6 anti-CD19 CAR T cells/kg (Cohort 2). Under circumstances where subjects initially respond and subsequently relapse, subjects may be eligible for a second course of conditioning chemotherapy and **KTE-X19** or axicabtagene ciloleucel. Refer to Section 6 for treatment details and Section 7.12.10 for retreatment details.
Procedures:	At specific time points as outlined in the schedule of assessments, subjects will undergo the following assessments/procedures: collection of informed consent; general medical history, including previous treatments for MCL; physical exam, including vital signs and performance status; neurological assessments; blood draws for complete blood count (CBC), chemistry panels, cytokines, C-reactive protein, lymphocyte subsets, anti-**CD19 CAR** antibodies, replication-competent retrovirus (RCR), and anti-CD19 CAR T cells analysis. Women of childbearing potential will undergo a urine or serum pregnancy test. Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), brain magnetic resonance image (MRI), a positron emission tomography-computed tomography (PET-CT), bone marrow aspirate/biopsy, and leukapheresis. Routinely throughout the conduct of the study, subjects will be asked to complete the EQ-5D questionnaire, report concomitant medications and AEs, and will have their disease assessed.
Data Safety Monitoring Board:	An independent Data Safety Monitoring Board (DSMB) will review safety and/or efficacy data 4 times during this study. The DSMB will first meet to review safety data when 10 subjects in Cohort 1 have been enrolled and treated with anti-CD19 CAR T cells and followed for 30 days. The DSMB will meet for the second time to review both safety and efficacy data after 20 subjects in Cohort 1 have been enrolled, treated, and have had the opportunity to complete the 3-month disease assessment. The DSMB will meet for the third time to review both safety and efficacy data after 10 subjects in Cohort 2 have been enrolled, treated, and have had the opportunity to be followed for 30 days. The DSMB will meet for the fourth time to review safety data after 44 subjects in Cohort 1 have been enrolled, treated, and have had the opportunity to be followed for at least 30 days, with focus on the safety data from the 6 **KTE-X19** subjects treated most recently in this cohort. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk vs benefit. The DSMB may meet more often as needed. Refer to Section 9.10 and Section 9.11.
Statistical Considerations:	This study uses an open-label, 2-cohort design. Among the Cohort 1 **KTE-X19** subjects, with a target 50% response rate per independent review, an alternative hypothesis will be tested against a null hypothesis that the response rate is 25% or less. For the test of efficacy in the Cohort 1 **KTE-X19** subjects, this study has at least 96% power to distinguish between an active therapy with a 50% true response rate from a therapy with a response rate of 25% or less with a 1-sided alpha level of 0.025. No hypothesis will be tested on Cohort 1 axicabtagene ciloleucel subjects and on Cohort 2. Four interim analyses will be performed in Cohort 1, and 1 interim analysis will be performed in Cohort 2. One primary analysis will be performed after 60 Cohort 1 **KTE-X19** subjects have been enrolled and treated and have had the opportunity to be assessed for response 6 months after the Week 4 disease assessment.

	• Cohort 1 interim analysis 1 will be conducted after 10 subjects in Cohort 1 have been enrolled and treated with anti-CD19 CAR T cells and followed for 30 days. This interim analysis will be for safety only. • Cohort 1 interim analysis 2 will be conducted after 20 subjects in Cohort 1 (Section 10.5) have been enrolled and treated with anti-CD19 CAR T cells and have had the opportunity to be evaluated for response 3 months after the investigational product (IP) infusion. This interim analysis will be for safety and efficacy (futility only). • Cohort 1 interim analysis 3 will occur after 38 subjects treated with anti-CD19 CAR T cells in Cohort 1 have had the opportunity to be assessed for response 6 months after the IP infusion. • Cohort 1 interim analysis 4 will be conducted after 44 subjects in Cohort 1 have been enrolled and treated with anti-CD19 CAR T cells and have had the opportunity to be followed for at least 30 days after the IP infusion. This interim analysis will assess safety only, with focus on the **KTE-X19** subjects treated most recently in this cohort. • Cohort 2 interim analysis will be conducted after 10 subjects in Cohort 2 have been enrolled and treated with **KTE-X19** and have had the opportunity to be followed for 30 days after the **KTE-X19** infusion. This interim analysis will assess safety and efficacy. The primary analysis will occur after 60 **KTE-X19** subjects in the modified intent-to-treat (mITT) set of Cohort 1 have been enrolled and treated with **KTE-X19** and have had the opportunity to be assessed for response 6 months after the Week 4 disease assessment.

Figure 1. Study Schema



Study KTE-C19-102 is a Phase 2, multicenter, open-label study evaluating the efficacy of **KTE-X19** in subjects with relapsed/refractory mantle cell lymphoma (r/r MCL).

Up to approximately 130 subjects with r/r MCL will be enrolled into 2 separate cohorts designated as Cohort 1 and Cohort 2.

- Cohort 1 will enroll and treat 90 subjects at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg, including 10 axicabtagene ciloleucel subjects and approximately 80 **KTE-X19** subjects.
- Cohort 2 will enroll and treat up to approximately 40 **KTE-X19** subjects at a target dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
alloSCT	Allogeneic stem cell transplant
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under curve
autoSCT	Autologous stem cell transplant
BTKi	Bruton's tyrosine kinase inhibitor
CAR	Chimeric antigen receptor
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CPF	Cell processing facility
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life-5 Dimensions
GCP	Good Clinical Practices
GOT	**Glutamic-oxaloacetic transaminase**
GPT	**Glutamic-pyruvic transaminase**
HEENT	Head, ears, eyes, nose, and throat
HIV	Human immunodeficiency virus

Abbreviation	Definition
HLH	Hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IP	Investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRRC	Independent Radiology Review Committee
IV	Intravenous
IWG	International Working Group
LDH	**Lactate dehydrogenase**
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MCL	Mantle cell lymphoma
mITT	Modified intent-to-treat
MMSE	Mini-Mental Status Exam
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET-**CT**	Positron emission tomography-**computed tomography**
PFS	Progression-free survival
PR	**Partial response**
qPCR	Quantitative polymerase chain reaction
RCR	Replication-competent retrovirus
r/r	Relapsed/refractory
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Stable disease

Abbreviation	Definition
SOA	Schedule of assessment
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale
WBC	White blood cell

1. OBJECTIVES

The primary objective is to evaluate the efficacy of **KTE-X19**, as measured by objective response rate (ORR), in subjects with relapsed/refractory (r/r) mantle cell lymphoma (MCL). Secondary objectives will include assessing the safety and tolerability of **KTE-X19**, additional efficacy endpoints, and the change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6.

2. DISEASE BACKGROUND AND RATIONALE

Mantle cell lymphoma is an aggressive, generally incurable, B-cell malignancy, representing approximately 6% of non-Hodgkin lymphomas (NHLs). Approximately 4000 new cases are diagnosed yearly in the United States (Leukemia & Lymphoma Society 2014). The lymphoma cells are thought to originate from naïve pregerminal center B cells within the mantle zone, and they typically express CD5, CD19, CD20, surface IgM, and surface IgD (Dreyling 2014), but not CD11c (Kraus et al, 2010). More than 95% of MCLs carry translocation t(11;14)(q13;q32), which places the cyclin D1 gene in proximity of the immunoglobulin heavy chain locus, resulting in overexpression of cyclin D1, which can be detected by cytogenetics or fluorescence in situ hybridization (National Comprehensive Cancer Network 2017). Most patients are male, and the median age of diagnosis is 68 years (Fakhri and Kahl 2017). Patients typically present with advanced lymphadenopathy, and also show extranodal involvement of the spleen, bone marrow, and gastrointestinal (GI) tract (Dreyling et al, 2014; Rajabi and Sweetenham 2015; National Comprehensive Cancer Network 2017; Vose 2017). Prognosis varies based on clinical and laboratory parameters and can be estimated using the mantle cell international prognostic index. This index uses the 4 independent prognostic factors of age, performance status, lactate dehydrogenase (LDH), and leukocyte count to classify patients as low risk (60% to 83% 5-year overall survival [OS]), intermediate (35% to 63% 5-year OS), or high risk (20% to 34% 5-year OS) (Hoster et al, 2008; Hoster et al, 2014).

2.1. First-line Therapy

Most patients require systemic therapy at the time of diagnosis. First-line therapy for MCL typically includes chemotherapy in combination with a CD20 targeting antibody (Table 1). Combination regimens include rituximab with cyclophosphamide, doxorubicin vincristine, and prednisone (R-CHOP); rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP); and bendamustine and rituximab (BR) (Lenz et al, 2005; Kluin-Nelemans et al, 2012; Flinn et al, 2014). Treatment intensification for younger patients with regimens, such as rituximab in combination with fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) alternating with high-dose methotrexate and cytarabine (MA) (R-HyperCVAD/MA) (Romaguera et al, 2005; Romaguera et al, 2010), or high-dose chemotherapy followed by autologous stem cell transplant (autoSCT) in first remission (Dreyling et al, 2005), have led to improved outcomes at the expense of additional toxicity. Despite high initial response rates to these therapies, almost all patients eventually develop progressive disease.

Table 1. Treatment Outcomes in First-line MCL

Regimen	N	Outcome	Reference
R-CHOP v CHOP	122	ORR[1] 94 v 75%; CR 34 v 7%, mTTF = 21 v 14 m	(Lenz et al, 2005)
R-CHOP v R-FC	560	ORR 86 v 78%; CR 34 v 40%; 4 yr OS 62 v 47%	(Kluin-Nelemans et al, 2012)
BR v R-CHOP/R-CVP	74	ORR 94 v 85%; CR 50 v 27%	(Flinn et al, 2014)
R-HyperCAD/MA	97	CR 77%, mTTF= 4.6 y	(Romaguera et al, 2005) (Romaguera et al, 2010)
ASCT v IFN-α in first remission	122	mPFS 39 v 17m; 2 year OS 86 v 82%	(Dreyling et al, 2005)

Abbreviations: ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; IFN-α, interferon-alpha; CR, complete response; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisone; R-FC, rituximab + fludarabine + cyclophosphamide; R-HyperCAD, rituximab + fractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone; m, month; MA, methotrexate + cytarabine; mPFS, median progression-free survival; mTTF, median time-to-treatment failure; ORR, objective response rate; OS, overall survival; y, year.

2.2. Therapy for Relapsed/Refractory MCL

There is no established paradigm for the treatment of r/r MCL. Treatment options includes cytotoxic chemotherapy, proteasome inhibitors, immunomodulatory drugs, tyrosine kinase inhibitors, and stem cell transplant (SCT). The choice of regimen is influenced by prior therapy, comorbidities, and tumor chemosensitivity.

Cytotoxic chemotherapy combination regimens used in r/r MCL include fludarabine, cyclophosphamide (FC), although this regimen is less efficacious in the relapsed setting than as a first-line treatment, and is associated with substantial toxicities (Cohen et al, 2001). For patients with poorer fitness, less intensive therapies are considered based on first-line treatment data, including rituximab alone, chlorambucil, cladribine, or thalidomide, usually in combination with rituximab, but these single cytotoxic agent-based regimens have limited efficacy compared to multi-agent approaches (Foran et al, 2000; Kaufmann et al, 2004; Inwards et al, 2008; Sachanas et al, 2011).

Stem cell transplant has a role in r/r MCL, although its use is limited to those patients who are younger and have good fitness. AutoSCT is more commonly used than allogeneic, and, in eligible patients, results in approximately 25% to 35% event-free survival after 2 to 3 years of follow-up (Ketterer et al, 1997; Vose et al, 2000). Allogeneic stem cell transplant (alloSCT) has been investigated in multiple single institution and registry studies in relapsed and refractory disease, including patients who have previously undergone autoSCT. Results from these studies are variable, likely in part due to selection bias in single institution and registry based studies, but suggest approximately 25% of patients undergoing alloSCT achieve durable remissions if their disease is demonstrated to be chemosensitive prior to transplant (Rajabi and Sweetenham 2015).

However, in these studies, alloSCT has been associated with high morbidity and non-relapse mortality, mostly due to graft versus host disease and its complications and affecting 30% to 40% of patients.

The agents bortezomib, lenalidomide, ibrutinib, and acalabrutinib have been approved in the United States within the last 10 years for the treatment of r/r MCL (see Table 2), and temsirolimus is approved in the EU. Bortezomib is an inhibitor of the 26S proteasome and was evaluated in a single‑arm, open-label, multicenter trial of 155 patients with r/r MCL who had received at least 1 prior therapy (Fisher et al, 2006). Thirty-seven percent had disease refractory to the last treatment regimen. The ORR based on independent radiologic review of computed tomography (CT) scans was 31%, including 6% complete responses. The median duration of response (DOR) was 9.3 months, and the median time to progression was 6.1 months (bortezomib USPI). The most common Grade 3 or greater toxicities were peripheral neuropathy (13%), fatigue (12%), and thrombocytopenia (11%).

