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
EudraCT Number:	2015-005008-27
Clinical Study Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Key Sponsor Contact:	The medical monitor name and contact information is provided on the Key Study Team Contact List
Version:	Amendment # 9
Date:	07 November 2022

CONFIDENTIALITY STATEMENT

SPONSOR AND INVESTIGATOR SIGNATURE PAGE

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

STUDY ACKNOWLEDGMENT

A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)

Amendment # 9, 07 November 2022

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

PPD
Kite Medical Monitor Name (Printed)

[See appended electronic signature]
Signature

[See appended electronic signature]
Date

INVESTIGATOR STATEMENT

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

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

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

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

PROTOCOL SYNOPSIS

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 and Cohort 2 will include subjects with r/r MCL who have been treated with up to 5 prior regimens including a Bruton's tyrosine kinase inhibitor (BTKi). Prior therapy must have included all of the following: anthracycline- or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, and ibrutinib or acalabrutinib. Cohort 3 will include subjects with r/r MCL who have been treated with up to 5 prior regimens but have not received prior therapy with a BTKi. Prior therapy must have included anthracycline-, bendamustine-, or high-dose cytarabine-containing chemotherapy and anti-CD20 monoclonal antibody therapy. Cohort 1 will enroll and treat up to approximately 90 subjects with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2×10^6 anti-CD19 chimeric antigen receptor (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 in Cohort 1. As of 28 May 2019, Cohort 1 has completed enrollment. Cohort 2 will enroll and treat up to 40 KTE-X19 subjects with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 0.5×10^6 anti-CD19 CAR T cells per kg body weight. As of 01 May 2018, Cohort 2 has completed enrollment. Cohort 3 will enroll and treat up to approximately 90 KTE-X19 subjects with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2×10^6 anti-CD19 CAR T cells per kg body weight. Each subject will proceed through the following study periods: • Screening • Enrollment/Leukapheresis • 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 and additional efficacy endpoints including duration of response (DOR). Secondary objectives related to patient-reported outcomes (PROs) in Cohort 1 and Cohort 2 will include change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6. Secondary objectives related to PROs in Cohort 3 will include change in EQ-5D and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) scores from baseline over time.
Hypothesis:	This study uses an open-label 3-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. Among the Cohort 3 subjects, with a target 75% ORR per independent review, an alternative hypothesis will be tested against a null hypothesis that the ORR is 57% or less. The hypothesis is that the ORR to KTE-X19 per independent review is significantly greater than 57% in Cohort 3 subjects. No hypothesis will be tested in Cohort 1 axicabtagene ciloleucel subjects and Cohort 2 KTE-X19 subjects. CCI [redacted]
Primary Endpoint:	ORR (complete response [CR] + partial response [PR]) per the Lugano Classification {Cheson 2014} per Independent Radiology Review Committee (IRRC) review
Secondary Endpoints:	• DOR • 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 • Changes over time in the EORTC-QLQ-C30 score (Cohort 3 only)
Exploratory Endpoints:	CCI [redacted]

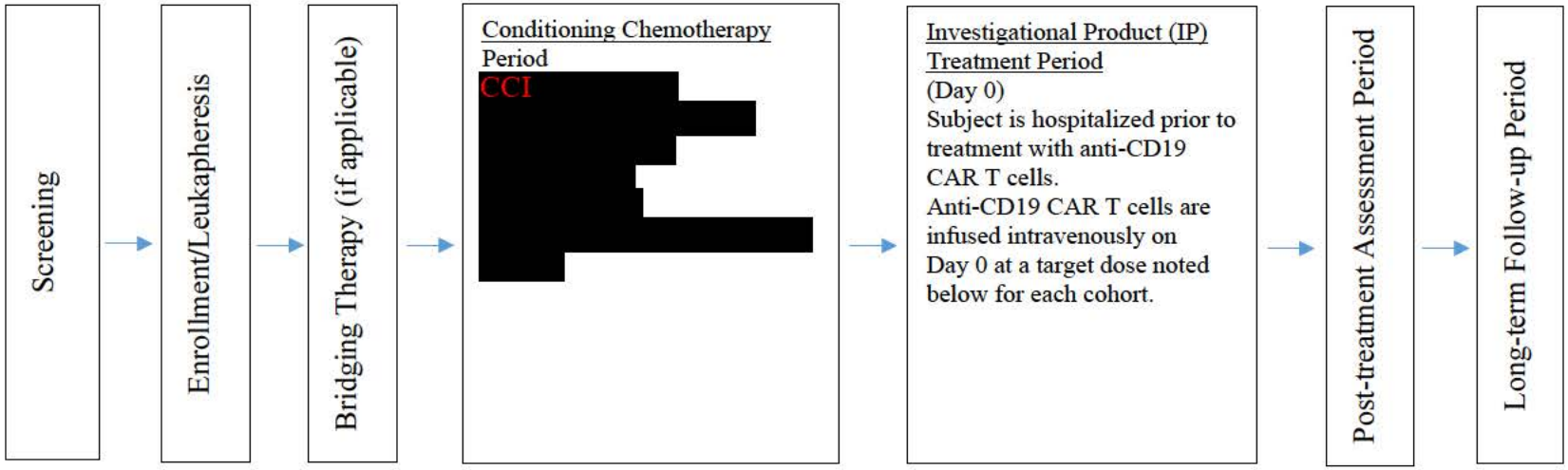
Sample Size:	• Up to approximately 220 subjects will be enrolled and treated in the study: — 90 subjects in Cohort 1 (10 axicabtagene ciloleucel subjects and approximately 80 KTE-X19 subjects) at 2 x 10^6 anti‑CD19 CAR T cells per kg body weight — Up to 40 KTE-X19 subjects in Cohort 2 at 0.5 x 10^6 anti‑CD19 CAR T cells per kg body weight — Up to approximately 90 KTE-X19 subjects in Cohort 3 at 2 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: • Cohort 1 and Cohort 2: — 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 ≥ 1,000 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. • Cohort 3: — At the discretion of the investigator and per institutional guidelines and standard of care and after discussion with the medical monitor, bridging therapy is recommended for all subjects, particularly those with rapidly progressing disease, clinical deterioration, or high disease burden at screening (eg, > 25% marrow involvement and/or ≥ 1,000 leukemic phase mantle cells/mm^3 in the peripheral circulation). — Bridging therapy is allowed with (1) dexamethasone or other corticosteroid, (2) palliative radiotherapy to localized lesions, (3) specified chemotherapy, or (4) any combination of 1 specified chemotherapy and/or corticosteroid and/or radiotherapy, as detailed in Section 6.2.1.2. Bridging regimen should be discussed with the Kite medical monitor, and BTKis are not permitted for bridging therapy. If radiotherapy is considered for bridging, the radiotherapy modality should be discussed with the Kite medical monitor. Irradiated lesions can no longer serve as target lesions, and other target lesions must be present to allow for response assessment. — If prescribed, bridging therapy must be administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, 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.

	IP: • 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 and Cohort 3) or 0.5 x 10^6 anti-CD19 CAR T cells/kg (Cohort 2). In Cohort 3, under circumstances where subjects initially respond and subsequently relapse, subjects may be eligible for a second course of conditioning chemotherapy and KTE-X19. 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; demographic data; general medical history, including previous treatments for MCL and disease staging at study entry (per the Lugano Classification {Cheson 2014} for subjects in Cohort 3); physical exam, including vital signs and performance status; neurological assessments; blood draws for complete blood count (CBC), chemistry panels, cytokines, C-reactive protein, ferritin, lactate dehydrogenase, lymphocyte subsets, anti-CD19 CAR antibodies, replication-competent retrovirus (RCR), and anti-CD19 CAR T cells analysis; and bone marrow aspirate or biopsy and blood draws for minimal residual disease (MRD) analysis. Females of childbearing potential will undergo a urine or serum pregnancy test. Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO) (or multigated acquisition [MUGA] scan for subjects in Cohort 3), brain magnetic resonance image (MRI) (or computed tomography [CT] scan with contrast for subjects in Cohort 3 with a contraindication for MRI), a positron emission tomography-computed tomography (PET-CT), bone marrow aspirate or biopsy, and leukapheresis. Routinely throughout the conduct of the study, subjects will be asked to complete the EQ-5D questionnaire, EORTC-QLQ-C30 (Cohort 3 only), report concomitant therapies 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 from Cohort 1 and Cohort 2 at 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 for Cohort 1 and Cohort 2 based on an analysis of risk vs benefit. The DSMB may meet more often as needed. Refer to Section 9.10 and Section 9.12.
Scientific Steering Committee (Cohort 3):	A scientific steering committee, comprising the study sponsor and at least 3 study investigators, will be specifically chartered to review the safety data from Cohort 3 and make recommendations on further study conduct. The scientific steering committee will meet after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days, and again after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months. The scientific steering committee may meet more often as needed. Refer to Section 9.11 and Section 9.12.

Statistical Considerations:	This study uses an open-label, 3-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. Among the Cohort 3 subjects, with a target 75% ORR per independent review, an alternative hypothesis will be tested against a null hypothesis that the ORR is 57% or less. For the test of efficacy in Cohort 3, this study has at least 90% power to distinguish between an active therapy with a 75% true response rate and a therapy with a response rate of 57% or less with a 1-sided alpha level of 0.025. No hypothesis will be tested on Cohort 1 axicabtagene ciloleucel subjects or Cohort 2 subjects. Four interim analyses will be performed in Cohort 1, 1 interim analysis will be performed in Cohort 2, and 2 interim analyses (for safety only) will be performed in Cohort 3. The primary analysis in Cohort 1 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. The primary analysis in Cohort 3 will be conducted after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier. • 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 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. • Cohort 3 interim analysis 1 will be conducted after 15 subjects in Cohort 3 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 be for safety only. • Cohort 3 interim analysis 2 will be conducted after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months after the KTE-X19 infusion. This interim analysis will be for safety only.

	The primary analysis in Cohort 1 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. The primary analysis in Cohort 3 will occur after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier. A follow-up analysis will be performed after 86 subjects in Cohort 3 have had the opportunity to be assessed for response 18 months after the first objective response to further evaluate the risk-benefit profile of KTE-X19, including the durability of response.

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 220 subjects with r/r MCL will be enrolled and treated in 3 separate cohorts designated as Cohort 1, Cohort 2, and Cohort 3.

Cohort 1 and Cohort 2 will include subjects with r/r MCL who have been treated with up to 5 prior regimens including a Bruton's tyrosine kinase inhibitor (BTKi).

- 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.

Cohort 3 will include subjects with r/r MCL who have been treated with up to 5 prior regimens but have not received prior therapy with a BTKi.

- Cohort 3 will enroll and treat up to approximately 90 KTE-X19 subjects at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg.

Note: After the end of KTE-C19-102, subjects who received an infusion of anti-CD19 CAR T cells will complete the remainder of the 15-year follow-up assessments in a separate long-term follow-up study, KT-US-982-5968.