Lenalidomide, a second-generation thalidomide derivative, was studied in a single-arm, open-label, multicenter, trial of 134 patients with r/r MCL (Goy et al, 2013). Patients were required to have received prior treatment with an anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib. Fifty-three percent had 4 or more prior therapies, 60% had disease refractory to bortezomib, and 29% had a prior autoSCT. The ORR based on independent radiologic review of CT scans was 26%; 1% achieved a complete response (CR) (lenalidomide USPI). The median DOR was 16.6 months, and the median progression-free survival **(**PFS) was 4 months. The most common Grade 3 or Grade 4 adverse events (AEs) were neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (8%), and fatigue (7%).

Ibrutinib is a covalent inhibitor of Bruton's tyrosine kinase. The safety and efficacy of ibrutinib was evaluated in a single-arm, open-label, multicenter, trial of 111 patients with r/r MCL who had received at least 1, but no more than 5 prior therapies (Wang et al, 2013). The ORR based on investigator review of CT scans was 68%, including 21% complete responses. The median DOR was 17.5 months, and the median PFS was 13.9 months. The most common Grade 3 or higher toxicities were neutropenia (16%), thrombocytopenia (11%), and diarrhea (6%).

Despite available therapies, almost all patients with r/r MCL die from progressive disease (refer to Table 3**)**. Martin et al, conducted a large (n = 114) retrospective cohort study of response and survival in patients treated after primary or acquired ibrutinib resistance (Martin et al, 2016). Of the 104 patients with data available, 73 patients underwent subsequent treatment after stopping ibrutinib, and 61 subjects were evaluable for efficacy. Outcomes were poor, with an ORR of 26%, CR rate of 7%, and median OS of 5.8 months. Cheah et al, reported similar results (ORR 32% and median OS of 8.4 months) in a cohort of 31 patients (Cheah et al, 2015). There are limited other data on the efficacy of bortezomib, lenalidomide, or other agents in patients who have progressed on ibrutinib therapy. There is an urgent unmet need for new treatment options that can induce durable responses in a significant fraction of patients.

Most recently, acalabrutinib, an oral Bruton's tyrosine kinase inhibitor (BTKi), was approved in the US for the treatment of relapsed or refractory MCL (acalabrutinib USPI). This agent was studied in an open-label, multicenter, Phase 2 study of 124 patients with MCL who had at least 1 prior therapy (median 2 prior lines of therapy; range: 1 to 5 prior lines), and those who had

previously been treated with any BTKi were excluded from the study (acalabrutinib USPI ; Wang et al, 2017). Thus, this population was less heavily pretreated compared with patients in the trials of bortezomib, lenalidomide, and ibrutinib. After a median follow-up of 15.2 months, the ORR was 81% and the CR rate was 40% (acalabrutinib USPI). Among all treated patients, the medians for DOR, PFS, and OS were not reached, and the 12-month PFS and OS rates were 67%, and 87%, respectively. The most common Grade 3 and higher AEs were neutropenia (13 patients, 10%), anemia (11 patients, 9%), and pneumonia (6 patients, 5%) (Wang et al, 2017).

Table 2. Outcomes with Available Therapies in r/r MCL

Regimen	N	Outcome	Reference
Bortezomib[a]	155	ORR 31%; CR 8%, DOR 9.3m	(Fisher et al, 2006)
Lenalidomide[b]	134	ORR 26%; CR 7%; DOR 16.6m	(Goy et al, 2013)
Ibrutinib	111	ORR 68%; CR 21%; DOR 17.5m	(Wang et al, 2013)
Acalabrutinib	124	ORR 81%; CR 40%; DOR NR	(Wang et al, 2017)

Abbreviations: CR, complete response; DOR, duration of response; m, month; NR, no response; ORR, objective response rate.
a Retrospective cohort studies of patients with primary or acquired ibrutinib resistant MCL treated with salvage therapy.
b Patients enrolled in this study had not failed ibrutinib.

Table 3. Treatment Outcomes in r/r MCL After Progressing on Ibrutinib

N	Outcome	Reference
61	ORR 26%; CR rate 7%, mOS 5.8m	(Martin et al, 2016)
31	ORR 32% 19% CR rate; mOS 8.4m	(Cheah et al, 2015)

Abbreviations: CR, complete response; m, month; mOS, median overall survival; ORR, objective response rate.

2.3. CD19 and Expression

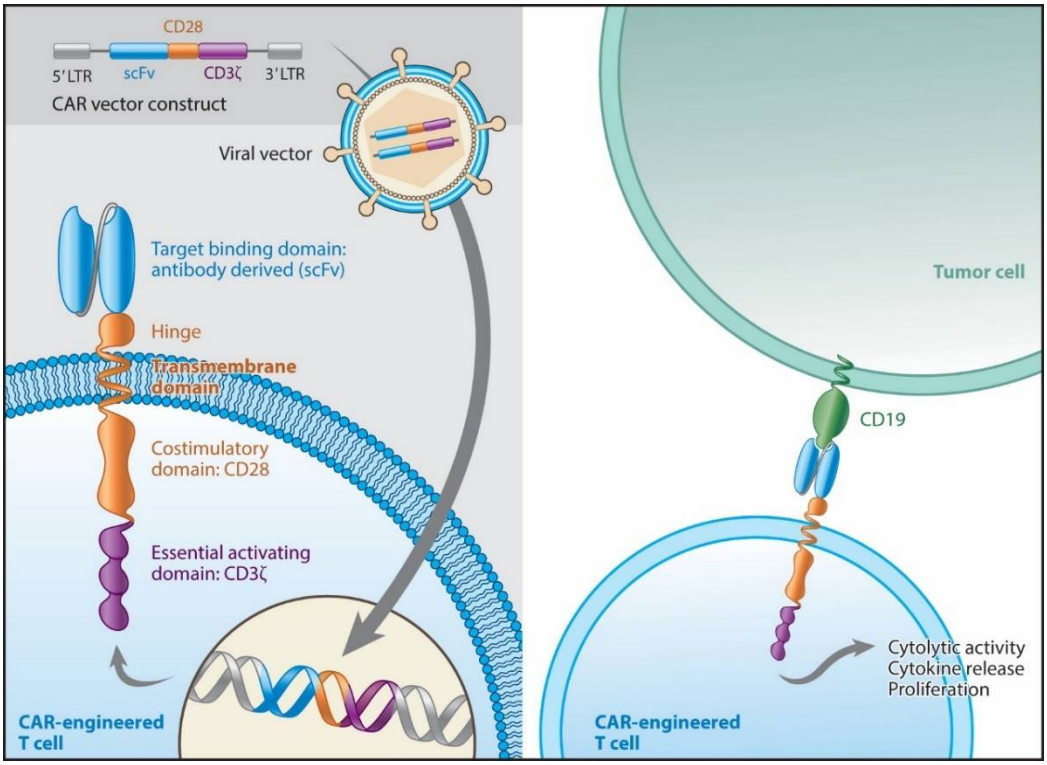
CD19 is a 95 kD transmembrane protein expressed only in the B-cell lineage. It is expressed in all normal B cells starting at the pre-B-cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is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

2.4. 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 with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem.

An anti-CD19 CAR vector construct has been designed, optimized, and initially tested at the Surgery Branch of the National Cancer Institute (NCI; 09-C-0082; IND 13871) (Figure 2)(Kochenderfer et al, 2009; Kochenderfer et al, 2010) is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 (Nicholson et al, 1997)CD19 CAR T cells (Kowolik et al, 2006)-cell activation. These fragments were cloned into the murine stem cell virus-based vector, utilized to genetically engineer the autologous T cells. Treatment with anti-CD19 CAR T cells is currently being administered to subjects with CD19+ B-cell malignancies in ongoing NCI protocol (09-C-0082; IND 13871). The same CAR vector construct will be used in this study. The same CAR vector construct will be used in this study.

Figure 2. Anti-CD19 Chimeric Antigen Receptor



Abbreviations: CAR, chimeric antigen receptor; scFV, single-chain variable region fragment; LTR, long terminal repeat.

2.4.1. Axicabtagene Ciloleucel

Axicabtagene ciloleucel is manufactured for subjects with lymphomas that are characterized as not being associated with circulating tumor cells (ie, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma). Briefly, peripheral blood mononuclear cells (PBMCs) are obtained by leukapheresis and Ficoll separation. PBMCs are activated by culturing with an anti-CD3 antibody in the presence of recombinant 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.

Patients with r/r MCL may have tumor cells in the peripheral blood, which is associated with a poor prognosis (Argatoff et al, 1997). When the first 10 subjects in Cohort 1 were dosed with axicabtagene ciloleucel, it was observed that the incidence and amount of circulating leukemic

phase MCL appeared to be higher than rates that are typically for MCL (Argatoff et al, 1997; Cheah et al, 2015; Cheah et al, 2016). Because the axicabtagene ciloleucel manufacturing process is not optimized to remove circulating tumor cells from the manufacturing process stream, all subsequent patients were dosed using **KTE-X19**.

2.4.2. KTE-X19

KTE-X19 is manufactured for subjects with lymphomas that are characterized by having high numbers of CD19-expressing circulating tumor cells (B-cell acute lymphoblastic leukemia, CLL, and MCL). Briefly, from the leukapheresis product, the T cells in the harvested leukocytes are enriched by binding to magnetic beads coated with anti-CD4 and anti-CD8 antibodies. T cells are activated by culturing with anti-CD3 and anti-CD28 antibodies, and are then transduced with a retroviral vector containing an anti-CD19 CAR gene. These engineered T cells are then propagated in culture to generate a sufficient number of cells for administration.

2.5. Prior Experience with KTE-X19 and Other Anti-CD19 CAR T Cells

Refer to the current **KTE-X19** Investigator's Brochure (IB) for the most current anti-CD19 CAR T cells nonclinical and clinical information.

In regards to ZUMA-2, the interim analysis 2 of Cohort 1 was performed and was reviewed by the Data Safety Monitoring Board (DSMB) for safety and futility. The DSMB recommended that the study proceed without any changes to the study conduct. Only the safety data from this interim analysis are reported in detail below. As of 31 Dec 2017, 28 subjects have been enrolled, treated with conditioning chemotherapy and **KTE-X19** (see Table 4). Four subjects died on study: 3 due to progressive disease and 1 due to an **adverse event** (AE) (organizing pneumonia, which was considered related to conditioning chemotherapy but unrelated to **KTE-X19**).

Table 4. Subject Disposition, Full Analysis Set

	axicabtagene ciloleucel (N=13)	KTE-**X19** (N=28)	Cohort 1 (N=43)
Subjects Enrolled n(%)	13 (100)	28 (100)	43 (100)
Subjects Leukapheresed n(%)	13 (100)	28 (100)	43 (100)
Subjects treated with Conditioning Chemotherapy n(%)	11 (85)	28 (100)	40 (93)
Primary reason for ending study for subjects treated with KTE-X19 n(%)	1 (8)	4 (14)	5 (12)
Death	1 (8)	4 (14)	5 (12)

Note: Percentages are based on number of subjects enrolled.
Data Source: ADSL
Output Source: Table 14.1.2
PROGRAM NAME: t_disp DATE: 12:13/07FEB2018

Table 5 presents an overall summary of treatment-emergent adverse events (TEAEs) in Cohort 1 that were reported by 31 DEC 2017. Twenty-seven subjects (96%) in Cohort 1 **KTE-X19** subjects experienced TEAE(s) of Grade 3 or higher, including 1 Grade 5 event (organizing pneumonia) that is not considered to be **KTE-X19**-related (see Table 6). The most frequently (≥ 10%) reported incidences of Grade 3 or higher TEAEs by preferred terms are summarized in Table 7.

The incidence of cytokine release syndrome (CRS) and neurologic toxicities in the **KTE-X19**-treated subjects in Cohort 1 are also summarized in Table 5. Five subjects (18%) have experienced Grade 3 or Grade 4 CRS, and 13 subjects (46%) have experienced Grade 3 or Grade 4 neurologic toxicities. No Grade 5 (death) CRS or neurologic toxicity has been reported.

Table 5. Overall Summary of AEs, Safety Analysis Set

	axicabtagene ciloleucel (N=10) n (%)	**KTE-X19** (N=28) n (%)	Cohort 1 (N=38) n (%)
Any TEAE	10 (100)	28 (100)	38 (100)
Worst Grade 5	0 (0)	1 (4)	1 (3)
Worst Grade ≥ 3	10 (100)	27 (96)	37 (97)
Any Serious TEAE	8 (80)	22 (79)	30 (79)
Worst Grade 5	0 (0)	1 (4)	1 (3)
Worst Grade ≥ 3	8 (80)	22 (79)	30 (79)
Any TE CRS	10 (100)	27 (96)	37 (97)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	3 (30)	5 (18)	8 (21)
Any TE Neurologic Toxicities infusion	8 (80)	17 (61)	25 (66)
Worst Grade 5	0 (0)	0 (0)	0 (0)
Worst Grade ≥ 3	6 (60)	13 (46)	19 (50)

Abbreviations: TEAE, treatment-emergent adverse event; TE, treatment-emergent.
Note: CRS events were graded by Lee et al 2014. All other events were graded by **Common Terminology Criteria for Adverse Events (**CTCAE) version 4.03.
Treatment-emergent adverse event (TEAE) is an AE with a start date on or after the **infusion** date of **anti-C19 CAR T cells**.
Data Source: ADSL, ADAE
Output Source: Table 14.4.1.0
PROGRAM NAME: T_AE_SUMRY DATE: 12:14/07FEB2018

Table 6. Subject Listing of Deaths, Safety Analysis Set

Subject ID	Age/Sex	Leukapheresis date	Conditioning Chemotherapy start date/ end date	**KTE-X19** infusion date	Death date/ Study Day	Primary cause of death
PPD						Progressive Disease
						Progressive Disease
						Progressive Disease
						Adverse Event (Organizing pneumonia)

Data Source: ADSL, ADAE
Output Source: \\sasprod01\stat_prog\KTE-C19\KTE-C19-102\analysis\C1IA3\program\tfl\output\L_16_6_1_DEATH_SAF_C1
PROGRAM NAME: L_DEATH DATE: 11:28/02MAR2018

Table 7. Subject Incidence of Frequent (≥ 10%) Grade 3 or Higher Treatment-emergent Adverse Events by Preferred Terms and Worse Grade, Safety Analysis Set (n = 28)

MedDRA Preferred Term n(%)	Any Grade 3 or Higher	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any Grade 3 or Higher TE Adverse Event	27 (96)	11 (39)	15 (54)	1 (4)
Anaemia	15 (54)	15 (54)	0 (0)	0 (0)
Platelet count decreased	11 (39)	6 (21)	5 (18)	0 (0)
Neutropenia	10 (36)	7 (25)	3 (11)	0 (0)
Neutrophil count decreased	9 (32)	4 (14)	5 (18)	0 (0)
White blood cell count decreased	8 (29)	4 (14)	4 (14)	0 (0)
Encephalopathy	7 (25)	3 (11)	4 (14)	0 (0)
Hypertension	5 (18)	5 (18)	0 (0)	0 (0)
Acute kidney injury	4 (14)	1 (4)	3 (11)	0 (0)
Confusional state	4 (14)	4 (14)	0 (0)	0 (0)
Aphasia	3 (11)	3 (11)	0 (0)	0 (0)
Hypotension	3 (11)	2 (7)	1 (4)	0 (0)
Hypoxia	3 (11)	1 (4)	2 (7)	0 (0)
Pneumonia	3 (11)	3 (11)	0 (0)	0 (0)
Pyrexia	3 (11)	3 (11)	0 (0)	0 (0)
Respiratory failure	3 (11)	1 (4)	2 (7)	0 (0)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TE, treatment-emergent.
Note: Preferred terms are sorted in descending order of total frequency count.
Adverse events are coded using MedDRA Version 19.0 and graded per CTCAE 4.03.
Percentages are calculated using the total number of subjects in the treatment group as the denominator.
Data Source: ADSL, ADAE
Output Source: \\sasprod01\stat_prog\KTE-C19\KTE-C19-102\analysis\C1IA3\program\tfl\output\T_14_3_8_1_2_G3_TEAE_SAF_XLP
PROGRAM NAME: T_G3_TEAE DATE: 11:25/02MAR2018

2.6. KTE-X19

Kite Pharma, Inc., (hereafter referred to as Kite) is developing an eACT™ (**KTE-X19**) that targets CD19 expression on B-cell malignancies. The CAR vector construct is identical to the one used in the NCI protocol (09-C-0082; IND 13871). Kite, in conjunction with the NCI Surgery Branch, has developed a rapid, closed, and bead-less process for the generation of the anti-CD19 CAR T cells. Closing the process retains the characteristics of the T-cell product (Better et al, 2014). Refer to the current IB for more details.

3. STUDY DESIGN

3.1. General Study Design

Study KTE-C19-102 is a Phase 2, multicenter, open-label study evaluating the safety and efficacy of **KTE-X19** in subjects with r/r MCL.

This study is designed to examine the safety and efficacy of **KTE-X19** in patients who have r/r MCL that has progressed on prior chemotherapy, anti-CD20 antibody, and ibrutinib **or acalabrutinib**. The study will evaluate the ORR and durability of response after treatment with **KTE-X19**. An open-label, 2-cohort design is used, with a target ORR in the alternative hypothesis of 50% and a futility criterion that the ORR is no more than 25%. Up to approximately 130 subjects with r/r MCL in total will be enrolled and treated to evaluate the efficacy of **KTE-X19**. Cohort 1 will treat up to approximately 90 subjects at a target dose of CCI [redacted] cells/kg, including up to approximately 80 **KTE-X19** subjects and 10 axicabtagene ciloleucel subjects. The Cohort 1 **KTE-X19** subjects will form the basis for statistical hypothesis testing on the primary endpoint. Cohort 2 will treat up to 40 **KTE-X19** subjects at a target dose of CCI [redacted] anti-CD19 CAR T cells/kg.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Bridging therapy, if applicable
- Conditioning chemotherapy
- Investigational product (IP) treatment
- Post-treatment assessment
- Long-term follow-up (LTFU)

An independent DSMB will review safety and/or efficacy data 4 times during this study. The DSMB will first meet to review safety data when 10 Cohort 1 subjects have been enrolled and treated with anti-CD19 CAR T cells and followed for 30 days. The DSMB will meet for the second time to review safety and efficacy data after 20 Cohort 1 subjects have been enrolled and treated with anti-CD19 CAR T cells and have had the opportunity to complete the 3-month disease assessment. The DSMB will meet for the third time to review both safety and efficacy data after 10 subjects in Cohort 2 have been enrolled and treated with **KTE-X19** and have had the opportunity to be followed for 30 days. The DSMB will meet for the fourth time to review safety data after 44 subjects in Cohort 1 have been enrolled and treated with anti-CD19 CAR T cells and have had the opportunity to be followed for at least 30 days, with focus on the safety data from the 6 **KTE-X19** subjects treated most recently in this cohort. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk vs benefit. The DSMB may meet more often as needed.

For details surrounding the DSMB, refer to Section 9.10 and Section 9.11.

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

A study schema is included in Figure 1.

3.2. Participating Sites

Approximately 40 centers located in North America and Europe will participate in this study. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

Sites that do not enroll a subject within 3 months of their site being activated, will be considered for closure.

3.3. Number of Subjects

Participants in this trial will be referred to as "subjects." It is anticipated that up to approximately 130 subjects will be enrolled and treated in this study.

It should be noted that Kite may choose to close enrollment at any time. Refer to Section 10 for statistical considerations of the protocol, including sample size estimations.

3.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified numbers of subjects are attained in the modified intent-to-treat (mITT) set. Subjects who have not received the target dose of anti-CD19 CAR T cells will be retained in the analyses of disposition and safety, where appropriate (refer to Section 10.5).

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary. For a subject who completes the entire protocol from the date of informed consent through the completion of the LTFU period, the duration of the study will take approximately 15 years to complete. However, individual study duration will vary depending on a subject's screening requirements, response to treatment, and survival.

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

3.5.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes the LTFU period visit, is considered lost to follow-up, withdraws consent, or dies.

4. SUBJECT SCREENING AND ENROLLMENT

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

Each subject who enters the screening period, which starts when the subject signs the informed consent form, will receive a unique subject identification **(**ID**)** number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. The subject identification will never be changed even if the subject is rescreened.

Furthermore, the subject ID number must remain constant throughout the entire clinical study; it must not be changed after enrollment or if the subject is rescreened or retreated.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

101) Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or presence of t(11;14)

102) Up to 5 prior regimens for MCL. Prior therapy must have included:

- Anthracycline or bendamustine-containing chemotherapy, and
- Anti-CD20 monoclonal antibody therapy, and
- Ibrutinib or acalabrutinib

103) Relapsed or refractory disease, defined by the following:

- Disease progression after last regimen, or
- Refractory disease is defined failure to achieve a partial response (PR) or CR to the last regimen

104) At least 1 measurable lesion. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

- If the only measurable disease is lymph node disease, at least 1 lymph node should be ≥ 2 cm

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

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

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

108) Age 18 years or older

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

110) Absolute neutrophil count (ANC) ≥ 1 000/uL

111) Platelet count ≥ 75 000/uL

112) Absolute lymphocyte count ≥ 100/uL

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

- Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min
- Serum alanine aminotransferase/aspartate aminotransferase ≤ 2.5 upper limit of normal (ULN)
- Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome
- Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings
- No clinical significant pleural effusion
- Baseline oxygen saturation > 92% on room air

114) 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 nonmelanomatous skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease-free for at least 3 years

202) AutoSCT within 6 weeks of planned **KTE-X19 or axicabtagene ciloleucel** infusion

203) History of allogeneic stem cell transplantation

204) Prior CD19 targeted therapy with the exception of subjects who received **KTE-X19 or axicabtagene ciloleucel** in this study and are eligible for re-treatment

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

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

207) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite medical monitor

208) History of human immunodeficiency virus (HIV) infection or acute or chronic active hepatitis B or C infection. Subjects with a history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing.

209) Presence of any in-dwelling line or drain (eg, percutaneous nephrostomy tube, in-dwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Ommaya reservoirs and dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted.

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

211) History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement

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

213) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

214) History of symptomatic deep vein thrombosis or pulmonary embolism within the last 6 months of enrollment

215) Possible requirement for urgent therapy due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome)

216) Primary immunodeficiency

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

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

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

220) Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant

221) Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of **KTE-X19 or axicabtagene ciloleucel infusion**

222) 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.

223) History of autoimmune disease (eg Crohn's disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

6. PROTOCOL TREATMENT

6.1. Treatment Terminology

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

- Bridging therapy, if administered, after discussion with the medical monitor will be dexamethasone, ibrutinib, or acalabrutinib.
- The conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The IP for this study is named **KTE-X19 and axicabtagene ciloleucel**.
- The term study treatment refers to all protocol-required therapies.

6.2. Study Treatment

6.2.1. Bridging Therapy

Bridging therapy will be supplied by the investigative site unless otherwise noted. Sites should refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management. At the discretion of the investigator and after discussion with the medical monitor, bridging therapy may be considered for any subject, particularly those with high disease burden at screening (eg, > 25% marrow involvement and/or ≥ 1000 leukemic phase mantle cells/mm^3 in the peripheral circulation).

Bridging therapy is to be administered after leukapheresis and must be completed at least 5 days prior to initiating conditioning chemotherapy.

CCI [redacted]

If bridging therapy is administered, the subject must undergo another **positron emission tomography-computed tomography (**PET-CT**)** to assess disease status prior to receiving conditioning chemotherapy and subsequent **anti-CD19 CAR T cells** infusion.

6.2.2. Conditioning Chemotherapy

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

Subjects will receive a non-myeloablative conditioning regimen consisting of CCI [redacted] to induce lymphocyte depletion and create an optimal environment for expansion of **anti-CD19 CAR T cells** in vivo. **Conditioning chemotherapy should only commence when the product is available, if required by country regulatory agencies.**

6.2.2.1. Fludarabine

Fludarabine phosphate (hereafter, fludarabine) 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.

6.2.2.2. Cyclophosphamide

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

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

6.2.2.3. 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 will be administered around the cyclophosphamide dose according to institutional standards. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.2.3. KTE-X19

Refer to the current version of the IB regarding **KTE-X19** and related clinical experience. Refer to the Investigational Product Manual for details and instruction on storage and administration of **KTE-X19**.

KTE-X19 is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing **KTE-X19** 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.

KTE-X19 is a subject-specific product, and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of **KTE-X19** infused, the thaw start/stop time, and **KTE-X19** administration start/stop time will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion. Refer to the Investigational Product Manual for details and instruction on storage, thawing, and administration of **KTE-X19**.

If any problems related to the use of **KTE-X19** or any products that support the management of **KTE-X19** (eg, cryostorage bags, subject identification labels) required in this study are identified, refer to the current Investigational Product Manual for information regarding issue reporting and resolution.