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LIST OF ABBREVIATIONS

AE	Adverse event
alloSCT	Allogeneic stem cell transplant
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC_{0-28}	Area under curve from Day 0 to Day 28
autoSCT	Autologous stem cell transplant
BR	Bendamustine and rituximab
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
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EU	European Union
EQ-5D	European Quality of Life-5 Dimensions
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
GVHD	Graft-versus-host-disease
HEENT	Head, ears, eyes, nose, and throat
HIV	Human immunodeficiency virus

HLH	Hemophagocytic lymphohistiocytosis
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
Ig	Immunoglobulin
IND	Investigational new drug
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
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
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
PO	Orally
PR	Partial response
PRO	Patient-reported outcome
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
R-BAC	Rituximab with bendamustine and cytarabine
R-CHOP	Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone

R-DHAP	Rituximab with dexamethasone, high-dose cytarabine, and cisplatin
RCR	Replication-competent retrovirus
r/r	Relapsed/refractory
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Stable disease
SOA	Schedule of assessments
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
US	United States
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 and additional efficacy endpoints including duration of response (DOR).

Secondary objectives related to patient-reported outcomes (PROs) in Cohort 1 and Cohort 2 will include change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6. Secondary objectives related to PROs in Cohort 3 will include change in EQ-5D and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) scores from baseline over time.

2. DISEASE BACKGROUND AND RATIONALE

MCL 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 (US) {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 immunoglobulin (Ig)M, and surface IgD {Dreyling 2014a} but not CD11c {Kraus 2010}. More than 95% of MCLs carry translocation t(11;14)(q13;q32), which places the cyclin D1 gene in proximity of the Ig 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 2017}. Patients typically present with advanced lymphadenopathy, and also show extranodal involvement of the spleen, bone marrow, and gastrointestinal (GI) tract {Dreyling 2014b, National Comprehensive Cancer Network 2017, Rajabi 2015, 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 2008, Hoster 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) {Dreyling 2017, National Comprehensive Cancer Network (NCCN) 2020}. Common 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) {Flinn 2014, Kluin-Nelemans 2012, Lenz 2005}. Treatment intensification for younger patients combines aggressive chemotherapy regimens with autologous stem cell transplant (autoSCT). Regimens such as rituximab with dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) alternating with R-CHOP (R-CHOP/R-DHAP) {Hermine 2016}, rituximab in combination with fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) alternating with high-dose methotrexate and cytarabine (MA) (R-HyperCVAD/MA) {Romaguera 2005, Romaguera 2010}, or high-dose chemotherapy followed by autoSCT in first remission with or without maintenance rituximab {Dreyling 2005, Le Gouill 2016} have led to improved outcomes at the expense of additional toxicity. For patients who are unfit for intensive chemotherapy or are not candidates for autoSCT, less aggressive regimens are given, such as BR, R-CHOP with or without maintenance rituximab, or rituximab with bendamustine and cytarabine (R-BAC) {Dreyling 2017, National Comprehensive Cancer Network (NCCN) 2020, Visco 2013}. Despite high initial response rates to these therapies, almost all patients eventually develop progressive disease (PD).

Table 1. Treatment Outcomes in First-line MCL

Regimen	N	Outcome	Reference
R-CHOP v CHOP	122	ORR 94 v 75%; CR 34 v 7%, mTTF = 21 v 14 m	{Lenz 2005}
R-CHOP v R-FC	560	ORR 86 v 78%; CR 34 v 40%; 4 yr OS 62 v 47%	{Kluin-Nelemans 2012}
BR v R-CHOP/R-CVP	74	ORR 94 v 85%; CR 50 v 27%	{Flinn 2014}
R-CHOP/R-DHAP v R-CHOP	497	ORR 94 v 90%; CR[a] 55 v 39%	{Hermine 2016}
R-HyperCAD/MA	97	CR 77%, mTTF= 4.6 yr	{Romaguera 2005} {Romaguera 2010}
ASCT v IFN-α in first remission	122	mPFS 39 v 17m; 2 yr OS 86 v 82%	{Dreyling 2005}
RM v no RM after R-DHAP plus ASCT	290	4 yr EFS 79 v 61%; 4 yr PFS 82 v 65%; 4 yr OS 89 v 81%	{Le Gouill 2016}
R-BAC	20[b]	ORR 100%; CR 95%; 2 yr PFS 95%	{Visco 2013}

Abbreviations: ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; CR, complete response; EFS, event-free survival; IFN-α, interferon-alpha; m, month; MA, methotrexate + cytarabine; MCL, mantle cell lymphoma; mPFS, median progression-free survival; mTTF, median time-to-treatment failure; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R-BAC, rituximab + bendamustine + cytarabine; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisone; R-DHAP, rituximab + dexamethasone + high-dose cytarabine + cisplatin; R-FC, rituximab + fludarabine + cyclophosphamide; R-HyperCAD, rituximab + fractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone; RM, rituximab maintenance; yr, year.

a CR rates include unconfirmed CR.

b Data based on previously untreated subjects.

2.2. Therapy for R/R 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 R-BAC {Visco 2013} and 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 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 2000, Inwards 2008, Kaufmann 2004, Sachanas 2011}.

SCT 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 1997,

Vose 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 2015}. However, in these studies, alloSCT has been associated with high morbidity and non-relapse mortality, mostly due to graft-versus-host disease (GVHD) and its complications and affecting 30% to 40% of patients.

Targeted therapies such as bortezomib, lenalidomide, ibrutinib, acalabrutinib, and zanubrutinib have been approved in the US within the last 2 decades for the treatment of r/r MCL (see Table 2), and temsirolimus is approved in the European Union (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 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 response (CR). The median DOR was 9.3 months, and the median time to progression was 6.1 months {VELCADE 2017}. 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 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 CR {REVLIMID 2015}. 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 2013}. The ORR based on investigator review of CT scans was 68%, including 21% CR. 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 PD (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 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 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.

More recently, acalabrutinib, an oral Bruton's tyrosine kinase inhibitor (BTKi), was approved in the US for the treatment of relapsed or refractory MCL {Calquence 2017}. 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 of 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 {Calquence 2017, Wang 2018}. 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% {Calquence 2017}. 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 2018}.

In November 2019, zanubrutinib, an oral BTKi, was approved in the US for the treatment of adult patients with MCL who have received at least 1 prior therapy. Approval was based on a single-arm, open-label, multicenter Phase 2 trial of 86 subjects with r/r MCL who had received at least 1 prior therapy (median of 2 prior lines of therapy; range: 1 to 4 prior lines) {BRUKINSA 2019}. Similar to the acalabrutinib pivotal trial, subjects who had prior exposure to a BTKi were excluded, although it was noted that this trial included a higher proportion of subjects with refractory disease (52% vs 24% in the acalabrutinib trial) {Song 2020}. The ORR as assessed by independent review was 84% and the CR rate was 69%. The median DOR was 19.5 months with a median follow-up for response of 16.4 months, and the median PFS was 22.1 months based on a median follow-up of 19.2 months. The most common Grade 3 and higher AEs were neutropenia (17 subjects, 20%) and lung infection/pneumonia (8 subjects, 9%).

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 2006}
Lenalidomide[b]	134	ORR 26%; CR 7%; DOR 16.6m	{Goy 2013}
Ibrutinib	111	ORR 68%; CR 21%; DOR 17.5m	{Wang 2013}
Acalabrutinib	124	ORR 81%; CR 40%; DOR NR	{Wang 2018}
Zanubrutinib	86	ORR 84%; CR 69%; DOR 19.5m	{Song 2020}

Abbreviations: CR, complete response; DOR, duration of response; m, month; MCL, mantle cell lymphoma; NR, no response; ORR, objective response rate; r/r, relapsed/refractory.
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 2016}
31	ORR 32% 19% CR rate; mOS 8.4m	{Cheah 2015}

Abbreviations: CR, complete response; m, month; MCL, mantle cell lymphoma; mOS, median overall survival; ORR, objective response rate; r/r, relapsed/refractory.

2.2.1. Rationale for Cohort 3

Despite relatively high ORRs, treatment with BTKi is not considered curative. As noted in Section 2.2, most patients experience disease progression following BTKi treatment, and these patients have limited treatment options and poor outcomes to salvage therapy. Furthermore, approximately one-third of patients demonstrate primary resistance to BTKi {Martin 2016}.

Certain features of aggressive MCL such as p53 mutations, blastoid morphology, and high Ki-67 index are associated with poor response to BTKi {Liebers 2018, Rule 2017, Rule 2019, Wang 2016}. A pooled analysis of 370 subjects with r/r MCL who received ibrutinib across 3 clinical studies demonstrated an association between disease morphology and clinical outcomes: compared with subjects who had nonblastoid MCL, subjects with blastoid MCL had shorter median DOR (8.5 vs 18.8 months), median PFS (5.1 vs 14.6 months), and median OS (12.8 months vs not reached at 2 years) {Rule 2017}. In a follow-up to this analysis, p53 mutational status was also found to be associated with clinical outcomes: compared with subjects bearing wildtype p53, subjects with mutated p53 had worse ORR (55% [with no CRs] vs 70%), median PFS (4.0 vs 12.0 months), and median OS (10.3 vs 33.6 months) {Rule 2019}. Additionally, in a study of 50 subjects with r/r MCL who were treated with ibrutinib in combination with rituximab, subjects with a Ki-67 index ≥ 50% had worse outcomes compared with subjects with a Ki-67 index < 50% (ORRs of 50% vs 100% and CR rates of 17% vs 54%) {Wang 2016}. These results are further compounded by the finding that poor prognostic factors increase with increasing lines of therapy {Kumar 2019, Rule 2017}.

Thus, new treatment strategies based on novel targets or different mechanisms of action are needed to induce earlier, more durable responses in r/r MCL with aggressive clinical features. Cohort 3 of this study will specifically evaluate the efficacy and safety profile of a chimeric antigen receptor (CAR) T-cell therapy, KTE-X19, in subjects with BTKi-naïve r/r MCL.

2.2.1.1. Selection of Historical Control ORR

A meta-analysis was performed to determine the historical control ORR among patients with r/r MCL. This meta-analysis included published clinical studies that reported ORRs of therapies for BTKi-naïve patients with r/r MCL, including studies of commonly used regimens for r/r MCL such as BR, bortezomib plus rituximab, and lenalidomide plus rituximab. The studies included in this meta-analysis are outlined in Table 4. The results of this meta-analysis demonstrated a historical control ORR of 57%. Thus, a historical control ORR of 57% will be used for hypothesis testing for the primary efficacy endpoint in Cohort 3.