6.2.3.1. Dose Rationale

This study is designed to evaluate safety:efficacy of two anti-C19 CAR T cell doses, both of which are administered after the same lymphodepleting regimen. CCI [redacted]

The recommended treatment regimen for Cohort 1 CCI [redacted] is based on the favorable safety:efficacy profile seen in the ZUMA-1 trial—a Phase 1/2 multicenter study investigating the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL, which met its primary endpoint with an ORR of 82% and CR rate of 54% (Locke et al, 2017).

At the time of the interim analysis **3**, 13 subjects (46%) had experienced Grade 3 or Grade 4 neurologic toxicities (Section 2.5). A pharmacokinetic analysis of **KTE-X19** in subjects dosed with **KTE-X19** in ZUMA-2 Cohort 1 (data cutoff: **15 June 2017**) demonstrated an approximate 3- to 4-fold higher peak expansion and cumulative exposure (**area under curve** (AUC_{0-28}) relative to that seen in subjects treated in ZUMA-1). Given that CAR T cell peak and AUC_{0-28} are associated with Grade 3 or higher neurologic toxicities in ZUMA-1 patients (Neelapu et al, 2016), the sponsor opted to reduce the KTE-**X**19 target dose to CCI [redacted] anti-CD19 CAR T cells/kg to evaluate safety:efficacy of a lower dose. Therefore, subjects enrolled into ZUMA-2 Cohort 2 are administered a target dose of CCI [redacted] anti-CD19 CAR T cells/kg, with a maximum dose of CCI [redacted] anti-CD19 CAR T cells for subjects ≥ 100 kg.

6.2.4. Concomitant Therapy

Investigators may additionally prescribe any other concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF) and routine anti-emetic prophylaxis and treatment except those medications listed in the excluded medication Section 6.2.5.

All concurrent therapies, including medications, intubation, dialysis, oxygen, and blood products, should be recorded from the date of the informed consent through 3 months after completing treatment with **anti-CD19 CAR T cells**. After 3 months of follow-up, only targeted concomitant medication will be collected for 24 months after **anti-CD19 CAR T cells** infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

For subjects who are enrolled, but not dosed with **anti-CD19 CAR T cells**, concurrent therapies will only be recorded from the date of the informed consent through 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy). For subjects who are not enrolled (eg, screen failure or not leukapheresed), only concurrent therapies related to any serious adverse events (SAEs) will be recorded.

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

6.2.5. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to **anti-CD19 CAR T cells** administration unless used for bridging therapy (refer to Section 6.3.2).

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after **anti-CD19 CAR T cells** administration unless used to manage **anti-CD19 CAR T cell** related toxicities (refer to Section 6.4). Other medications that may interfere with evaluation of the IP, such as non-steroidal anti-inflammatory agents, should also be avoided for the same time period unless medically necessary.

Treatment for the subject's lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited except as needed for treatment of disease progression after **anti-CD19 CAR T cells** infusion. If permissibility of a specific medication/treatment is in question, contact the Kite medical monitor.

6.2.6. Subsequent Therapy

Subsequent therapy administered after **anti-CD19 CAR T cells** infusion for a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as SCT and radiation therapy, must be documented until subject completes the LTFU period, is considered lost to follow-up, withdraws consent, or dies.

6.3. Study Treatment Schedule

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

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells [WBCs]) for the manufacturing of **KTE-X19 or axicabtagene ciloleucel**. Leukapheresed cells obtained at participating centers will be shipped to the cell processing facility (CPF) overnight as described in the Investigational Product Manual.

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

Upon arrival at the CPF, each subject's leukapheresed product will be processed to enrich for the T cell containing PBMC fraction. T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the IP per CPF standard operating procedures (SOPs). After the product has passed certain release tests, it will be shipped back to the treating facility. Following completion of each subject's conditioning chemotherapy regimen, subjects will receive their respective **KTE-X19 or axicabtagene ciloleucel** infusion.

6.3.2. Bridging Therapy (Administered after Leukapheresis and Completed at Least 5 Days Prior to Initiating Conditioning Chemotherapy)

At the discretion of the investigator and after discussion with the medical monitor, bridging therapy may be considered for any subject, particularly those with high disease burden at screening (eg, > 25% marrow involvement and/or ≥ 1000 leukemic phase mantle cells/mm^3 in the peripheral circulation).

Bridging therapy is to be administered after leukapheresis and must be completed at least 5 days prior to initiating conditioning chemotherapy.

CCI [redacted]

If bridging therapy is administered, the patient must undergo another PET-CT to assess disease status prior to receiving conditioning chemotherapy and subsequent **anti-CD19 CAR T cells** infusion.

6.3.3. Cyclophosphamide and Fludarabine (Days –5 Through –3 Before Infusion of anti-CD19 CAR T cells)

Subjects will receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine to induce lymphocyte depletion and create an optimal environment for expansion of **anti-CD19 CAR T cells** in vivo. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine CCI [redacted] before the receiving **anti-CD19 CAR T cells**. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

The 3-day conditioning regimen of fludarabine and cyclophosphamide is described below. Hydration for cyclophosphamide may alternatively be performed according to local institutional guidelines.

- IV hydration with 1 L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500 mg/m^2 IV over approximately 60 minutes followed by:
- CCI [redacted]
- CCI [redacted]
- 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. Another balanced crystalloid solution (such as Ringer's lactate) can be used in place of 0.9% NaCl if deemed more appropriate in the investigator's opinion.

6.3.3.1. Dosing Rationale

Administration of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy (Dudley et al, 2008). Specifically, there appears to be a link between adequate lymphodepletion and adoptively-transferred T-cell expansion and function. The depth and duration of the lymphodepletion in pre-clinical models correlate with the anti-tumor activity of the adoptively-transferred, tumor-specific CD8$^+$ T cells (Gattinoni et al, 2005). Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating regulatory T cells, or enhancing the activation of antigen-presenting cells (Klebanoff et al, 2005). Combined treatment with cyclophosphamide and fludarabine represents a potent lymphodepleting regimen. The ZUMA-1 study of axicabtagene ciloleucel in aggressive large B-cell lymphoma used the same cyclophosphamide/fludarabine conditioning regimen that is being used in the ZUMA-2 study (axicabtagene ciloleucel USPI). This regimen was tolerated prior to infusion of the cellular product and resulted in a favorable risk-benefit profile. Similar doses of cyclophosphamide and fludarabine have been administered to subjects with B-cell malignancies prior to anti-CD19 CAR T cell infusion (NCI Protocol 09-C-0082) (Kochenderfer et al, 2016) and were shown to increase levels of cytokines known to support T-cell expansion and survival (Kochenderfer et al, 2017). This treatment combination was also used as a reduced non-myeloablative conditioning regimen for patients with B-cell malignancies who were undergoing alloSCT and resulted in tolerable toxicities (Khouri et al, 1998).

6.3.4. KTE-X19 or axicabtagene ciloleucel (Day 0, after Fludarabine and Cyclophosphamide)

All subjects will be hospitalized to receive treatment with **KTE-X19 or axicabtagene ciloleucel** followed by an observation period of at least 7 days **unless otherwise required by country regulatory agencies (refer to Section 18.3)**.

The following pre **anti-CD19 CAR T cells** infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the Kite medical monitor.

- Acetaminophen 650 mg PO (500 mg to 1000 mg in EU)
- Diphenhydramine 12.5 mg to 25 mg IV or 25 mg PO

Subjects in Cohort 1 will receive **anti-CD19 CAR T cells** treatment consisting of a single infusion of CAR-transduced autologous T cells administered intravenously at a target dose of CCI anti-CD19 CAR T cells/kg. A minimum dose of CCI anti-CD19 CAR T cells/kg may be administered for subjects in Cohort 1. Subjects in Cohort 2 will receive **KTE-X19** treatment consisting of a single infusion of CAR-transduced autologous T cells administered intravenously at a target dose of CCI anti-CD19 CAR T cells/kg. For subjects weighing > 100 kg, a maximum flat dose of CCI anti-CD19 CAR T cells will be administered for Cohort 1 or CCI anti-CD19 CAR T cells for Cohort 2. Refer to the Investigational Product Manual for all details surrounding the dosing of **anti-CD19 CAR T cells**.

Subjects will remain in the hospital through Day 7 after treatment with **anti-CD19 CAR T cells**. Subjects should not be discharged from the hospital until all **anti-CD19 CAR T cells**-related non-hematological toxicities return to Grade ≤ 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg, renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing **anti-CD19 CAR T cells**-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1, or if deemed necessary by the treating investigator.

6.4. Toxicity Management

To date, the following important risks have been identified with **KTE-X19 and axicabtagene ciloleucel**: CRS, neurologic toxicity, infections, and cytopenias. Refer to Section 6 of the current IB for details regarding these events and management guidance.

As the safety experience with **KTE-X19** increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the **KTE-X19** IB for guidance regarding managing **KTE-X19** related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with **KTE-X19**, as well as possible complications associated with malignancy and cancer treatment.

7. STUDY PROCEDURES

Research staff should refer to the SOAs (Table 8 and Table 9) for an outline of the procedures required. The visit schedule is calculated from **anti-CD19 CAR T cells** 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 informed consent form (ICF) prior to any study-specific activity or procedure is performed.

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

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

7.2. Demographic Data

Demographic data will be collected to include sex, age, race, 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 AE reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

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

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

7.4. Physical Exam, Vital Signs, Performance Status, and European Quality of Life-5 Dimensions

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 AE.

During IP administration/hospitalization, vital signs, including blood pressure, heart rate, oxygen saturation, and temperature, will be monitored before and after the **anti-CD19 CAR T cells** infusion and then routinely (every 4 to 6 hours) while hospitalized. If the subject has a fever (temperature 38.3°C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

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

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

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

7.5. Neurological Assessment

Neurological assessments will be standardized by using the Mini-Mental State Examination (MMSE) standard version 2.0. The MMSE is a 5 to 10 minute, 11-question measure that examines various areas of cognitive function: orientation, attention, immediate recall, short-term recall, language, and the ability to follow simple verbal and written commands.

The MMSE is divided into 2 sections. The first part requires vocal responses to the examiner's questions. In the second part of the exam, the subject is asked to follow verbal and written instructions, write a sentence spontaneously, and copy a geometric figure.

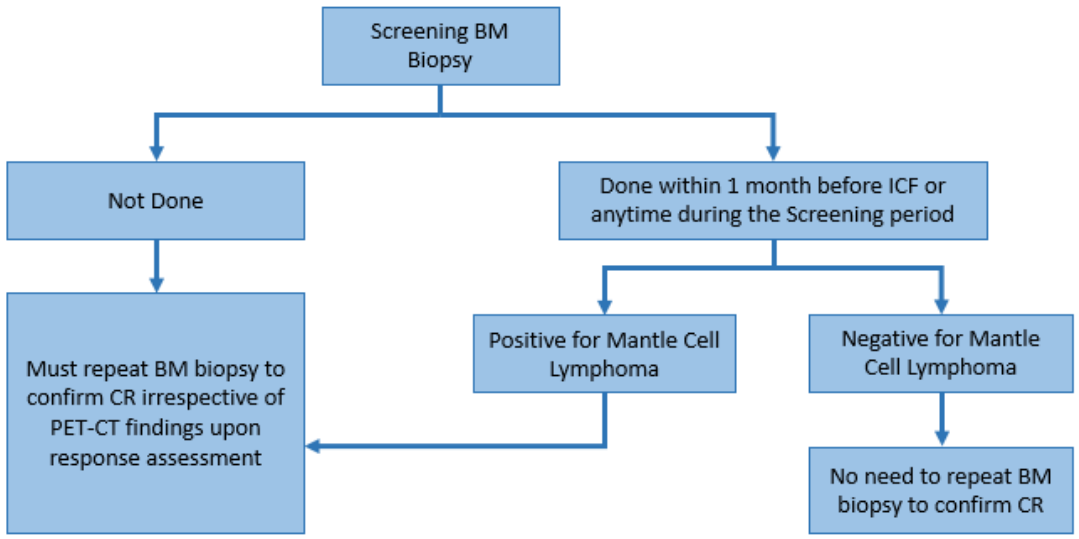
A full neurological assessment will be completed during screening to establish a baseline. For subjects enrolled in Cohort 1, subsequent post-baseline assessments will be performed before **anti-CD19 CAR T cells** administration on Day 0, Day 1, Day 3, Day 5, Day 7, and every other day while hospitalized, as well as on Day 28 and Month 3. For subjects enrolled in Cohort 2, a subsequent post-baseline assessment will be performed on Day 28. If the assessment shows neurologic function has not returned to baseline (± 3 points) on Day 28, then the MMSE will continue to be performed at Month 3 and every 3 months until the results have returned to baseline (± 3 points) or until Month 24.

Every attempt should be made to dedicate a single research staff member familiar with or trained in the administration of the MMSE to conduct the assessment to minimize inter-rater variability. If CNS symptoms persist, continue to perform the MMSE every 2 days until resolution of symptoms or discharged from the hospital.

7.6. Bone Marrow Biopsy

A bone marrow aspirate/biopsy will be performed at screening, if not previously performed within 4 weeks of signing consent, to assess bone marrow involvement. The bone marrow aspirate and biopsy will be assessed and confirmed for the presence of MCL. Subjects with a positive bone marrow at screening or those who do not have a baseline bone marrow biopsy available, must undergo another bone marrow aspirate and biopsy upon first determination of a complete response via PET. Subjects with a negative bone marrow aspirate/biopsy (ie, no MCL) at screening, and patients with a partial metabolic response, stable disease (SD) or progressive disease (PD) at any disease response assessment time point do not require a follow-up bone marrow aspirate and biopsy (Figure 3)

Figure 3. Bone Marrow Assessment Schema



Abbreviations: BM, bone marrow; ICF, informed consent form; PET-CT, positron emission tomography-computed tomography; CR, complete response.

To confirm a CR, 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. **After CR is confirmed by bone marrow biopsy, additional bone marrow biopsies are only required in case of clinical suspicion of disease progression in the bone marrow only.** Refer to Section 7.8, Appendix 1 (Section 18.1), and Appendix 2 (Section 18.2) for treatment response assessment requirements per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson et al, 2007) and Lugano Classification (Cheson et al, 2014).

Bone marrow aspirate/biopsy should also be considered to evaluate hemophagocytic lymphohistiocytosis (HLH) as indicated (refer to the current IB). A portion of the bone marrow sample collected to evaluate HLH or other toxicities should be submitted to the central laboratory as outlined in the central laboratory manual.

7.7. Lumbar Puncture

Subjects with symptoms of central nervous system malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture performed at the screening visit for examination of cerebral spinal fluid. In addition, lumbar puncture should be performed as applicable for subjects with new onset of ≥ Grade 2 neurologic toxicities after **anti-CD19 CAR T cells** infusion (refer to the current IB). Adequate platelet support should be provided prior to performing a lumbar puncture (eg, platelet $> 50\ 000/mm^3$).

CCI [redacted]

7.8. Disease Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. For subjects enrolled in Cohort 1, disease assessments will be evaluated per the revised IWG Response Criteria for Malignant Lymphoma as described in Appendix 1 (Section 18.1) (Cheson et al, 2007). Flow cytometric, molecular, or cytogenetic studies will not be used to determine response. For subjects enrolled in Cohort 2, disease assessments by the site investigator will be evaluated per the Lugano Classification, as described in Appendix 2 (Section 18.2) (Cheson et al, 2014).

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 **anti-CD19 CAR T cells** infusion planned PET-CT tumor assessment 4 weeks following the **anti-CD19 CAR T cells** infusion and at regular intervals as highlighted in the SOA during the post-treatment and LTFU portion of the study.

Post **anti-CD19 CAR T cells** 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, as described in Appendix 1 (Section 18.1) and Appendix 2 (Section 18.2). Per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) and Lugano Classification (Cheson et al, 2014), a bone marrow aspirate and biopsy must be performed 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. Furthermore, if bone marrow involvement before the start of the study was unknown, a bone marrow evaluation must be conducted to confirm a CR. The bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology, it must be negative by immunohistochemistry to assign a CR to treatment.

In addition to the investigator's assessment, Independent Radiology Review Committee (IRRC) review per Lugano Classification **(**Cheson et al, 2014) will be performed for both Cohort 1 and Cohort 2. PET-CT scans of all subjects evaluated for disease response will be submitted to and reviewed by an independent central reviewer. For subjects who discontinue the study due to an assessment of progressive disease, any additional imaging data, subsequent to the image in question, will be submitted to the central reviewer to confirm disease status.

If the subject is eligible for retreatment with **KTE-X19**, the last scan prior to retreatment will be considered the baseline for the purpose of evaluating the response to retreatment.

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

7.9. Cardiac Function

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

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

7.10. Magnetic Resonance Imaging

Each subject will undergo a screening brain MRI, with contrast whenever possible or without contrast in case of contraindication, to rule out CNS metastasis during the screening period of the study. Evaluation of any new onset of ≥ Grade 2 neurologic toxicity should include a brain MRI as described in the current IB.

7.11. Laboratory

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

- Local lab analysis:
  - — Sodium, potassium, chloride, total bicarbonate, creatinine, glucose, blood urea nitrogen or urea (if blood urea nitrogen test cannot be analyzed by the local lab), albumin, calcium total magnesium total, inorganic phosphorus, alkaline phosphatase, **alanine aminotransferase/glutamic-pyruvic transaminase (**ALT/GPT**)**, **aspartate aminotransferase/glutamic-oxaloacetic transaminase (**AST/GOT**)**, total bilirubin, direct bilirubin, LDH, uric acid

— C-reactive protein (CRP) with chemistry panel

— Complete blood count (CBC) with differential

A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study and the result is positive, the investigator should contact the Kite 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 medical monitor for instructions.

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

- Central lab analysis:

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

  — Serum samples will also be drawn for anti-**CD19 CAR** antibodies and human anti-bovine antibodies

    ■ For serum samples that demonstrate increased anti-**CD19 CAR** antibodies at the Month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first.

  — Archived tumor tissue will be collected for central path review and evaluation of prognostic markers specific for MCL and pertaining to the tumor immune environment. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. CCI [redacted]

  — CSF and possibly bone marrow samples will also be collected and analyzed at the central laboratory as outlined in the schedule of assessments and per Section 7.11.1.

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

7.11.1. Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for **anti-CD19 CAR T cells**. Prognostic markers specific for MCL and related to the tumor immune environment may also be evaluated in archived and fresh tumor biopsies.

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

Levels of serum cytokines will also be evaluated in the blood. The following cytokines may be included in the panel: CCI [redacted]

Cerebral spinal fluid (CSF), as well as any additional subject samples (eg, pleural fluid), should be collected from subjects who develop a neurologic toxicity or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable, lymphocyte populations residing in the CSF or other additional subject samples may also be monitored for the purpose of understanding the safety profile of **KTE-X19**.

CCI [redacted]

Because **anti-CD19 CAR T cells** comprises retroviral vector transduced T cells, the presence of RCR in the blood of treated subjects will be monitored.

In addition, baseline leukapheresis and final **anti-CD19 CAR T cells** samples will be banked and may be analyzed by immunophenotyping, qPCR, and/or gene expression profiling. CCI [redacted].

Archived tumor tissue will be collected for central pathologic review and evaluation of prognostic markers specific for MCL and pertaining to the tumor immune environment. Additional analysis may include CD19 expression, gene expression profiling, and analysis of somatic DNA alterations. CCI [redacted].

CCI [redacted]

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

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

7.12. 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 enrollment. Informed consent must be obtained before completion of any study-specific procedures. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA.

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled into the study. If, at any time prior to enrollment, the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure 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
- EQ-5D questionnaire (prior to any other assessments/procedures being performed)
- Physical examination, including height and weight
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
    - Subjects with symptoms of central nervous system malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture for examination of cerebral spinal fluid.

- ECOG performance status
- Neurological assessment with MMSE
- ECG
- LVEF (ECHO) and pericardial effusion assessment (ECHO)
- Imaging studies
  - Brain MRI
  - Baseline PET-CT of the neck, chest, abdomen, and pelvis
    - PET-CT performed following the subject's last line of therapy and prior to signing the consent may be used for confirmation of eligibility
    - If PET-CT will be > 28 days at the initiation of conditioning chemotherapy or if the subject receives any anti-cancer therapy between screening and conditioning chemotherapy (including bridging therapy), the scans must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible.
- Bone marrow aspirate/biopsy as needed (if not done within 4 weeks prior to screening)
- Labs
  - β-HCG pregnancy test (serum or urine) on all women of childbearing potential
  - Chemistry panel with CRP
  - CBC with differential
- SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- CCI [redacted]

7.12.2. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the 28-day screening period will be permitted to rescreen one time. Subjects will retain the same subject ID number that was assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, only the procedure(s)/assessment(s) that did not originally meet the eligibility criteria 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 original informed consent, subjects must be re-consented 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.

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

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

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

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

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Weight
- Labs (to be drawn prior to leukapheresis, on the day of or day before leukapheresis)
  - Chemistry panel
  - CRP; if CRP is ≥ 100 mg/L, a call must be made to the Kite medical monitor before proceeding with conditioning chemotherapy.
  - CBC with differential
  - Cytokine levels
  - Anti-**CD19 CAR** antibodies
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells)
- Leukapheresis
- AE/SAE reporting
- Concomitant medications documentation

7.12.4. Bridging Therapy

If prescribed, bridging therapy with either a corticosteroid or ibrutinib (or acalabrutinib) must be administered after leukapheresis and completed at least 5 days prior to initiating conditioning chemotherapy (refer to Section 6.3.2). If bridging therapy is administered, PET-CT scans (and bone marrow aspirate/biopsy, if applicable) must be repeated prior to the start of conditioning chemotherapy to establish a new baseline.

- AE/SAE reporting
- Concomitant medications documentation

7.12.5. Conditioning Chemotherapy Period

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

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

7.12.5.1. Requirements for Initiating Conditioning Chemotherapy

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

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the workup listed in Section 7.12.7 must be performed to determine the potential cause if there is no identified source of infection.

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

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy.
- Complete history and physical exam, including head, ears, eyes, nose, and throat (HEENT) exam; cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of antimicrobials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator and in consultation with infectious disease service (if applicable).
- The most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, polymerase chain reaction (PCR), stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

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

7.12.5.2. Conditioning Chemotherapy Administration

The following procedures will be completed during CCI [redacted] at the time points outlined in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy)
  - Chemistry panel with CRP
  - CBC with differential
- Fludarabine and cyclophosphamide administration
- AE/SAE reporting
- Concomitant medications documentation

7.12.6. Investigational Product Treatment Period

Subjects will be hospitalized to receive treatment with **anti-CD19 CAR T cells** followed by a minimum 7-day observation period **unless otherwise required by country regulatory agencies (refer to Section 18.3)**.

7.12.6.1. Requirements for Initiating **KTE-X19** Infusion

If any of the following criteria are met prior to the initiation of **KTE-X19** infusion, then the workup listed in Section 7.12.7 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature **>** 38° Celsius within 72 hours of **KTE-X19** infusion
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- WBC count or WBC differential, which is suggestive of infectious process, and is observed between enrollment and the initiation of **KTE-X19** infusion (eg, WBC > 20 000/μL, rapidly increasing WBC, or differential with high percentage of segs/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of **KTE-X19** infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with **KTE-X19** infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam, including HEENT exam, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems, must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before **KTE-X19** infusion (prophylactic use of antimicrobials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (if applicable).
- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

After the above criteria are met, then the subject can proceed with administration of **KTE-X19**.

If the **KTE-X19** infusion is delayed > 2 weeks, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

7.12.6.2. Hospitalization for KTE-X19 Infusion

Subjects will remain in the hospital through Day 7 after treatment with **anti-CD19 CAR T cells unless otherwise required by country regulatory agencies (refer to Section 18.3)**. Subjects should not be discharged from the hospital until all **anti-CD19 CAR T cells**-related non-hematological toxicities return to Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg, renal insufficiency) even if > Grade 1 if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing **anti-CD19 CAR T cells**-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 a neurologic toxicity in the outpatient setting after discharge, subjects and their family members/caregivers should be educated on potential symptoms of these syndromes such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the principal investigator or seek immediate medical attention.

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

- Neurological assessment including MMSE
  - MMSE will be administered before treatment with **anti-CD19 CAR T cells** on Day 0, then on Day 1, and every other day while hospitalized for subjects enrolled in Cohort 1. MMSE will not be administered during the investigational treatment period for subjects enrolled in Cohort 2.
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature, every 4 to 6 hours during hospitalization
- Labs (before **anti-CD19 CAR T cells** infusion, as described in the SOA)
  - Chemistry panel with CRP
  - CBC with differential
  - Cytokine levels
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis)

- Infusion of **KTE-X19 or axicabtagene ciloleucel**
- CCI [redacted]
- CCI [redacted]
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

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

7.12.7. Requirements to Work Up Potential Infectious and/or Inflammatory States

In the absence of an identified source of infection (eg, line infection, pneumonia on chest x-day), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or **KTE-X19** consists of:

- Call Kite medical monitor
- Infectious Disease service consult (if available)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x2 bottles each) and UA and urine culture. Deep/induced sputum culture if clinically indicated.
  - All indwelling lines such as central venous catheters should be examined for any signs of infection and additional cultures should be drawn from the line
  - Nasopharyngeal-throat swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)
  - Collection of appropriate serum viral studies (eg, **cytomegalovirus** [CMV])

- If a central nervous system process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed
- Any additional sign or symptom-directed investigation should be performed as clinically indicated

Prior to proceeding with conditioning chemotherapy and/or **KTE-X19** infusion, the above workup must not suggest the presence of an active infection, and all requirements for conditioning chemotherapy and/or **KTE-X19** infusion must be satisfied. If the **KTE-X19** infusion is delayed > 2 weeks following conditioning chemotherapy, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

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

7.12.8. Post-treatment Assessment Period

After completing **anti-CD19 CAR T cells** infusion and being discharged from the hospital, all subjects will be followed in the post-treatment assessment period. Counting from Day 0 (**anti-CD19 CAR T cells** infusion), subjects will return to the clinic at the following intervals.