Table 4. Studies Included in the Meta-analysis to Determine Historical Control ORR

Primary Author	Treatment	ITT (N)	Number of Responders (n)
{Wang 2018}	Acalabrutinib	124	100
{Ohmachi 2010}	Bendamustine	11	11
{Goy 2005}	Bortezomib	29	12
{Goy 2009}	Bortezomib	141	45
{Strauss 2006}	Bortezomib	24	7
{Kouroukis 2011}	Bortezomib + gemcitabine	25	15
{Agathocleous 2010}	Bortezomib + rituximab	19	11
{Baiocchi 2011}	Bortezomib + rituximab	14	4
{Chiappella 2010}	Bortezomib + rituximab	25	16
{Czuczman 2015}	BR	45	37
{Robinson 2008}	BR	12	11
{Rummel 2005}	BR	16	12
{Rummel 2016}	BR	24	17
{Forstpointner 2004}	FCM	24	11
{Dreyling 2016}	Ibrutinib	139	107
{Furtado 2012}	Ibrutinib	8	5
{Maruyama 2016}	Ibrutinib	16	14
{Wang 2014}	Ibrutinib	120	75
{Wang 2015}	Ibrutinib	111	74
{Goy 2017}	Ibrutinib + lenalidomide + rituximab	16	6
{Jerkeman 2018}	Ibrutinib + lenalidomide + rituximab	50	38
{Jain 2018}	Ibrutinib + rituximab	50	44
{Eve 2012}	Lenalidomide	26	8
{Goy 2015}	Lenalidomide	136	38
{Habermann 2009}	Lenalidomide	15	8
{Trneny 2016}	Lenalidomide	170	78
{Zinzani 2013}	Lenalidomide	57	25
{Sharman 2019}	Lenalidomide + rituximab	70	38
{Wang 2015}	Lenalidomide + rituximab	46	26
{Visco 2013}	R-BAC	20	16
{Igarashi 2002}	Rituximab	13	6

Primary Author	Treatment	ITT (N)	Number of Responders (n)
{Rummel 2016}	Rituximab + fludarabine	23	6
{Ansell 2008}	Temsirolimus	27	11
{Dreyling 2016}	Temsirolimus	141	65
{Jurczak 2018}	Temsirolimus	90	23
{Verhoef 2008}	Temsirolimus	54	12
{Verhoef 2008}	Temsirolimus	54	3
{Witzig 2005}	Temsirolimus	34	13
{Davids 2017}	Venetoclax	28	21
{Tam 2018}	Venetoclax + ibrutinib	24	17
{Song 2020}	Zanubrutinib	86	72
{Tam 2019}	Zanubrutinib	37	32

Abbreviations: BR, bendamustine + rituximab; FCM, cyclophosphamide + fludarabine + mitoxantrone; ITT, intent-to-treat; ORR, objective response rate; R-BAC, rituximab + bendamustine + cytarabine.

2.3. Novel T-cell Immunotherapies

T cells play a central role in the immune system by destroying diseased cells, including tumor cells, throughout the body {Kershaw 2013}. Studies with tumor vaccines {Kantoff 2010}, immune checkpoint inhibitors {Hamid 2013, Wolchok 2013}, tumor-infiltrating lymphocytes {Rosenberg 2011}, the bispecific CD19-directed CD3 T-cell engager blinatumomab {BLINCYTO 2019}, and CAR T cells {KYMRIAH 2018, YESCARTA 2019a, YESCARTA 2019b} have demonstrated the potential of T cells to treat cancer.

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

2.4. CD19 and Expression

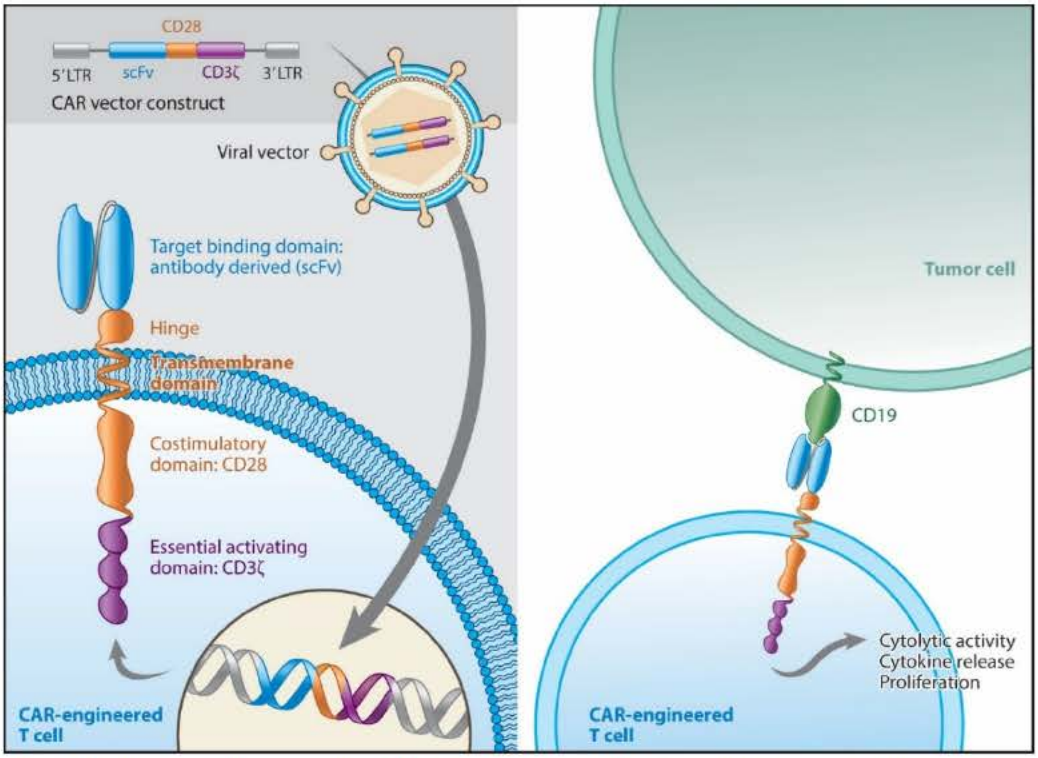
CD19 is a 95 kD transmembrane protein expressed in the B-cell lineage. It is expressed in normal B cells starting at the pro-B-cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained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

2.5. Anti-CD19 CAR T-cell Product

Anti-CD19 CAR T cells are autologous human T cells that have been engineered to express an extracellular single-chain variable fragment 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; investigational new drug [IND] 13871) (Figure 2) {Kochenderfer 2009, Kochenderfer 2010} is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 {Nicholson 1997}CD19 CAR T cells {Kowolik 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.

Figure 2. Anti-CD19 CAR



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

2.5.1. 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 CCI [redacted] 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 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 1997, Cheah 2015, Cheah 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.

2.5.2. 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, CCI [redacted], 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.

2.6. 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.

2.7. KTE-X19

Kite Pharma, Inc., (hereafter referred to as Kite) is developing an engineered autologous cell therapy (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 2014}. Refer to the current IB for more details.

3. STUDY DESIGN

3.1. General Study Design

Study KTE-C19-102 (hereafter referred to as ZUMA-2) 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 and anti-CD20 antibody therapy with or without ibrutinib or acalabrutinib. The study will evaluate the ORR and durability of response after treatment with KTE-X19. An open-label, 3-cohort design is used, with the following cohorts:

- Cohort 1 and Cohort 2 will include subjects with r/r MCL who have been treated with up to 5 prior regimens including a BTKi. Prior therapy must have included all of the following: anthracycline or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, and ibrutinib or acalabrutinib.
- Cohort 3 will include subjects with r/r MCL who have been treated with up to 5 prior regimens but have not received prior therapy with a BTKi. Prior therapy must have included anthracycline-, bendamustine-, or high-dose cytarabine-containing chemotherapy and anti-CD20 monoclonal antibody therapy.

Up to approximately 220 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 2 x 10^6 anti-CD19 CAR T 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 in Cohort 1, with a target ORR in the alternative hypothesis of 50% and a futility criterion that the ORR is no more than 25%. As of 28 May 2019, Cohort 1 has completed enrollment.
- Cohort 2 will treat up to 40 KTE-X19 subjects at a target dose of 0.5 x 10^6 anti-CD19 CAR T cells/kg. As of 01 May 2018, Cohort 2 has completed enrollment.
- Cohort 3 will enroll and treat up to approximately 90 KTE-X19 subjects at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg, with a target ORR in the alternative hypothesis of 75% and a null hypothesis that the ORR is 57% or less.

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 Data Safety Monitoring Board (DSMB) will review safety and/or efficacy data from Cohort 1 and Cohort 2 at 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 for Cohort 1 and Cohort 2 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 9.12.

A scientific steering committee, comprising the study sponsor and at least 3 study investigators, will be specifically chartered to review the safety data from Cohort 3 and make recommendations on further study conduct. The scientific steering committee will meet after 15 subjects in Cohort 3 have been enrolled, treated with KTE-X19, and have had the opportunity to be followed for 30 days, and again after 50 subjects in Cohort 3 have been enrolled, treated with KTE-X19, and have had the opportunity to be followed for 3 months. The scientific steering committee may meet more often as needed. For details surrounding the scientific steering committee, refer to Section 9.11 and Section 9.12.

For study requirements assigned to each study period, refer to the schedules 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 220 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 participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and, if applicable, timing of transition to the separate LTFU study, KT-US-982-5968 (discussed in Section 3.5.3).

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

3.5.2. Completion of Study

Completion of the study for subjects in Cohorts 1 and 2 is defined as the time at which the last subject in Cohorts 1 and 2 completes at least 24 months of assessments and transitions to KT-US-982-5968, is considered lost to follow-up, withdraws consent, or dies.

Completion of the study for subjects in Cohort 3 is defined as the time at which the last subject in Cohort 3 completes at least 24 months of assessments and transitions to KT-US-982-5968, is considered lost to follow-up, withdraws consent, or dies.

Upon activation of KT-US-982-5968 at the subject's study site, the subject will be offered the opportunity to complete LTFU assessments under the KT-US-982-5968 protocol.

3.5.3. LTFU

All subjects who received an infusion of anti-CD19 CAR T cells will be provided the opportunity to transition to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/serious AEs (SAEs) suspected to be possibly related to anti-CD19 CAR T cells as defined in KT-US-982-5968, presence of replication-competent retrovirus (RCR), and/or insertional mutagenesis for up to 15 years from the time of anti-CD19 CAR T-cell infusion (also refer to Section 7.12.9).

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

4. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the 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 (ICF), will receive a unique subject identification (ID) number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. The subject 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.

— Cohort 1 and Cohort 2: Prior therapy must have included:

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

— Cohort 3: Prior therapy must have included anthracycline-, bendamustine-, or high-dose cytarabine-containing chemotherapy and anti-CD20 monoclonal antibody therapy. Subjects in Cohort 3 must not have received prior therapy with a BTKi.

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 $\geq$ 2 cm

105) For subjects in Cohort 1 and Cohort 2 only: 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; as applicable for subjects in Cohort 1 and Cohort 2) 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/μL

111) Platelet count ≥ 75,000/μL. For subjects in Cohort 3 with bone marrow involvement, platelet count ≥ 50,000/μL is acceptable.

112) Absolute lymphocyte count ≥ 100/μL

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

- Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min
- Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 2.5 upper limit of normal (ULN)
- Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome
- Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings. For subjects in Cohort 3, a multigated acquisition (MUGA) scan may be used in place of ECHO.
- No clinically significant pleural effusion for subjects in Cohort 1 and Cohort 2, and no clinically significant pleural effusion, pericardial effusion, or ascites for subjects in Cohort 3
- 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 alloSCT, with the exception of subjects in Cohort 3 with no donor cells detected on chimerism > 100 days after alloSCT

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

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. For subjects in Cohort 3 enrolled in France, those with any history of acute or chronic hepatitis B or C infection are excluded.

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 (CSF) malignant cells or brain metastases or with a history of CNS lymphoma, CSF 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 deep vein thrombosis or pulmonary embolism requiring therapeutic anticoagulation within 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) Females 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 at the discretion of the investigator and after discussion with the medical monitor, will be:
  - Cohort 1 and Cohort 2: dexamethasone, ibrutinib, or acalabrutinib
  - Cohort 3: dexamethasone, radiotherapy, specified chemotherapy, or any combination thereof, as detailed in Section 6.2.1.2
- 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

6.2.1.1. Cohort 1 and Cohort 2

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 ≥ 1,000 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.

In Cohort 1 and Cohort 2, bridging therapy is allowed with (1) dexamethasone at a dose of 20 to 40 mg or equivalent, either orally (PO) or IV daily for 1 to 4 days, (2) ibrutinib at a dose of 560 mg PO daily or most recent dose if there had been a dose adjustment, or (3) acalabrutinib 100 mg PO every 12 hours or most recent dose if there had been a dose adjustment. Choice of corticosteroid and dose can be adjusted for age/comorbidities or per local or institutional guidelines.

If bridging therapy is administered, the subject must undergo another positron emission tomography-computed tomography (PET-CT) or diagnostic CT to assess disease status prior to receiving conditioning chemotherapy and subsequent anti-CD19 CAR T-cell infusion (refer to Section 7.8 for detailed timing and imaging requirements).

6.2.1.2. Cohort 3

At the discretion of the investigator and per institutional guidelines and standard of care and after discussion with the medical monitor, bridging therapy is recommended for all subjects, particularly those with rapidly progressing disease, clinical deterioration, or high disease burden at screening (eg, > 25% marrow involvement and/or ≥ 1,000 leukemic phase mantle cells/mm^3 in the peripheral circulation). When administered in this context, bridging therapy allows for standard-of-care therapies to be administered to subjects during the period between leukapheresis and the manufacturing of KTE-X19. A retrospective analysis demonstrated the impact of bridging therapy in patients with high tumor burden: no significant differences in the incidence of cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) were observed for patients who received bridging therapy compared with those who received no bridging therapy, demonstrating the potential for bridging therapy to reduce tumoral mass while maintaining the safety profile of CAR T-cell therapy {Lutfi 2020}.

If prescribed, bridging therapy must be administered after leukapheresis and must be completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy.

Bridging therapy is allowed with the following regimens as shown in Table 5:
(1) dexamethasone at a dose of 20 to 40 mg or equivalent, either PO or IV daily for 1 to 4 days; (2) palliative radiotherapy to localized lesions at a dose of up to 30 Gy in 10 fractions or equivalent; (3) specified chemotherapy; or (4) any combination of 1 specified chemotherapy and/or corticosteroid and/or radiotherapy. Bridging regimen should be discussed with the Kite medical monitor, and BTKis are not permitted for bridging therapy. Dose can be adjusted for age/comorbidities or per local or institutional guidelines. If radiotherapy is considered for bridging, the radiotherapy modality should be discussed with the Kite medical monitor. Radiotherapy should be administered per local or institutional guidelines. Irradiated lesions can no longer serve as target lesions, and other target lesions must be present to allow for response assessment. Use of any other chemotherapeutic or targeted agent or palliative radiotherapy is to be discussed with the Kite medical monitor.

If bridging therapy is administered, the subject must undergo another PET-CT or diagnostic CT to assess disease status prior to receiving conditioning chemotherapy and subsequent anti-CD19 CAR T-cell infusion (refer to Section 7.8 for detailed timing and imaging requirements).

Bridging therapy will be supplied by the investigative site unless otherwise noted. Sites should refer to the current agent-specific product label(s) for guidance on packaging, storage, preparation, administration (including necessary dose reductions for organ dysfunction, pregnancy testing requirements, etc.), and toxicity management associated with the administration of the agent(s) selected.

Table 5. Bridging Therapy for Cohort 3

Bridging Regimen Options	
(1) Corticosteroid	Dexamethasone at a dose of 20 to 40 mg or equivalent, either PO or IV daily for 1 to 4 days Choice of corticosteroid and dose can be adjusted for age/comorbidities or per local or institutional guidelines
(2) Radiotherapy	Radiotherapy to localized lesions up to 30 Gy in 10 fractions or equivalent
(3) Chemotherapy	Cytarabine 1 to 2 g/m² IV for a maximum of 2 days
	Cyclophosphamide 1 to 2 g/m² IV for a maximum of 2 days, or hyperfractionated cyclophosphamide 300 mg/m² administered every 12 hours for 6 doses
(4) Any combination of the following: 1 of the above chemotherapies AND/OR choice of corticosteroid as stated above AND/OR radiotherapy to localized lesions as stated above	

Abbreviations: IV, intravenous; PO, oral.
Note: Use of any other chemotherapeutic or targeted agent or palliative radiotherapy is to be discussed with the Kite medical monitor.

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 fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days to induce lymphocyte depletion and create an optimal environment for expansion of anti-CD19 CAR T cells in vivo. Conditioning chemotherapy should only commence when the KTE-X19 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.

In exceptional cases, a KTE-X19 product lot that does not meet certain release specification criteria may be administered to a subject, when necessary to avoid an immediate significant hazard to the subject and having considered alternative options including the product lot remanufacture. Relevant country regulations will be followed and notifications to concerned regulatory agencies and IRBs/IECs will be performed as necessary per local requirements, in case such out-of-specification product lot is supplied and administered to a subject.

6.2.3.1. Dose Rationale

This study is designed to evaluate safety:efficacy of two anti-CD19 CAR T cell doses, both of which are administered after the same lymphodepleting regimen. The higher cell dose of 2×10^6 anti-CD19 CAR T cells/kg is evaluated in Cohort 1 and Cohort 3. The lower dose of 0.5×10^6 anti-CD19 CAR T cells/kg is evaluated in Cohort 2.

The recommended treatment regimen for Cohort 1 and Cohort 3 (lymphodepletion with cyclophosphamide 500 mg/m^2 dose and fludarabine 30 mg/m^2 given concurrently for 3 days followed by a target dose of 2×10^6 anti-CD19 CAR T cells/kg, with a maximum dose of 2×10^8 anti-CD19 CAR T cells for subjects ≥ 100 kg) 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 2017}. The recommended treatment regimen for Cohort 3 is further supported by the favorable safety:efficacy profile seen in subjects treated with KTE-X19 in ZUMA-2 Cohort 1.

At the time of the interim analysis 3, 13 subjects (46%) had experienced Grade 3 or Grade 4 neurologic toxicities (data on file). 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 from Day 0 to Day 28 [$AUC_{0\text{-}28}$]) relative to that seen in subjects treated in ZUMA-1. Given that CAR T cell peak and $AUC_{0\text{-}28}$ are associated with Grade 3 or higher neurologic toxicities in ZUMA-1 patients {Neelapu 2016}, the sponsor opted to reduce the KTE‑X19 target dose to 0.5×10^6 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 0.5×10^6 anti-CD19 CAR T cells/kg, with a maximum dose of 0.5×10^8 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, granulocyte colony-stimulating factor [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 therapies will be collected for 5 years after the anti-CD19 CAR T-cell infusion or until disease progression or subsequent therapy, whichever occurs first. Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, vaccinations, and anticancer therapies (eg, chemotherapy, immunotherapy, targeted therapy, hormone therapy, SCT/bone marrow transplant, high-dose corticosteroids, radiation, surgery, and investigational products).

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) or until initiation of a

new anticancer therapy, whichever occurs first. For subjects who are not enrolled (eg, screen failure or not leukapheresed), only concurrent therapies related to SAEs will be recorded from the date of the screening informed consent through 30 days after the last study-specific screening procedure.

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, such as non-study specified chemotherapy, immunotherapy, targeted agents, SCT, or radiation therapy, administered after anti-CD19 CAR T-cell infusion that is necessary to treat a subject's disease will be recorded for all subjects until one of the following happens: the subject transitions to the KT-US-982-5968 LTFU study, is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled but do not receive an anti-CD19 CAR T-cell infusion, any additional anticancer therapy will also be collected until the subject completes their participation in the current study (refer to Section 3.5.2), is considered lost to follow-up, withdraws consent, or dies, whichever occurs first.

6.3. Study Treatment Schedule

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

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells [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 [redacted]. 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

6.3.2.1. Cohort 1 and Cohort 2

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 ≥ 1,000 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.

In Cohort 1 and Cohort 2, bridging therapy is allowed with (1) dexamethasone at a dose of 20 to 40 mg or equivalent, either PO or IV daily for 1 to 4 days, (2) ibrutinib at a dose of 560 mg PO daily or most recent dose if there had been a dose adjustment, or (3) acalabrutinib 100 mg PO every 12 hours or most recent dose if there had been a dose adjustment. Choice of corticosteroid and dose can be adjusted for age/comorbidities or per local or institutional guidelines.

If bridging therapy is administered, the subject must undergo another PET-CT or diagnostic CT to assess disease status prior to receiving conditioning chemotherapy and subsequent anti-CD19 CAR T-cell infusion (refer to Section 7.8 for detailed timing and imaging requirements).

6.3.2.2. Cohort 3

At the discretion of the investigator and per institutional guidelines and standard of care and after discussion with the medical monitor, bridging therapy is recommended for all subjects, particularly those with rapidly progressing disease, clinical deterioration, or high disease burden at screening (eg, > 25% marrow involvement and/or ≥ 1,000 leukemic phase mantle cells/mm^3 in the peripheral circulation).

If prescribed, bridging therapy must be administered after leukapheresis and must be completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy.

Bridging regimen options for Cohort 3 are described in Section 6.2.1.2.

If bridging therapy is administered, the subject must undergo another PET-CT or diagnostic CT to assess disease status prior to receiving conditioning chemotherapy and subsequent anti-CD19 CAR T-cell infusion (refer to Section 7.8 for detailed timing and imaging requirements).

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 beginning on Day –5 through Day –3 with 2 rest days 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
- Cyclophosphamide 500 mg/m^2 IV over approximately 60 minutes
- Fludarabine 30 mg/m^2 IV over approximately 30 minutes
- An additional 1 L of 0.9% NaCl at the completion of the cyclophosphamide infusion
- Add mesna per institutional guidelines

Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours). In general, subjects should be kept well - hydrated, but closely monitored, to prevent fluid overload. 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 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 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 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 {YESCARTA 2017}. 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 2016} and were shown to increase levels of cytokines known to support T-cell expansion and survival {Kochenderfer 2017a}. 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 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 or other antihistamine used as per local institution

Subjects in Cohort 1 and Cohort 3 will receive anti-CD19 CAR T-cell treatment consisting of a single infusion of CAR-transduced autologous T cells administered IV at a target dose of 2×10^6 anti-CD19 CAR T cells/kg. A minimum dose of 1×10^6 anti-CD19 CAR T cells/kg may be administered for subjects in Cohort 1 and Cohort 3. Subjects in Cohort 2 will receive KTE-X19 treatment consisting of a single infusion of CAR-transduced autologous T cells administered IV at a target dose of 0.5×10^6 anti-CD19 CAR T cells/kg. For subjects weighing > 100 kg, a maximum flat dose of 2×10^8 anti-CD19 CAR T cells will be administered for Cohort 1 and Cohort 3 or 0.5×10^8 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 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.

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 (Cohort 1 and Cohort 2: Table 7 and Table 8; Cohort 3: Table 9 and Table 10) 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 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. Subjects in Cohort 3 will have disease staging at study entry performed per the Lugano Classification {Cheson 2014} (refer to Section 18.2).