- Week 2 (± 2 days)
- Week 4 (± 3 days)
- Month 2 (± 1 week)
- Month 3 (± 1 week)

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

- EQ-5D questionnaire prior to any other assessments/procedures being performed.
- Neurological assessment including MMSE. For subjects enrolled in Cohort 1, the MMSE will be performed on Week 4 and Month 3. For subjects enrolled in Cohort 2, the MMSE will be performed on Day 28. If the assessment has not returned to baseline (± 3 points) on Day 28, then continue to perform the MMSE at Month 3 and every 3 months until the results have returned to baseline (± 3 points) or until Month 24.
- PET-CT for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated. Refer to the current version of the imaging site manual for detailed instructions.

- As applicable, bone marrow aspirate/biopsy to confirm response (ie, for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment)
- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs
  - β-HCG pregnancy test (serum or urine) on all women of childbearing potential
  - Chemistry panel with CRP
  - CBC with differential
  - Anti-**CD19 CAR** antibodies
  - Cytokine levels
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis)
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is discharged from the hospital and is subsequently re-admitted to the hospital with any **anti-CD19 CAR T cells** related AEs, the following procedures will be performed as outlined in the SOA:

- Anti-CD19 CAR T cell levels on day of admission, then weekly, and on day of discharge
- Cytokine levels on day of admission, then weekly, and on day of discharge

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

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

7.12.9. Long-term Follow-up Period

All enrolled subjects will be followed in the LTFU period for survival and disease status if applicable. Subjects will begin the LTFU period after they have completed the Month 3 visit of the post-treatment assessment period (whether they have responded to treatment or went straight to the Month 3 visit due to disease progression).

- Every 3 months (± 2 weeks) through Month 18
- Every 6 months (± 1 month) between Month 24 to Month 60
- Beginning with Year 6, Month 72 (± 3 months), subjects will return to the clinic 1 time annually up to 15 years.

The following procedures will be completed for subjects who are enrolled and receive **anti-CD19 CAR T cells** at the time points outlined in the SOA:

- EQ-5D questionnaire (prior to any other assessments/procedures being performed)
- For subjects enrolled in Cohort 2, if the MMSE performed on Day 28 and Month 3 has not returned to baseline (± 3 points), then continue to perform the MMSE at Month 6 and every 3 months until the results have returned to baseline (± 3 points) or until Month 24.
- Physical exam
- PET-CT scan/disease assessment: through 24 months or until disease progression, whichever occurs first. If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per standard of care.
- Survival status
- Labs
  - CBC with differential
  - Anti-**CD19 CAR** antibodies (refer to Section 7.11)
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis)
- Targeted AE/SAE reporting (for 24 months or until disease progression whichever occurs first) (refer to Section 9 for safety reporting guidelines)
- Targeted concomitant medication documentation (for 24 months or until disease progression, whichever comes first)
  - Including gammaglobulin, immunosuppressive drugs, anti-infective, and vaccinations

- Subsequent therapy for the treatment of lymphoma
- CCI [redacted]

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

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

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

The following procedures/assessments will be completed for subjects who are enrolled, but do not receive **anti-CD19 CAR T cells**, at the time points outlined in the SOA:

- Subsequent therapy
- Survival status – subjects may be contacted by telephone to confirm survival status
- Disease assessment per standard of care:
- AE/SAE reporting and concomitant medication documentation until 30 days after last procedure (eg, leukapheresis, conditioning chemotherapy)

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

Subjects who undergo an alloSCT will be contacted to confirm the status of their disease and survival status and will have blood collected for PBMCs per the LTFU schedule.

7.12.10. Retreatment

Subjects who achieved a PR or CR will have an option to receive a second course of conditioning chemotherapy and **KTE-X19** under the following conditions:

- Subject had a PR or CR at the Month 3 disease assessment
- Subject's disease subsequently progressed greater than 3 months after **axicabtagene ciloleucel or KTE-X19** infusion

- CD19 tumor expression confirmed locally by biopsy after disease progression and prior to re-treatment. A portion of the biopsy should be sent to the central laboratory.

- Subject continues to meet the original study eligibility criteria with exception of prior **axicabtagene ciloleucel or KTE-X19** use in this study. Screening assessments should be repeated if clinically indicated, as determined by the investigator, to confirm eligibility.

- Subject has not received subsequent therapy for the treatment of lymphoma.

- Subject did not experience a Grade 4 CRS event per Lee 2014 (except for Grade 4 hematology laboratory events, including pancytopenia, anemia, neutropenia, neutropenic fever, leukopenia, and thrombocytopenia) or Grade 4 neurologic toxicity

- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to re-treatment.

- Subject does not have known neutralizing antibodies (exception: if a non-neutralizing antibody develops, subjects may be retreated if they meet the original study eligibility criteria).

The decision to administer re-treatment should be made in consultation with the Kite medical monitor. In addition, a discussion regarding benefits and risks of retreatment and including the need to undergo leukapheresis a second time for the manufacturing of **KTE-X19** should occur with the subject prior to performing any study-related procedures or treatment. This conversation should also be recorded in the subject's source document.

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

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

Table 8. Schedule of Assessments (1 of 2)

Procedures	Screening	Enrollment/ Leukapheresis	Bridging Therapy Period	Conditioning Chemotherapy Period					IP Administration Period[10]		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	**Within 28 days of enrollment**	**Within approx. 5 days of eligibility confirmation**	**Completed within 5 days prior to Conditioning Chemotherapy**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1 - 7**	**Week 2 (± 2 days)**	**Week 4 (± 3 days)**	**Month 2 (± 1 week)**	**Month 3 (± 1 week)**
Medical history	X													
ECOG Performance Status	X													
EQ-5D Questionnaire	X											X		X
Neurological assessment including MMSE[6] for Cohort 1	X								X	QOD		X		X
Neurological assessment including MMSE[8] for Cohort 2	X											**X**		**X**
ECG	X													
ECHO	X													
Archival/Fresh tumor to central lab [1]		X								between Day 7 & Day 14				
Brain MRI	X													
PET-CT/ disease assessment [2]	X		X									X		X
Bone Marrow Assessment[9]	**X**											**X**		**X**
Physical exam	X										X	X	X	X
Vital signs (BP, HR, O_2 sat, temp)	X	X	X	X	X	X			X	X	X	X	X	X
Weight (plus height at screening)	X	X												
Pregnancy test (serum or urine)	X													X
Lumbar Puncture [3]	X									X				
Blood draw for Chemistry panel with CRP	X	X		X	X	X			X	X	X	X	X	X
Blood draw for CBC w/differential	X	X		X	X	X			X	X	X	X	X	X
Blood draw for C-reactive protein (CRP)	**X**	X		X	X	X			**X**	**X**	**X**	**X**	**X**	**X**
Blood draw for Anti-**CD19 CAR** antibody [4]		X										X		X
Blood draw for PBMCs [5, 7]		X							X	Day 7	X	X		X
Blood draw for cytokines[7]		X							X	Day 3 & 7	X	X		
Leukapheresis		X												
Bridging Therapy (if applicable)			X											

Procedures	Screening	Enrollment/ Leukapheresis	Bridging Therapy Period	Conditioning Chemotherapy Period					IP Administration Period[10]		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	Within 28 days of enrollment	Within approx. 5 days of eligibility confirmation	Completed within 5 days prior to Conditioning Chemotherapy	-5	-4	-3	-2	-1	0	1 - 7	Week 2 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Fludarabine/Cyclophosphamide				X	X	X								
KTE-X19 infusion IV									X					
Adverse events/ Concomitant medication	X	→												

Schedule of Assessments Footnotes

Abbreviations: EQ-5D, European Quality of Life-5 Dimensions; MMSE, Mini-Mental Status Exam; MRI, magnetic resonance imaging; BP, blood pressure; HR, heart rate; sat, saturation; temp, temperature; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ECHO, echocardiogram; PET-CT, positron emission tomography-computed tomography; CAR, chimeric antigen receptor; AE, adverse event; SAE, serious adverse event; NHL, non-Hodgkin lymphoma; CBC, complete blood count; CRP, C-reactive protein; PBMC, peripheral blood mononuclear cell; IV, intravenous; IP, investigational product; approx., approximate.

1 Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. CCI [redacted]

2 PET-CT (Neck-Chest-Abdomen-Pelvis)/disease assessment: If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. A repeat baseline PET-CT is required after bridging therapy and prior to conditioning chemotherapy.

3 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 after **KTE-X19** infusion will have lumber puncture performed to assess cerebral spinal fluid. CCI [redacted]

4 Blood draw for Anti-**CD19 CAR** antibody: Baseline antibody sample to be collected prior to start of conditioning chemotherapy. Anti-**CD19 CAR** post 3-month samples; see Section 7.11.

5 PBMCs: Blood draw for PBMCs include the analysis of lymphocytes, anti **KTE-X19** CAR T cells, and RCR.

6 MMSE: Subjects enrolled in Cohort 1 will have the MMSE assessment at screening, before **KTE-X19** administration on Day 0, every other day through hospitalization, Day 28, and Month 3.

7 If subject is subsequently re-admitted to the hospital with any **KTE-X19** related adverse events, blood samples for **KTE-X19** CAR T cells and cytokines will be collected on day of admission, then weekly, and on day of discharge. Blood samples for anti-CD19 CART cells and cytokines should also be collected at the time of disease progression.

8 MMSE: Subjects enrolled in Cohort 2 will have the MMSE assessments at screening and Day 28. If the assessment has not returned to baseline (± 3 points) on Day 28, then continue to perform the MMSE at Month 3 and every 3 months until the results have returned to baseline (± 3 points) or until Month 24.

9 **Bone Marrow Assessment:** Bone marrow aspirate/biopsy as needed (if not done within 4 weeks before screening). As applicable, bone marrow aspirate/biopsy will be performed to confirm **complete** response (ie, for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). Bone marrow samples may also be collected for subjects who develop toxicities after **KTE-X19** infusion and will be analyzed centrally. See Section 7.11. A repeat bone marrow biopsy (if applicable) is required after bridging therapy and prior to conditioning chemotherapy. **After CR is confirmed by bone marrow biopsy, additional bone marrow biopsies are only required in case of clinical suspicion of disease progression in the bone marrow only**.

10 **Refer to Section 18.3 for requirements by country regulatory agencies.**

Table 9. Schedule of Assessment (2 of 2)

Procedure	Long-term Follow-up Period [1] (Each visit calculated from Day 0)												
Visit Frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Thereafter**
EQ-5D Questionnaire	X												
Neurological assessment including MMSE[10] **for Cohort 2**	X	X	X	X	X	X							
Physical exam[1]	X	X	X	X	X	X							
PET-CT Disease Assessment[2]	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Bone Marrow Assessment[11]	**X**	**X**	**X**	**X**	**X**	**X**							
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/differential [3]	X	X	X	X	X	X							
Anti-**CD19 CAR** antibody [4]													
Blood draw for PBMCs [5]	X	X	X	X	X	X		X		X		X	X
Targeted AE/SAEs [6]	X	X	X	X	X	X							
Targeted concomitant medication [7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for NHL [8]	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]													

1 Physical exams will continue through the first 24 months.
2 PET Scans/disease assessments will continue through Month 24 or until disease progression, whichever comes first. If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per standard of care.
3 Subjects will continue to provide samples for CBC with differential and lymphocyte subsets through Month 24.
4 Anti-**CD19 CAR antibodies** post 3-month samples; refer to Section 7.11.
5 Blood draw for PBMCs include the analysis of lymphocytes, anti **KTE-X19** CAR T cells, and RCR.
6 Targeted AEs and SAEs will continue for 24 months or until disease progression (whichever occurs first).
7 Targeted concomitant medications will continue for 24 months or until disease progression (whichever occurs first).
8 Subsequent therapy administered after **KTE-X19** infusion for a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy, must be collected until subject completes the LTFU period, is considered lost to follow-up, withdraws consent, or dies. Subjects may be contacted by telephone to collect information about subsequent therapy for NHL and to assess survival status.
9 CCI [redacted]
10 MMSE: For subjects enrolled in Cohort 2, if the MMSE performed on Day 28 and Month 3 have not returned to baseline (± 3 points), then continue to perform the MMSE at Month 6 and every 3 months until the results have returned to baseline (± 3 points) or until Month 24.
11 **Bone Marrow Assessment: As applicable, bone marrow aspirate/biopsy will be performed to confirm complete response (ie, for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). After CR is confirmed by bone marrow biopsy, additional bone marrow biopsies are only required in case of clinical suspicion of disease progression in the bone marrow only**.