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

7.4. Physical Exam, Vital Signs, Performance Status, and PROs

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.

7.4.1. PROs

7.4.1.1. EQ-5D

The EQ-5D will be completed by all subjects, prior to any other assessment (excluding blood draws and imaging), 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.

7.4.1.2. EORTC-QLQ-C30 (Cohort 3 Only)

For subjects in Cohort 3 only, the EORTC-QLQ-C30 will be completed by the subject, prior to any other assessment (excluding blood draws and imaging), at the screening visit and at other times noted in the SOA.

This measure provides a multidimensional assessment of health-related quality of life (HRQoL). The EORTC-QLQ-C30 version 3.0 includes the following content:

- 5 multi-item functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning)
- 3 multi-item symptom scales (fatigue, nausea and vomiting, pain)
- 6 single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties)
- 1 global health status/quality of life (QoL) scale

Each scale is measured from 0 to 100 after a linear transformation. Higher scores for functional scales and for the global health status/QoL scale indicate a higher level of functioning and a better HRQoL, whereas higher scores in symptom scales represent a higher level of symptoms.

This instrument does not sum together all items, which can potentially group differences and allows an assessment of change across the 15 different domains. In its current version (version 3), the questionnaire takes approximately 11 minutes to complete.

7.5. Neurological Assessment

7.5.1. Cohort 1 and Cohort 2

For subjects in Cohort 1 and Cohort 2, 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.

The severity of neurologic events in Cohort 1 and Cohort 2 will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 as described in Section 9.2.1.

7.5.2. Cohort 3

For subjects in Cohort 3, neurological assessments, including an immune effector cell-associated encephalopathy (ICE) cognition assessment (Table 17), will be performed according to the time points specified in the SOA.

The subject's neurological status will be evaluated at screening to establish a baseline. A subsequent postbaseline assessment will be performed at Week 4. If the ICE assessment has not returned to baseline (± 1 point) at Week 4, then the assessment will continue to be performed at Month 3 and every 3 months until the results have returned to baseline (± 1 point) or until Month 24.

The severity of neurologic events in Cohort 3 will be graded using CTCAE version 4.03 and the American Society for Transplantation and Cellular Therapy (ASTCT) ICANS consensus grading system as described in Section 9.2.1.

For subjects who are hospitalized with neurologic events of Grade 2 or higher, grading should be continued daily during any period of Grade 2 or higher neurologic events until symptoms return to baseline. Changes in neurological status should be reported as an AE if considered clinically significant at the discretion of the investigator.

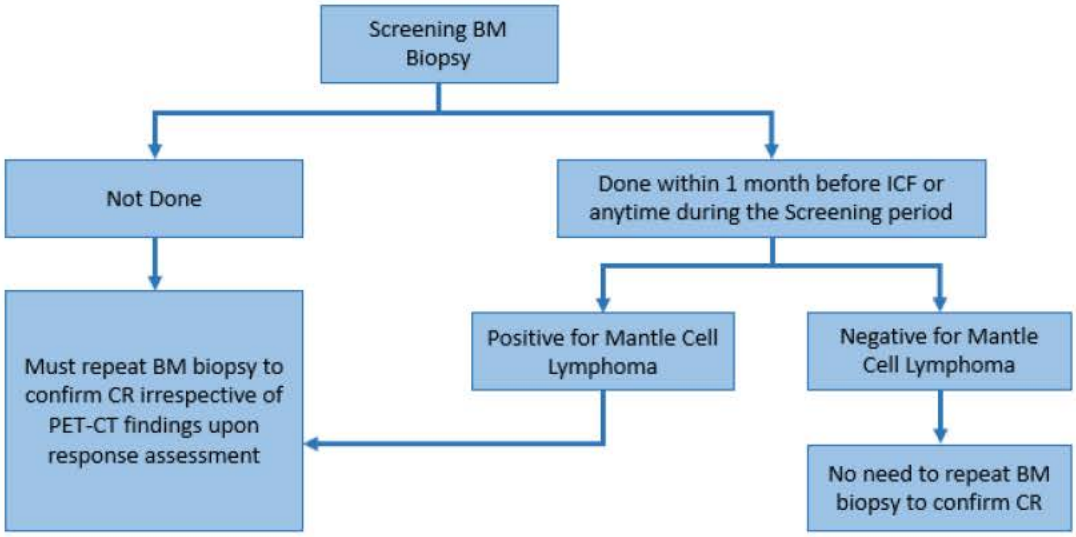
7.6. Bone Marrow Assessment

A bone marrow aspirate or biopsy will be performed at screening, if there is a prior history or suspicion of bone marrow involvement and not previously performed within 4 weeks of signing consent. The bone marrow aspirate or 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 aspirate or biopsy available must undergo another bone marrow aspirate or biopsy upon first determination of a CR via PET. Subjects with a negative bone marrow aspirate or biopsy (ie- no MCL) at screening, and patients with a partial metabolic response, stable disease (SD) or PD at any disease response assessment time point do not require a follow-up bone marrow aspirate or biopsy (Figure 3).

For subjects in Cohort 3 only, if collected at screening, bone marrow aspirate or biopsy should also be submitted to the central laboratory as formalin-fixed paraffin-embedded (FFPE) block(s) or slides for minimal residual disease (MRD) analysis.

Figure 3. Bone Marrow Assessment Schema



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

To confirm a CR, the bone marrow aspirate or 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 aspirate or biopsy, additional bone marrow aspirates or biopsies are only required in case of clinical suspicion of disease progression in the bone marrow only. Refer to Section 7.8, Section 18.1 (Cohort 1), and Section 18.2 (Cohort 2 and Cohort 3) for treatment response assessment requirements per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma {Cheson 2007} and Lugano Classification {Cheson 2014}.

Bone marrow aspirate or 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 CNS malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture performed at the screening visit for examination of CSF. In addition, lumbar puncture should be performed 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 Section 18.1 {Cheson 2007}. Flow cytometric, molecular, or cytogenetic studies will not be used to determine response. For subjects enrolled in Cohort 2 and Cohort 3, disease assessments by the site investigator will be evaluated per the Lugano Classification, as described in Section 18.2 {Cheson 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. PET-CT performed following the subject's last line of therapy and prior to signing the consent may be used for confirmation of eligibility. PET-CT should be performed as close to enrollment as possible. If PET-CT will be older than 28 days at the initiation of conditioning chemotherapy or if the subject receives any bridging therapy between the last PET-CT and conditioning chemotherapy, PET-CT must be repeated prior to the initiation of conditioning chemotherapy to establish a new baseline. However, if the subject receives bridging therapy and the original PET-CT scan is within 28 days of the initiation of conditioning chemotherapy, only the diagnostic CT portion of the scan needs to be repeated prior to the initiation of conditioning chemotherapy.

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 PD occurs. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA.

A bone marrow aspirate or biopsy will be performed in subjects who are being assessed for CR, as described in Section 18.1 (Cohort 1) and Section 18.2 (Cohort 2 and Cohort 3). Per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2007} and Lugano Classification {Cheson 2014}, a bone marrow aspirate or 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 or 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 2014} will be performed for all cohorts. 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 PD, 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. For subjects in Cohort 3, a MUGA scan may be used in place of ECHO.

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

7.10. Brain MRI

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. For subjects in Cohort 3, a brain MRI performed within 28 days prior to signing the consent is also acceptable.

Evaluation of any new onset of ≥ Grade 2 neurologic toxicity should include a brain MRI as described in the current IB.

For subjects in Cohort 3 with a contraindication for MRI, a CT scan of the brain may be used but must include contrast.

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:
  - Chemistry panel: 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, ALT/glutamic-pyruvic transaminase (GPT), AST/glutamic-oxaloacetic transaminase (GOT), total bilirubin, direct bilirubin, uric acid
  - C-reactive protein (CRP)
  - LDH

- Ferritin
- Complete blood count (CBC) with differential (for clinical/safety evaluation)

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 CBC with differential will be collected and sent to the central laboratory for pharmacokinetic assessments at the time points specified in the SOA. Note that these samples are distinct from samples collected and sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation.
  - Blood draws for PBMC (including the analysis of lymphocyte subsets, anti-CD19 CAR T cells, and RCR) and cytokine analysis will be performed at intervals outlined in the SOA.
    - Cohort 1 and Cohort 2: After Month 24, PBMC samples will only be collected if an RCR event is clinically suspected and/or a subject's PBMC sample tested positive for RCR at any time point within the first year. If the latter, samples will continue to be collected and tested annually for up to 15 years or as clinically indicated.
    - Cohort 3:
      - PBMCs for RCR testing will be collected at baseline (before leukapheresis) and at Months 3, 6, and 12. Thereafter, samples will only be collected if an RCR event is clinically suspected and/or a subject's PBMC sample tested positive for RCR at any time point within the first year. If the latter, samples will continue to be collected and tested annually for up to 15 years or as clinically indicated.
      - PBMCs for analysis of lymphocyte subsets and anti-CD19 CAR T cells will continue to be collected at the time points specified in the SOA even if PBMCs for RCR testing are no longer required to be collected.
    - All cohorts: If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.

— Serum samples will also be drawn for anti-CD19 CAR antibodies

  - Cohort 1 and Cohort 2: 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.

  - Cohort 3: Serum samples for anti-CD19 CAR antibodies are not required after the Month 3 visit.

— Archived and/or fresh (newly acquired) tumor tissue will be collected as outlined in the SOAs and per Section 7.11.1 for central pathologic review, evaluation of prognostic markers including p53 and Ki-67, CCI [redacted] 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 SOAs 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 CCI [redacted] related to the tumor immune environment may also be evaluated in archived and fresh (newly acquired) 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. CCI [redacted]

Unless medically contraindicated, CSF, as well as any additional subject samples (eg, pleural fluid), should be collected from subjects who develop ≥ Grade 2 neurologic toxicity after KTE-X19 infusion 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

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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. If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.

In addition, baseline leukapheresis and final anti-CD19 CAR T cells samples will be banked and may be analyzed by immunophenotyping, qPCR, genomic analysis, and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of immune- or disease-related genomic DNA, RNA, or protein markers.

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For subjects who sign the optional portion of the consent form (and for all subjects with accessible tumor at select sites), on-study paired core biopsies of tumor will be performed at baseline, during the IP treatment period (see Section 7.12.6.2 and SOA for timing by cohort), and at Month 6 following anti-CD19 CAR T cells infusion when expansion and tumor infiltration with CAR T cells is expected. (Note: Optional consent for baseline fresh [newly acquired] tumor biopsy applies only to subjects in Cohort 1 and Cohort 2. For subjects in Cohort 3, a new tumor biopsy is requested to be collected and submitted prior to leukapheresis if clinically feasible.) In addition, persisting, relapsing, or emerging lesions could also be biopsied to help determine eligibility for retreatment or mechanisms of tumor resistance. Exploratory analysis of tumor or immune cell markers that correlate with response to KTE-X19 or disease prognosis will be executed.

These samples and any other components from these samples may be stored up to 15 years from the date the last subject is dosed 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:

- Demographic data
- Medical history (including disease staging at study entry per the Lugano Classification {Cheson 2014} for subjects in Cohort 3)
- EQ-5D questionnaire (prior to any other assessments/procedures being performed, excluding blood draws and imaging)
- EORTC-QLQ-C30 (Cohort 3 only; prior to any other assessments/procedures being performed, excluding blood draws and imaging)
- Physical examination, including height and weight
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
    - Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture for examination of CSF.
- ECOG performance status

- Neurological assessment including MMSE (Cohort 1 and Cohort 2) or ICE (Cohort 3)
- ECG
- LVEF and pericardial effusion assessment by ECHO (or MUGA for subjects in Cohort 3)
- Imaging studies
  - Brain MRI (or CT with contrast for subjects in Cohort 3 with a contraindication for 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. PET-CT should be performed as close to enrollment as possible. Refer to Section 7.8 for detailed timing and imaging requirements, including the potential need for repeat baseline scans prior to conditioning chemotherapy.
- Bone marrow aspirate or biopsy as needed due to prior history or suspicion of bone marrow involvement (if not done within 4 weeks prior to screening)
  - If collected at screening, bone marrow aspirate or biopsy should be submitted to the central laboratory as FFPE block(s) or slides for MRD analysis (Cohort 3 only)
- Labs
  - β-HCG pregnancy test (serum or urine) on all females of childbearing potential
  - Chemistry panel with CRP
  - Creatinine clearance (as estimated by Cockcroft Gault)
  - CBC with differential (local laboratory)
- SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant therapies documentation and previous cancer treatment history
- After eligibility is confirmed, collection of archived tumor sample. For subjects who signed the optional portion of the consent, fresh (newly acquired) tumor sample(s) and CSF samples may also be provided.
  - Note: Optional consent for baseline fresh tumor biopsy applies only to subjects in Cohort 1 and Cohort 2. For subjects in Cohort 3, a new tumor biopsy is requested to be collected and submitted prior to leukapheresis if clinically feasible.

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 or that become out of window relative to the initiation of conditioning chemotherapy (eg, PET-CT scan, blood testing) need to be repeated; all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs > 28 days from the signing of the original informed consent or if leukapheresis is delayed > 28 days from the signing of the original informed consent, subjects must be reconsented and repeat all screening procedures/assessments.

7.12.3. Enrollment/Leukapheresis

Criteria that must be met before initiating leukapheresis are described in Section 7.12.3.1.1 for subjects in Cohort 1 and Cohort 2 and in Section 7.12.3.1.2 for subjects in Cohort 3. Procedures to be performed on the leukapheresis collection day for all subjects are described in Section 7.12.3.2.

7.12.3.1. Requirements for Initiating Leukapheresis

7.12.3.1.1. Cohort 1 and Cohort 2

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.

7.12.3.1.2. Cohort 3

Leukapheresis is to be performed within approximately 5 days after eligibility confirmation. Refer to Section 6.3.1 for a description and definition of leukapheresis. Before leukapheresis commences, the following criteria must be met:

- In general, all criteria that were confirmed during screening for eligibility must not be known to be violated before leukapheresis, except that allowance will be made for expected normal variation of within 5% of laboratory test value cutoffs noted in the inclusion criteria. Additionally, the investigator must review and confirm that the last CBC with differential and chemistry panel results from the blood draw before the start of leukapheresis meet the criteria detailed in Section 5.1 ± 5%. If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and the results are outside the criteria listed in Section 5.1 (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria), the subject should not be leukapheresed and the Kite medical monitor must be consulted.

- Subjects must have no evidence of clinically significant infection before leukapheresis. Should a subject have clinically significant infection immediately before leukapheresis, cell collection must be delayed until the event resolves.

- If leukapheresis is delayed > 5 days after eligibility confirmation, a CBC with differential and chemistry panel must be repeated. If leukapheresis is delayed > 28 days from the signing of the original informed consent, subjects must be reconsented and repeat all screening procedures/assessments (refer to Section 7.12.2).

- If the WBC count from a sample collected at the time of leukapheresis is > 20,000 cells/µL, the Kite medical monitor must be consulted before proceeding with leukapheresis.

- Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days before leukapheresis (refer to Section 6.2.5).

Refer to Section 6.2.5 for medications that are not allowed before leukapheresis occurs.

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

7.12.3.2. Procedures/Requirements at Leukapheresis

For all subjects, the following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA:

- ECOG performance status (Cohort 3 only)

- 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 unless otherwise specified)

  — β-HCG pregnancy test (serum or urine) on all females of childbearing potential within 7 days before the initiation of leukapheresis (Cohort 3 only)

  - Serology (serum) within 30 days before leukapheresis and/or on the day of leukapheresis (EU sites only)
  - Chemistry panel
  - CRP; if CRP is ≥ 100 mg/L, a call must be made to the Kite medical monitor before proceeding with conditioning chemotherapy.
  - LDH (Cohort 3 only)
  - CBC with differential (local and central laboratory)
  - Cytokine levels
  - Anti-CD19 CAR antibodies
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells)
  - Blood draw (plasma) for MRD analysis (Cohort 3 only)
- Leukapheresis
- AE/SAE reporting
- Concomitant therapies documentation

7.12.4. Bridging Therapy

If prescribed, bridging therapy as described in Section 6.2.1 must be administered after leukapheresis and completed at least 5 days prior to initiating conditioning chemotherapy for subjects in Cohort 1 and Cohort 2, or at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy for subjects in Cohort 3 (refer to Section 6.3.2). If bridging therapy is administered, PET-CT or diagnostic CT must be repeated prior to the start of conditioning chemotherapy to establish a new baseline (refer to Section 7.8 for detailed timing and imaging requirements).

- AE/SAE reporting
- Concomitant therapies 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.

As described in Section 7.8, if PET-CT will be older than 28 days at the initiation of conditioning chemotherapy or if the subject receives any bridging therapy between the last PET-CT and conditioning chemotherapy, the PET-CT must be repeated prior to the initiation of

conditioning chemotherapy to establish a new baseline. However, if the subject receives bridging therapy and the original PET-CT scan is within 28 days of the initiation of conditioning chemotherapy, only the diagnostic CT portion of the scan needs to be repeated prior to the initiation of conditioning chemotherapy.

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 both conditioning chemotherapy and 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°C 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 (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria), 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 Day –5 to Day –3 at the time points outlined in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy)
  - β-HCG pregnancy test (serum or urine) on all females of childbearing potential within 7 days before the initiation of conditioning chemotherapy (Cohort 3 only)
  - Chemistry panel with CRP
  - CBC with differential (local laboratory)
- Fludarabine and cyclophosphamide administration
- AE/SAE reporting
- Concomitant therapies documentation

7.12.6. IP 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°C within 72 hours of KTE-X19 infusion
- CRP > 100 mg/L anytime between enrollment to start of KTE-X19 infusion

- 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 (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria), 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:

- EQ-5D and EORTC-QLQ-C30 (Cohort 3 only; prior to any other assessments/procedures being performed, excluding blood draws and imaging)
- ECOG performance status (Cohort 3 only)
- Neurological assessment including MMSE (Cohort 1)
  - 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 and as described in the SOA)
  - Chemistry panel
    - If hospitalization continues beyond Day 7 (or as otherwise required by country regulatory agencies [Section 18.3]), blood draws for chemistry panel should continue to be performed daily during the extended hospitalization. Extended hospitalization and post-treatment monitoring will be conducted as medically indicated in EU countries and the United Kingdom (UK).
  - CRP, ferritin, and LDH

    Monitoring of CRP, ferritin, and LDH levels may assist with the diagnosis and define the clinical course regarding CRS/neurologic toxicity. CRP, ferritin, and LDH are to be monitored daily starting at Day 0 and continuing through hospitalization. If hospitalization continues beyond Day 7 (or as otherwise required by country regulatory agencies [Section 18.3]), CRP, ferritin, and LDH should continue to be monitored daily if levels remain elevated or are uptrending. In addition, lactate should be monitored as clinically indicated.

- CBC with differential (local and/or central laboratory)
  - If hospitalization continues beyond Day 7 (or as otherwise required by country regulatory agencies [Section 18.3]), blood draws for local laboratory assessment of CBC with differential should continue to be performed daily during the extended hospitalization. Extended hospitalization and post-treatment monitoring will be conducted as medically indicated in EU countries and the UK.
- Cytokine levels
- Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis)
  - If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.

- Infusion of KTE-X19 or axicabtagene ciloleucel
- As applicable, lumbar puncture for subjects with new onset Grade ≥ 2 neurologic symptoms after anti-CD19 CAR T cells infusion, or subjects who signed the optional portion of the consent should be completed for examination of CSF
- Collection of fresh (newly acquired) tumor sample(s) for subjects who signed the optional portion of the consent
  - Cohort 1 and Cohort 2: Tumor sample will be collected anytime between Day +7 and Day +14
  - Cohort 3: Optional tumor sample will be collected on Day 5 ± 2 days
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant therapies documentation

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-ray), 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 urinalysis (UA) and urine culture. Deep/induced sputum culture if clinically indicated.
  - All indwelling lines such as central venous catheters should be examined for any signs of infection and additional cultures should be drawn from the line
  - Nasopharyngeal-throat swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, Fungitell®)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus [CMV])
- If a CNS process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral 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 > 100 mg/L, CRP should be repeated. If CRP continues to increase significantly, an evaluation should be performed for any other potential infectious or inflammatory condition that was not previously evaluated.

7.12.8. 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 at the time points outlined in the SOA:

- EQ-5D questionnaire (prior to any other assessments/procedures being performed, excluding blood draws and imaging)
- EORTC-QLQ-C30 (Cohort 3 only; prior to any other assessments/procedures being performed, excluding blood draws and imaging)
- Neurological assessment including MMSE (Cohort 1 and Cohort 2) or ICE (Cohort 3)
  - 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.
  - For subjects enrolled in Cohort 3, a neurological assessment, including an ICE cognition assessment, will be performed at Week 4. If the ICE assessment has not returned to baseline (± 1 point) at Week 4, then continue to perform the assessment at Month 3 and every 3 months until the results have returned to baseline (± 1 point) 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 or biopsy to confirm CR (ie, for subjects presenting with bone marrow involvement prior to therapy, for subjects without a bone marrow aspirate or biopsy at baseline, 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 females of childbearing potential
  - Chemistry panel with CRP
  - CBC with differential (local and/or central laboratory)
  - Anti-CD19 CAR antibodies

  - Cytokine levels
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis)
    - If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.
  - Blood draw (plasma) for MRD analysis (Cohort 3 only)

- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant therapies 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 retreatment or chooses not to pursue retreatment, 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.

If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.

7.12.9. LTFU 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 (for Cohort 1 and Cohort 2) or through Month 21 (for Cohort 3)
- Month 24 (± 1 month)

Beginning with Protocol Amendment 8 and after completion of at least 24 months of assessments in KTE-C19-102 (refer to Section 3.5.2), subjects who received an infusion of anti-CD19 CAR T cells will be given the opportunity to transition to a separate LTFU study, KT-US-982-5968, after providing signed informed consent. Before a subject transitions to KT-US-982-5968, all assessments will be completed under the ZUMA-2 protocol according to the frequency specified in the SOA (Table 8 and Table 10). Upon transition to KT-US-982-5968, subsequent assessments will be completed under the KT-US-982-5968 study according to the requirements detailed in the KT-US-982-5968 protocol.