8. SUBJECT WITHDRAWL

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

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

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

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

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

The investigator and/or sponsor can also decide to withdraw a subject from the IP 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:

- AE
- Subject request
- Product not available
- Lost to follow-up
- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

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

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

9. SAFETY REPORTING

9.1. AEs

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

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

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

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

For situations when an AE or SAE is due to the disease under investigation, report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as AEs in the appropriate section of the CRF.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. If a subject requests to withdraw from protocol-required therapies or the study due to an AE, the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.2. Reporting of AEs

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur from enrollment (ie, commencement of leukapheresis) through 3 months after treatment with **anti-CD19 CAR T cell** infusion are monitored and reported. After 3 months, targeted AEs (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) will be monitored and reported for 24 months after treatment with **anti-CD19 CAR T cells** or until disease progression, whichever occurs first.

See Section 9.4 for reporting of non-serious CRS events Grade ≥ 3.

For subjects who are enrolled but do not receive **anti-CD19 CAR T cells**, the AE reporting period ends 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy).

The investigator must address the below AEs:

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

AE grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov). CRS events will be reported using the Lee grading scale (Lee et al, 2014), as outlined in the current IB. In reviewing AEs, investigators must assess whether the AE is possibly related to 1) the IP (**axicabtagene ciloleucel or KTE-X19**), 2) conditioning chemotherapy, or 3) any protocol-required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.

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

The investigator is expected to follow reported AEs until stabilization or resolution. If a subject begins a new anti-cancer therapy, the AE reporting period for non-serious AE ends at the time the new treatment is started.

9.3. Definition of SAEs

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

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

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

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

9.4. Reporting of SAEs and Non-serious CRS Events Grade ≥ 3

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject that occur after signing of the consent through 3 months after the **anti-CD19 CAR T cell** infusion. After 3 months, only serious targeted AEs (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) observed by the investigator or reported by the subject will be reported for 24 months after **anti-CD19 CAR T cell** infusion or until disease progression, whichever occurs first. For subjects who screen fail or are enrolled but do not receive **anti-CD19 CAR T cells**, the reporting period for SAEs ends 30 days after the last procedure (eg, screen procedure, leukapheresis, conditioning chemotherapy).

Serious events that the investigator assesses as related to **axicabtagene ciloleucel or KTE-X19** should be reported regardless of the time period.

All SAEs and non-serious CRS events ≥ Grade 3 (Lee et al, 2014) must be submitted **via email to** PPD within 24 hours following the investigator's knowledge of the event using a SAE Report Form. Subsequently, all SAEs will be reported **in accordance with EU guidelines, or, if applicable, as** per local reporting guidelines.

Progression of the malignancy during the study should not be reported as an SAE. SAEs associated with disease progression may be reported as an SAE. If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy or **anti-CD19 CAR T cell-infusion,** then the event leading to death must be recorded as an SAE with CTCAE Grade 5.

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

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of the **anti-CD19 CAR T cell** infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring greater than 3 months after the **anti-CD19 CAR T cell** infusion requires expedited reporting within 24 hours only if it is considered related to treatment.

9.5. Reporting Deaths

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

9.6. Diagnosis Versus Signs and Symptoms

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

9.7. Pregnancy and Lactation

There is no relevant clinical experience with **KTE-X19** in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

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

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

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of **anti-CD19 CAR T cell infusion** through 6 months for female subjects and for 6 months for the female partner of the male subjects.

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

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

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

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

9.8. Hospitalization and Prolonged Hospitalization

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

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

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

9.9. Abnormal Vital Signs Values

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

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

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

9.10. Data Safety Monitoring Board

An independent DSMB will review safety and/or efficacy data **4** times during this study. The DSMB will first meet to review safety data when 10 subjects in Cohort 1 have been enrolled and treated with **anti-CD19 CAR T cells** and followed for 30 days. The DSMB will meet for the second time to review both safety and efficacy data after 20 subjects in Cohort 1 have been treated with **anti-CD19 CAR T cells** and have had the opportunity to complete the 3-month disease assessment. The DSMB will meet for the third time to review both safety and efficacy data after 10 subjects in Cohort 2 have been treated with **KTE-X19** and have had the opportunity to be followed for 30 days. The DSMB will meet for the fourth time after 44 subjects in Cohort 1 have been treated with anti‑CD19 CAR T cells and have had opportunity to be followed for 30 days after the IP infusion. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk vs benefit. The DSMB may meet more often as needed.

At the time of expedited reporting of suspected unexpected serious adverse reactions (SUSARs) to health authorities, Kite (or designee) will concurrently submit these reports to the DSMB chair. The DSMB chair will also review SAE narrative reports monthly. Finally, the DSMB or Kite may request additional analyses of safety data if a safety concern arises during the course of the trial.

9.11. Criteria to Pause Enrollment

As part of its oversight of the study, the DSMB also will assess criteria to pause enrollment after 10, 20, 30, and 50 subjects in Cohort 1 have been treated with **axicabtagene ciloleucel or KTE-X19** and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following criteria is met:

- Subject incidence of Grade 5 **axicabtagene ciloleucel or KTE-X19** related AEs within 30 days is > 10%

or

- Subject incidence of the following Grade 4 **axicabtagene ciloleucel or KTE-X19**-related AEs lasting more than 7 days is > 33%:
  - Neurologic toxicity
  - CRS (per Lee 2014 criteria)
  - Other non-hematological Grade 4 SAE
  - Infection (treatment-related)

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

This study uses an open-label, 2-cohort design. An alternative hypothesis will be tested among Cohort 1 **KTE-X19** subjects with a target 50% ORR per independent review against a null hypothesis that the ORR is 25% or less. The hypothesis is that the ORR to **KTE-X19** in Cohort 1 **KTE-X19** subjects is significantly greater than 25%. No hypothesis will be tested in Cohort 1 axicabtagene ciloleucel subjects and Cohort 2 subjects.

10.2. Study Endpoints

10.2.1. Primary

- ORR: Defined as the incidence of a CR or a PR per the Lugano Classification (Cheson et al, 2014), as determined by the IRRC. All subjects who do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders**,** including the subjects without any evaluable assessment and those without any assessment.

10.2.2. Secondary

- DOR: For subjects who experience an objective response, DOR is defined as the time from their first objective response to disease progression or death. 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

- Best objective response: the incidence of CR, PR, SD, progressive disease, or unevaluable as best response to treatment

- ORR (as determined by investigators): For subjects enrolled in Cohort 1, ORR, as determined by study investigators, is defined as the incidence of either a CR or PR per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007). For subjects enrolled in Cohort 2, ORR, as determined by investigators, is defined as the incidence of either a CR or PR per the Lugano Classification (Cheson et al, 2014). All subjects who do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders**,** including the subjects without any evaluable assessment and those without any assessment.

- PFS: defined as the time from the anti‑CD19 CAR T-cell infusion date to the date of disease progression or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

- OS: defined as the time from anti‑CD19 CAR T cell infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at the last date known alive or the data cutoff date for analysis, whichever is earlier.

- Incidence of AEs and clinically significant changes in laboratory values
- Incidence of anti-**CD19 CAR** antibodies, levels of anti-CD19 CAR T cells in blood, and levels of cytokines in serum
- Changes over time in the EQ-5D scale score and EQ-5D VAS score

10.2.3. Exploratory Endpoints

- ORR and duration of second response among subjects retreated with anti‑CD19 CAR T cells (Section 7.12.10)

10.3. Sample Size Considerations

This study uses an open-label, 2-cohort design to test for an improvement in ORR. Up to approximately 130 subjects with r/r MCL will be enrolled and treated with anti‑CD19 CAR T cells, including 10 axicabtagene ciloleucel subjects and up to approximately 80 **KTE-X19** subjects in Cohort 1 and up to 40 **KTE-X19** subjects in Cohort 2. The primary analysis will be conducted after 60 Cohort 1 **KTE-X19** subjects have been enrolled and treated and have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment. For the test of efficacy, 60 **KTE-X19** subjects in Cohort 1 will provide at least 96% power to distinguish between an active therapy with a 50% true response rate from a therapy with a response rate of 25% or less (undesirable response rate, for purposes of futility assessment) with a 1-sided alpha level of 0.025. No hypothesis will be tested in Cohort 1 axicabtagene ciloleucel subjects or Cohort 2 subjects. Exploratory analyses will be conducted on the data collected from these subjects.

In Cohort 1, 4 interim analyses will be performed:

- Cohort 1 interim analysis 1 will be conducted after 10 subjects in Cohort 1 have been enrolled and treated with anti‑CD19 CAR T cells and have had the opportunity to be followed for 30 days. This interim analysis will be for safety only.
- Cohort 1 interim analysis 2 will be conducted after 20 subjects in Cohort 1 have been enrolled and treated with anti‑CD19 CAR T cells and have had the opportunity to be evaluated for response 3 months after treatment with **anti‑CD19 CAR T cells**. In this interim analysis, the DSMB will review data for both safety and efficacy (futility only).
- Cohort 1 interim analysis 3 will occur after 38 subjects in Cohort 1 have been treated with anti‑CD19 CAR T cells and have had the opportunity to be assessed for response 6 months after **the treatment with anti‑CD19 CAR T cells**. This interim analysis will be performed for a Kite internal review of the accumulating data of safety and efficacy.
- Cohort 1 interim analysis 4 will occur after 44 subjects in Cohort 1 have been treated with anti‑CD19 CAR T cells and have had the opportunity to be followed for at least 30 days. In this interim analysis, the DSMB will review data for safety only, with focus on the 6 **KTE-X19** subjects treated most recently in this cohort.

In Cohort 2, one interim analysis will be performed:

- Cohort 2 interim analysis will be conducted after 10 subjects in Cohort 2 have been enrolled and treated with **KTE-X19** and have had the opportunity to be followed for 30 days after treatment with **KTE-X19**. This interim analysis will be for safety and efficacy.

Accrual to the study will continue during all interim analyses.

One primary analysis will be performed:

- The primary analysis will be performed with both Cohort 1 and Cohort 2 after 60 **KTE-X19** subjects in Cohort 1 have been enrolled and treated and have had the opportunity to be assessed for response 6 months after the Week 4 disease assessment.

At the primary analysis, the inferential testing will be performed with data from the Cohort 1 **KTE-X19** subjects only, using a 1-sided alpha level of 0.025. This procedure preserves the designated overall alpha level (1-sided) of 0.025 and has at least 96% power when 60 **KTE-X19** subjects are included. EAST version 6.4 were used for power calculation and evaluation of the operating characteristics of this design.

For Cohort 1, a rho (parameter = 0.30) beta spending function will be used to allocate the beta level between the futility analysis and the primary efficacy analysis.

10.4. Statistical Assumptions

As described in Section 3, an open-label, 2-cohort design is used. A target response rate of 50% and a historical control rate of 25% are assumed for statistical inference. The responses from subjects in the study population are assumed to be independent and follow binomial distribution, and, thus, the exact binomial test will be used to test the statistical hypothesis.

10.5. Analysis Subsets

- mITT set: will consist of all subjects enrolled and treated with anti‑CD19 CAR T cells at any dose. This analysis set will be used for analyses of the efficacy endpoints (objective response rate, best objective response, DOR, PFS, OS) for the study.

- **Inferential analysis set: will consist of the first 60 treated KTE-X19 subjects in Cohort 1. This analysis set will be used for the hypothesis testing of the primary endpoint ORR at the time of the primary analysis, as well as the analyses on the key secondary endpoints (best objective response [BOR], DOR, PFS, and OS).**

- Safety analysis set: defined as all subjects treated with any dose of anti‑CD19 CAR T cells. This analysis set will be used for all analysis of safety.

- Full analysis set (FAS): will consist of all enrolled subjects and will be used for the summary of subject disposition, sensitivity analyses of ORR and **key secondary endpoints**, and subject listings of deaths.

10.6. Access to Individual Subject Treatment Assignments

This is an open-label, 2-cohort study, and subjects and investigators will be aware of treatment received. Data handling procedures for the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study Statistical Analysis Plan, DSMB charter, and Trial Integrity Document.