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, excluding blood draws and imaging)
- EORTC-QLQ-C30 (Cohort 3 only; prior to any other assessments/procedures being performed, excluding blood draws and imaging)
- Neurological assessment including MMSE (Cohort 2) or ICE (Cohort 3)
  - For subjects enrolled in Cohort 2, if the MMSE performed on Day 28 and Month 3 had 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.
  - For subjects enrolled in Cohort 3, if the ICE assessments performed at Week 4 and Month 3 had not returned to baseline (± 1 point), then continue to perform the assessment at Month 6 and every 3 months until the results have returned to baseline (± 1 point) 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.
- As applicable, bone marrow aspirate or biopsy to confirm CR (ie, for subjects presenting with bone marrow involvement prior to therapy, for subjects without a bone marrow aspirate or biopsy at baseline, or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment)
- Survival status
- Labs
  - CBC with differential (local and/or central laboratory)
  - Anti-CD19 CAR antibodies (Cohort 1 and Cohort 2 only; refer to Section 7.11)

- Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis; refer to Section 7.11)
  - Cohort 1 and Cohort 2: After Month 24, PBMC samples will only be collected if an RCR event is clinically suspected and/or a subject's PBMC sample tested positive for RCR at any time point within the first year. If the latter, samples will continue to be collected and tested annually for up to 15 years or as clinically indicated.
  - Cohort 3:
    - In the follow-up period, PBMCs for RCR testing will be collected at Months 6 and 12. Thereafter, samples will only be collected if an RCR event is clinically suspected and/or a subject's PBMC sample tested positive for RCR at any time point within the first year. If the latter, samples will continue to be collected and tested annually for up to 15 years or as clinically indicated.
    - PBMCs for analysis of lymphocyte subsets and anti-CD19 CAR T cells will continue to be collected at the time points specified in the SOA even if PBMCs for RCR testing are no longer required to be collected.
  - All cohorts: If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.
- Blood draw (plasma) for MRD analysis (Cohort 3 only)

- Targeted AE/SAE reporting (for 15 years or until disease progression or initiation of subsequent anticancer therapy, whichever occurs first) (refer to Section 9 for safety reporting guidelines)
  - Any new/secondary malignancy, with the exception of a relapse of the primary malignancy, occurring after the administration of KTE-X19 should be reported as an SAE for up to 15 years regardless of disease progression.
- Targeted concomitant therapies documentation (for 5 years or until disease progression or subsequent therapy, whichever comes first)
  - Including gammaglobulin, immunosuppressive drugs, anti-infective drugs, vaccinations, and anticancer therapies
- Subsequent therapy for the treatment of lymphoma
- Collection of fresh (newly acquired) tumor sample(s) for subjects who signed the optional portion of the consent

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

If a subject progresses in the LTFU phase, the subject will continue to be followed for survival status, subsequent therapy for the treatment of MCL, and targeted SAE reporting for new/secondary malignancies. 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.

Subjects who are enrolled/leukapheresed, but do not receive anti-CD19 CAR T cells, will be followed only until the end of this study and will undergo the following assessments at the time points outlined in the SOA:

- Subsequent therapy
- Survival status – subjects may be contacted by telephone to confirm survival status
- Disease assessment per standard of care
- AE/SAE reporting and concomitant therapies documentation until 30 days after last study-specific procedure (eg, leukapheresis, conditioning chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first

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

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

Subjects must meet the criteria for retreatment as listed in Section 7.12.10.2 for Cohort 3. Beginning with Protocol Amendment 8, no further retreatment option is available for subjects treated in Cohort 1 and Cohort 2.

The decision to administer retreatment should be made in consultation with the Kite medical monitor. In addition, a discussion regarding benefits and risks of retreatment, including the potential 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 documents.

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

7.12.10.1. Cohort 1 and Cohort 2

Beginning with Protocol Amendment 8, no further retreatment option is available for subjects treated in Cohort 1 and Cohort 2. Prior to Protocol Amendment 8, subjects in Cohort 1 and Cohort 2 may have been retreated if they met the criteria listed below.

Subjects who achieved a PR or CR had 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 retreatment. 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 retreatment.

7.12.10.2. Cohort 3

Subjects 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 KTE-X19 infusion
- Subject received initial KTE-X19 infusion ≤ 24 months ago
- CD19 tumor expression confirmed locally by aspirate or biopsy after disease progression and prior to retreatment. When a biopsy is obtained, 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 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, except for bridging therapy as outlined below
- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of clinically insignificant toxicities (eg, alopecia), have resolved to severity of Grade 1 or lower or returned to baseline prior to retreatment
- Subject must not have had a Grade 2 or higher KTE-X19-related immediate hypersensitivity reaction
- Subject did not experience Grade 4 CRS, Grade 4 neurologic events, or any grade of edema in the brain with the first KTE-X19 infusion
- Any CRS and neurologic events have fully resolved before the retreatment

Bridging therapy is recommended for all subjects in Cohort 3 being considered for retreatment, particularly those with rapidly progressing disease, clinical deterioration, or high disease burden (eg, > 25% marrow involvement and/or ≥ 1,000 leukemic phase mantle cells/mm^3 in the peripheral circulation) at the discretion of the investigator and per institutional guidelines and standard of care and after discussion with the medical monitor.

Bridging therapy (including radiotherapy, corticosteroids, targeted therapy, and chemotherapy) will be supplied by the investigative site unless otherwise noted. Sites should refer to the current agent-specific product label(s) for guidance on packaging, storage, preparation, administration (including necessary dose reductions for organ dysfunction, pregnancy testing requirements, etc.), and toxicity management associated with the administration of the agent(s) selected.

In the context of retreatment, bridging therapy must be completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy.

Bridging regimen options for retreatment in Cohort 3 are listed in Table 6. Retreatment bridging regimen should be discussed with the Kite medical monitor. Dose can be adjusted for age/comorbidities or per local or institutional guidelines. If radiotherapy is considered for retreatment bridging, the radiotherapy modality should be discussed with the Kite medical monitor. Radiotherapy should be administered per local or institutional guidelines. Irradiated lesions can no longer serve as target lesions, and other target lesions must be present to allow for response assessment. Use of any other chemotherapeutic or targeted agent (such as lenalidomide, bortezomib, rituximab, venetoclax, and other BTKi) or palliative radiotherapy is to be discussed with the Kite medical monitor.

Table 6. Bridging Therapy for Cohort 3 Retreatment

Retreatment Bridging Regimen Options	
(1) Corticosteroid	Dexamethasone at a dose of 20 to 40 mg or equivalent, either PO or IV daily for 1 to 4 days Choice of corticosteroid and dose can be adjusted for age/comorbidities or per local or institutional guidelines
(2) Radiotherapy	Radiotherapy to localized lesions up to 30 Gy in 10 fractions or equivalent
(3) Chemotherapy	Cytarabine 1 to 2 g/m² IV for a maximum of 2 days
	Cyclophosphamide 1 to 2 g/m² IV for a maximum of 2 days, or hyperfractionated cyclophosphamide 300 mg/m² administered every 12 hours for 6 doses
(4) Any combination of the following: 1 of the above chemotherapies AND/OR choice of corticosteroid as stated above AND/OR radiotherapy to localized lesions as stated above	
(5) Ibrutinib 560 mg PO daily (or most recent dose if there had been a dose adjustment) for a maximum of 14 days, or acalabrutinib 100 mg PO every 12 hours (or most recent dose if there had been a dose adjustment) for a maximum of 14 days	

Abbreviations: BTKi, Bruton's tyrosine kinase inhibitor; IV, intravenous; PO, oral.
Note: Use of any other chemotherapeutic or targeted agent (such as lenalidomide, bortezomib, rituximab, venetoclax, and other BTKi) or palliative radiotherapy is to be discussed with the Kite medical monitor.

7.13. SOAs

Table 7. Schedule of Assessments Cohorts 1 & 2 (1 of 2)

Note: All subjects in Cohorts 1 and 2 are in the long-term follow-up period (refer to Table 8); thus, no additional changes will be made to this schedule of assessments.

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												

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)**
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											
Fludarabine/ Cyclophosphamide				X	X	X								
KTE-X19 infusion IV									X					
Adverse events/ Concomitant medication	X	→												

Schedule of Assessments Footnotes

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

1 Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. Fresh tumor sample for subjects who sign the optional portion of consent; refer to Section 7.11. Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. Post-treatment fresh tumor samples (if applicable) will be collected/submitted anytime between Day 7 and Day 14. See Section 7.11 and central laboratory manual for details.

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. In addition, subjects who sign the optional portion of the consent will have lumbar puncture for the collection of CSF performed at baseline prior to KTE-X19 infusion and post infusion (Day 5 ± 3 days).

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-CD19 CAR T cells, and RCR. If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to assay for RCR in blood and in a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue.

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 anti-CD19 CAR T cells and cytokines will be collected on day of admission, then weekly, and on day of discharge. Blood samples for anti-CD19 CAR T 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 8. Schedule of Assessments Cohorts 1 & 2 (2 of 2)

Procedure	Long-term Follow-up Period [12] (Each visit calculated from Day 0)												
Visit Frequency	**Month 6 (± 2w)**	**Month 9 (± 2w)**	**Month 12 (± 2w)**	**Month 15 (± 2w)**	**Month 18 (± 2w)**	**Month 24 (± 1m)[12]**	**Month 30 (± 1m)**	**Month 36 (± 1m)**	**Month 42 (± 1m)**	**Month 48 (± 1m)**	**Month 54 (± 1m)**	**Month 60 (± 1m)**	**Month 72 (± 3m) and Annually Thereafter Up to 15 Years**
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[5]		X[5]		X[5]	X[5]
Targeted AE/SAEs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted concomitant therapies[7]	X	X	X	X	X	X	X	X	X	X	X	X	
Subsequent therapy for MCL[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Fresh tumor sample to central lab [9]	X												

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CBC, complete blood count; CR, complete response; EQ-5D, European Quality of Life-5 Dimensions; LTFU, long-term follow-up; m, month; MCL, mantle cell lymphoma; MMSE, Mini-Mental Status Exam; PBMC, peripheral blood mononuclear cell; PET-CT, positron emission tomography-computed tomography; RCR, replication-competent retrovirus; SAE, serious adverse event; w, week.

1 Physical exams will continue through the first 24 months.

2 PET-CT 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-CD19 CAR T cells, and RCR. After Month 24, PBMC samples will only be collected if an RCR event is clinically suspected and/or a subject's PBMC sample tested positive for RCR at any time point within the first year. If the latter, samples will continue to be collected and tested annually for up to 15 years or as clinically indicated. If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.

6 Targeted AE and SAE reporting will continue for 15 years or until disease progression or initiation of subsequent anticancer therapy (whichever occurs first). Any new/secondary malignancy, with the exception of a relapse of the primary malignancy, occurring after the administration of KTE-X19 should be reported as an SAE for up to 15 years regardless of disease progression. Refer to Section 9.

7 Targeted concomitant therapies documentation will continue for 5 years or until disease progression or subsequent therapy (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 MCL and to assess survival status.

9 Fresh tumor sample for subjects who sign the optional portion of consent; refer to Section 7.11.1.

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.

12 After completion of at least 24 months of assessments in the KTE-C19-102 study, subjects who received an infusion of anti-CD19 CAR T cells will be provided an opportunity to transition to the long-term follow-up study (KT-US-982-5968) after providing signed informed consent, to complete the remainder of the 15-year long-term follow-up period.