10.7. Interim Analysis

10.7.1. Interim Analysis and Early Stopping Rules

An independent DSMB will be formed to review accumulating safety data after 10 subjects in Cohort 1 have been enrolled and treated with anti‑CD19 CAR T cells and have had the opportunity to be followed for 30 days for safety. The DSMB will review accumulating safety and efficacy data after 20 subjects in Cohort 1 have been treated with anti‑CD19 CAR T cells and have had the opportunity to complete the 3-month disease assessment after the **treatment with anti‑CD19 CAR T cells**. The DSMB will also review safety and efficacy after 10 subjects in Cohort 2 have been treated with **KTE-X19** and have had opportunity to be followed for 30 days after the **KTE-X19** infusion. The DSMB will review safety again after 44 subjects in Cohort 1 have been enrolled and treated with anti‑CD19 CAR T cells and have had the opportunity to be followed for 30 days after **the treatment with anti‑CD19 CAR T cells**, with focus on the safety data from the 6 **KTE-X19** subjects treated most recently within this cohort.

The DSMB will also monitor safety criteria to pause enrollment (see Section 9.11).

10.7.2. Safety Interim Analysis

The DSMB will review the safety data only twice, after 10 and 44 subjects in Cohort 1 have been enrolled and treated with anti‑CD19 CAR T cells and have had the opportunity to be followed for 30 days for safety**,** respectively. The DSMB will also review SAE information and SUSARs on a regular basis throughout subject treatment in the study. The DSMB may request additional safety data or modifying the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate and ensure timely DSMB review.

10.7.3. Efficacy Interim Analysis

In Cohort 1, two efficacy interim analyses will be performed.

Interim analysis 2 (Efficacy analysis 1) will be conducted after 20 subjects have been treated with anti‑CD19 CAR T cells and have had the opportunity to be followed for 3 month**s** after the **treatment with anti‑CD19 CAR T cells**. This interim analysis will be for futility only. If more than 5 responses are observed in the first 20 subjects, accrual in Cohort **1** will continue.

Interim analysis 3 (Efficacy analysis 2) will be conducted after 38 subjects in Cohort 1 have been treated with anti‑CD19 CAR T cells and have had the opportunity to be assessed for response 6 months after **the treatment with anti‑CD19 CAR T cells**. This interim analysis will be performed for a Kite internal review of the accumulating data of safety and efficacy.

A rho (parameter = 0.30) beta spending function will be used to allocate the beta level between this futility analysis and the primary efficacy analysis in Cohort 1.

In Cohort 2, one interim analysis will be conducted after 10 **KTE-X19** subjects have been enrolled and have had the opportunity to be followed for 30 days after treatment with **KTE-X19**. This interim analysis will be for safety and efficacy.

10.7.4. Other Interim Analysis

The sponsor reserves the right to conduct additional analyses of safety and efficacy during the time between the planned interim analyses and primary analysis for regulatory interaction purposes. If conducted, no formal hypothesis testing will be performed in such analyses.

10.8. Planned Methods of Analysis

The primary analysis will be performed after 60 **KTE-X19** subjects in Cohort 1 have been treated and have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment. In this primary analysis, inferential testing of efficacy will be performed with data from Cohort 1 **KTE-X19** subjects only, and the analysis with the data from Cohort 1 axicabtagene ciloleucel subjects and Cohort 2 will be descriptive. Additional analyses may occur after the primary analysis has been completed. These additional analyses will be descriptive and will occur after inferential testing in Cohort 1 has been performed. The final analysis will occur when all subjects in both cohorts have completed the study.

The primary endpoint of ORR will be based on IRRC review of disease assessments in the mITT set. Analyses of ORR based on investigator review of disease assessments will also be performed.

10.8.1. ORR

The incidence of objective response and exact 2-sided 95% confidence intervals will be generated for Cohort 1 **KTE-X19** subjects, Cohort 1 axicabtagene ciloleucel subjects, and Cohort 2 subjects. An exact binomial test will be used to compare the observed ORR per IRRC review in Cohort 1 **KTE-X19** subjects to a response rate of 25%.

10.8.2. Best Objective Response

The incidence of subjects with CR, PR, SD, progressive disease, and unevaluable as best response to treatment and exact 2-sided 95% confidence intervals about the incidence will be generated for Cohort 1 **KTE-X19** subjects, Cohort 1 axicabtagene ciloleucel subjects, and Cohort 2 subjects.

10.8.3. DOR

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for DOR for Cohort 1 **KTE-X19** subjects, Cohort 1 axicabtagene ciloleucel subjects, and Cohort 2 subjects. DOR will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (including SCT). The DOR for subjects who undergo SCT while in remission will be censored at the last evaluable assessment date prior to SCT; a sensitivity analysis will be conducted in which disease assessments obtained after SCT are included in the derivation of DOR.

10.8.4. PFS

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for PFS time for Cohort 1 **KTE-X19** subjects, Cohort 1 axicabtagene ciloleucel subjects, and Cohort 2 subjects. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided.

10.8.5. OS

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS for Cohort 1 **KTE-X19** subjects, Cohort 1 axicabtagene ciloleucel subjects, and Cohort 2 subjects. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

10.8.6. Safety

Subject incidence rates of AEs, including all, serious, fatal, CTCAE version 4.03 Grade 3 or higher, and TEAEs with onsets on or after the date of **KTE-X19** or axicabtagene ciloleucel infusion, will be tabulated by preferred terms and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths through the LTFU and treatment related SAEs will be provided.

10.8.7. Long-term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject receives his or her last **KTE-X19** or axicabtagene ciloleucel infusion. No formal hypothesis testing will be performed based on data obtained after the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

11. REGULATORY OBLIGATIONS

11.1. Independent Review Board/Independent Ethics Committee

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

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

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

11.2. Subject Confidentiality

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

- Subjects will be identified by a unique ID number.
- Date of birth or year of birth/age at time of enrollment will be reported according with local laws and regulations.

For reporting of SAEs, subjects will be identified by their respective subject ID number, initials, and date of birth or year of birth (as per their local reporting requirements for both initials and date of birth).

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

11.3. Investigator Signatory Obligations

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

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

12. PROTOCOL AMENDMENTS AND TERMINATION

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

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

Kite reserves the unilateral right, at is sole discretion, to determine whether to manufacture CAR T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13. STUDY DOCUMENTATION AND ARCHIVE

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

Source documents are original documents, data, and records for which the study data are collected and verified. 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. CRF entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

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

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

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

14. STUDY MONITORING AND DATA COLLECTION

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

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

By signing the Investigator's Agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

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

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

15. PUBLICATION

Authorship of publications from data generated in study KTE-C19-102 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 for review and approval. The study contract among the institution, principal investigator, and Kite or its delegate will outline the requirements for publication review.

16. COMPENSATION

Kite will provide compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

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18. APPENDIX

18.1. Appendix 1: Revised IWG Response Criteria for Malignant Lymphoma

Information in this section has been taken from (Cheson et al, 2007).

18.1.1. Complete Response

Complete response (CR) requires all of the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

- Typically fluorodeoxyglucose (FDG)-avid lymphoma (large cell, mantle cell, and follicular lymphomas are all typically FDG-avid): In subjects with no pre-treatment positron emission tomography (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 pre-treatment PET scan or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

- The spleen and/or liver, if considered to be enlarged before therapy on basis of physical exam or CT scan, must should be normal size on CT scan and not be palpable on physical examination, and nodules thought to represent lymphoma must no longer be present.

- A bone marrow aspirate and biopsy is performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology, or, if indeterminate by morphology, it must be negative by immunohistochemistry. The biopsy core sample must be a minimum of 20 mm in length.

18.1.2. Partial Response

A partial response (PR) requires all of the following:

- ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible, and should include mediastinal and retroperitoneal nodes if possible.

- No increase in size of nodes, liver, or spleen and no new sites of disease.

- If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for single nodules.

- Bone marrow is irrelevant for determination of a PR. If subject has persistent bone marrow involvement and otherwise meets criteria for CR, then the subject will be considered a PR.

- Typically FDG-avid lymphoma: for subjects with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least 1 previously involved site. Note: in subjects with follicular lymphoma or mantle cell lymphoma, a PET scan is only indicated in subjects with 1 or at most 2 residual masses that have regressed by 50% on CT scan.

18.1.3. Stable Disease

Stable disease (SD) requires:

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

18.1.4. Progressive Disease

Progressive disease (PD) is defined by at least one of the following:

- ≥ 50% increase from nadir in the sum of the products of at least 2 lymph nodes, or, if a single node is involved, at least a 50% increase in the product of the diameters of this 1 node

- Appearance of a new lesion > 1.5 cm in any axis even if other lesions are decreasing in size

- ≥ 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).

18.2. Appendix 2: Lugano Classification

Refer to imaging manual and (Cheson et al, 2014) for details of assessment.

Table 10. 5-point Scale (5PS)

Score	Description
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

From (Barrington et al, 2014)

18.2.1. Complete Response

18.2.1.1. Complete Metabolic Response

The designation of complete metabolic response (CMR) for PET-CT-based response requires all of the following:

- A 5-point scale (5PS) score of 1, 2, or 3, with or without a residual mass
  - In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
- No new sites of disease should be observed.

18.2.2. Complete Radiologic Response

The designation of complete radiologic response (CRR) for CT-based response requires all of the following:

- Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion (LDi).
- No extralymphatic sites of disease
- Absent non-measured lesion
- Organ enlargement regress to normal (eg, an enlarged spleen at baseline must be ≤ 13 cm at assessment)

- No new sites of disease should be observed.
- Bone marrow normal by morphology; if indeterminate, immunohistochemistry negative

18.2.3. Partial Response

18.2.3.1. Partial Metabolic Response

The designation of partial metabolic response (PMR) for PET-CT-based response requires all of the following:

- A 5PS score of 4 or 5, with reduced uptake compared to baseline (screening), and residual mass(es) of any size
- Note:
  - At interim, these findings suggest responding disease.
  - At end of treatment, these findings suggest residual disease.
- No new sites of disease should be observed.

If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with magnetic resonance imaging or biopsy or an interval scan.

18.2.3.2. Partial Radiologic Response

The designation of partial radiologic response (PRR) for CT-based response requires all of the following:

- ≥ 50% decrease in the SPD of up to 6 target measurable nodes and extra-nodal sites
  - When a lesion is too small to measure by CT, assign 5 mm x 5 mm as the default value.
  - For a node > 5 mm x 5 mm, but smaller than normal, use actual measurements for calculation.
- Absent/normal, regressed, but no increase of non-measured lesions
- Spleen must have regressed by > 50% in length beyond normal (ie, ≤ 13 cm). For example, if the spleen is 15 cm at baseline, it must be ≤ 14 cm at assessment to classify as a PRR.

18.2.4. Stable Disease

18.2.4.1. No Metabolic Response

The designation of no metabolic response (NMR) for PET-CT-based response requires all of the following:

- A 5PS score of 4 or 5, with no significant change in FDG uptake compared to baseline (screening), at an interim time point or end of treatment
- No new sites of disease should be observed.

18.2.4.1.1. Stable Radiologic Disease

The designation of stable radiologic disease (SRD) for CT-based response requires all of the following:

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

18.2.4.2. PD

18.2.4.2.1. Progressive Metabolic Disease

The designation of progressive metabolic disease (PMD) for PET-CT-based response requires at least 1 of the following:

- A 5PS score 4 or 5 with an increase in intensity of uptake from baseline, and/or
- New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment
- New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
- New or recurrent FDG-avid foci in bone marrow.

18.2.4.3. Progressive Radiologic Disease

The designation of progressive radiologic disease (PRD) for CT-based response requires at least 1 of the following:

- An individual node/lesion must be abnormal with:
  - LDi > 1.5 cm, and
  - Increase by ≥ 50% from cross-product of LDi and perpendicular diameter (PPD) nadir, and
  - An increase in LDi or shortest axis perpendicular to the LDi from nadir
    - 0.5 cm for lesions ≤ 2 cm
    - 1.0 cm for lesions > 2 cm
  - In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, the increase must be ≥ 2 cm from baseline;
  - New or recurrent splenomegaly
- New or clear progression of pre-existing non-measured lesions
- New lesion
  - Regrowth of previously resolved lesions
  - A new node > 1.5 cm in any axis
  - A new extra-nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
  - Assessable disease of any size unequivocally attributable to lymphoma
- New or recurrent bone marrow involvement

18.3. Appendix 3: Monitoring of Subjects After IP Administration per Country Regulatory Agencies

Germany:

The post-infusion monitoring of subjects, described in Section 7.12.6.2 in this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 8, column "IP administration period, 1-7." The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see Section 7.4), blood draw for chemistry panel with C-reactive protein (CRP), blood draw for complete blood count (CBC) with differential (see Section 7.11), and neurological assessment, including Mini-Mental Status Exam (MMSE) (see section 7.5). Any observed toxicity will be managed according to Section 6.4 of this protocol.