Table 9. Schedule of Assessments Cohort 3 (1 of 2)

Procedure	Screening	Enrollment/ Leukapheresis	Bridging Therapy Period	Conditioning Chemotherapy Period					IP Administration Period[1]		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	Within 28 days of enrollment	Within approx. 5 days of eligibility confirmation	Completed at least 7 days or 5 half-lives, whichever is shorter, 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)
Demographic data	X													
Medical history	X													
Disease staging[12]	X													
ECOG performance status	X	X							X					
PROs: EQ-5D and EORTC-QLQ-C30[2]	X								X			X		X
Neurological assessment including ICE[3]	X											X		X[3]
ECG	X													
ECHO or MUGA	X													
Archival/fresh tumor to central lab[4]	X									Day 5 ± 2 days				
Brain MRI[13]	X													
PET-CT/disease assessment[5]	X		X[5]									X		X
Bone marrow assessment[6]	X											X		X
Physical examination	X										X	X	X	X
Vital signs (BP, HR, O_2 sat, and temp)	X	X	X	X	X	X			X	X	X	X	X	X
Weight (plus height at screening)	X	X												
Lumbar puncture[7]	X									X				

Procedure	Screening	Enrollment/ Leukapheresis	Bridging Therapy Period	Conditioning Chemotherapy Period					IP Administration Period[1]		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	**Within 28 days of enrollment**	**Within approx. 5 days of eligibility confirmation**	**Completed at least 7 days or 5 half-lives, whichever is shorter, 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)**
Local laboratory assessments														
Pregnancy test (serum or urine)[14]	X	X[14]		X[14]										X
Serology for EU sites (serum)	X[15]	X[15]												
Blood draw for chemistry panel[16]	X	X		X	X	X			X	X[17]	X	X	X	X
Creatinine clearance (as estimated by Cockcroft Gault)	X													
Blood draw for CRP[18]	X	X		X	X	X			X	X[18]	X	X	X	X
Blood draw for LDH[18]		X							X	X[18]				
Blood draw for ferritin[18]									X	X[18]				
Blood draw for CBC with differential (local laboratory; for clinical/safety evaluation)	X	X		X	X	X			X	X[17]	X	X	X	X
Central laboratory assessments														
Blood draw for CBC with differential (central laboratory)[19]		X							X	Day 7	X	X		X
Blood draw for anti-CD19 CAR antibody[8]		X												X
Blood draw for PBMCs for lymphocyte subsets and anti-CD19 CAR T cells[10]		X							X	Day 7	X	X		X

Procedure	Screening	Enrollment/ Leukapheresis	Bridging Therapy Period	Conditioning Chemotherapy Period					IP Administration Period[1]		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	**Within 28 days of enrollment**	**Within approx. 5 days of eligibility confirmation**	**Completed at least 7 days or 5 half-lives, whichever is shorter, 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)**
Blood draw for PBMCs for RCR[9]		X												X
Blood draw (plasma) for MRD analysis		X										X		X
Blood draw for cytokines[10]		X							X	Day 3 & 7	X	X		
Leukapheresis		X												
Bridging therapy (if applicable)[11]			X											
Fludarabine/cyclophosphamide				X	X	X								
KTE-X19 infusion IV									X					
AEs/concomitant therapies	X	→												

Abbreviations: AE, adverse event; approx., approximately; BP, blood pressure; BTKi, Bruton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CBC, complete blood count; CNS, central nervous system; CR, complete response; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EU, European Union; EQ-5D, European Quality of Life-5 Dimensions; FFPE, formalin-fixed paraffin-embedded; HR, heart rate; ICE, immune effector cell-associated encephalopathy; IP, investigational product; IV, intravenous; LDH, lactate dehydrogenase; MRD, minimal residual disease; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PBMC, peripheral blood mononuclear cell; PET-CT, positron emission tomography-computed tomography; PRO, patient-reported outcome; RCR, replication-competent retrovirus; sat, saturation; temp, temperature.

1 Refer to Section 18.3 for requirements by country regulatory agencies.

2 PROs: Both PROs will be completed by the subject at the time points specified prior to any other assessment, excluding blood draws and imaging.

3 Neurological assessment: A neurological assessment, including an ICE cognition assessment, will be performed at screening and Week 4. If the ICE assessment has not returned to baseline (± 1 point) at Week 4, then continue to perform the assessment at Month 3 and every 3 months until the results have returned to baseline (± 1 point) or until Month 24. For subjects who are hospitalized with neurologic events of Grade 2 or higher, grading should be continued daily during any period of Grade 2 or higher neurologic events until symptoms return to baseline. See Section 7.5.2 and Section 9.2.1 for details of neurologic event grading and management.

4 Archival/fresh tumor sample: Submit archival samples at screening as FFPE tumor block(s) or 30 unstained slides. Once archival material is confirmed to be sufficiently available at screening, archived samples will be submitted to the central laboratory after eligibility has been confirmed and prior to Day 28. If archival material is unavailable or insufficient (< 20 slides), a new tumor biopsy is requested to be scheduled at eligibility confirmation, collected, and submitted prior to leukapheresis if clinically feasible. For subjects who sign the optional portion of the consent, a post-treatment fresh (newly acquired) tumor sample will be collected/submitted on Day 5 ± 2 days. See Section 7.11 and the central laboratory manual for details.

5 PET-CT (neck-chest-abdomen-pelvis)/disease assessment: Screening PET-CT should be completed as close to enrollment as possible. If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy, baseline scans must be repeated prior to conditioning chemotherapy. For subjects receiving bridging therapy, a repeat baseline PET-CT is required after bridging therapy and prior to conditioning chemotherapy; however, if the original PET-CT is within 28 days of the initiation of conditioning chemotherapy, only the diagnostic CT portion of the scan needs to be repeated. See Section 7.8 for details.

6 Bone marrow assessment: Bone marrow aspirate or biopsy will be performed at screening as needed due to prior history or suspicion of bone marrow involvement (if not done within 4 weeks before screening). If collected at screening, bone marrow aspirate or biopsy should be submitted to the central laboratory as FFPE block(s) or slides for MRD analysis. As applicable, bone marrow aspirate or biopsy will be performed to confirm CR (ie, for subjects presenting with bone marrow involvement prior to therapy, for subjects without a bone marrow aspirate or biopsy at baseline, 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. After CR is confirmed by bone marrow aspirate or biopsy, additional bone marrow aspirates or biopsies are only required in case of clinical suspicion of disease progression in the bone marrow only.

7 Lumbar puncture: Subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess CSF for possible CNS involvement. Subjects with new onset Grade 2 or higher neurologic symptoms after KTE-X19 infusion will have lumbar puncture performed to assess CSF. In addition, subjects who sign the optional portion of the consent will have lumbar puncture for the collection of CSF performed at baseline prior to KTE-X19 infusion and after infusion (Day 5 ± 3 days).

8 Blood draw for anti-CD19 CAR antibody: Baseline antibody sample to be collected prior to start of conditioning chemotherapy.

9 PBMCs for RCR: Samples will be collected at baseline (before leukapheresis) and at Months 3, 6, and 12 (refer to Table 10 for the follow-up period). If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.

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

11 Bridging therapy: Bridging therapy is allowed with (1) dexamethasone or other corticosteroid, (2) palliative radiotherapy to localized lesions, (3) specified chemotherapy, or (4) any combination of 1 specified chemotherapy and/or corticosteroid and/or radiotherapy. Bridging regimen should be discussed with the Kite medical monitor, and BTKis are not permitted for bridging therapy. See Section 6.2.1.2 for details.

12 Disease staging: Disease staging at study entry will be performed per the Lugano Classification {Cheson 2014} (Section 18.2).

13 A brain MRI performed during the screening period or within 28 days prior to signing the consent is acceptable. For subjects with a contraindication for MRI, a CT scan of the brain may be used but must include contrast.

14 Pregnancy test (serum or urine): The test will be completed within 7 days before both leukapheresis and conditioning chemotherapy for females of childbearing potential.

15 Serology for EU sites (serum): Serology tests (ie, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis) will be done per institutional guidelines and EU regulations. Testing may be done within the 30 days before leukapheresis/enrollment and/or on the day of leukapheresis/enrollment.

16 Blood draw for chemistry panel: See Section 7.11 for tests to be included in the chemistry panel.

17 If hospitalization continues beyond Day 7 (or as otherwise required by country regulatory agencies [Section 18.3]), blood draws for chemistry panel and local laboratory assessment of CBC with differential should continue to be performed daily during the extended hospitalization. Extended hospitalization and post-treatment monitoring will be conducted as medically indicated in EU countries and the UK.

18 Blood draw for CRP, ferritin, and LDH: CRP, ferritin, and LDH are to be monitored daily starting at Day 0 and continuing through hospitalization. If hospitalization continues beyond Day 7 (or as otherwise required by country regulatory agencies [Section 18.3]), CRP, ferritin, and LDH should continue to be monitored daily if levels remain elevated or are uptrending.

19 Blood draw for CBC with differential (central laboratory): At the time points at which PBMC samples are collected for the analysis of lymphocyte subsets and anti-CD19 CAR T cells, blood samples will also be collected and sent to the central laboratory for assessment of CBC with differential for pharmacokinetic assessments (these samples are distinct from samples collected and sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation).

Table 10. Schedule of Assessments Cohort 3 (2 of 2)

Procedure	LTFU Period[12] (Each visit calculated from Day 0)													
Visit Frequency	**Month 6 (± 2w)**	**Month 9 (± 2w)**	**Month 12 (± 2w)**	**Month 15 (± 2w)**	**Month 18 (± 2w)**	**Month 21 (± 2w)**	**Month 24 (± 1m)[12]**	**Month 30 (± 1m)**	**Month 36 (± 1m)**	**Month 42 (± 1m)**	**Month 48 (± 1m)**	**Month 54 (± 1m)**	**Month 60 (± 1m)**	**Month 72 (± 3m) and Annually Thereafter Up to 15 Years**
PROs: EQ-5D and EORTC-QLQ-C30[1]	X	X	X		X		X							
Neurological assessment including ICE[2]	X	X	X	X	X	X	X							
Physical examination[3]	X	X	X	X	X	X	X							
PET-CT/disease assessment[4]	X	X	X	X	X	X	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Bone marrow assessment[5]	X	X	X	X	X	X	X							
Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local laboratory assessments														
Blood draw for CBC with differential (local laboratory; for clinical/safety evaluation)[6]	X	X	X	X	X	X	X							
Central laboratory assessments														
Blood draw for CBC with differential (central laboratory)[6]	X	X	X	X	X	X	X		X		X			
Blood draw for PBMCs for lymphocyte subsets and anti-CD19 CAR T cells[7]	X	X	X	X	X	X	X		X		X			

Procedure	LTFU Period[12] (Each visit calculated from Day 0)													
Visit Frequency	**Month 6 (± 2w)**	**Month 9 (± 2w)**	**Month 12 (± 2w)**	**Month 15 (± 2w)**	**Month 18 (± 2w)**	**Month 21 (± 2w)**	**Month 24 (± 1m)[12]**	**Month 30 (± 1m)**	**Month 36 (± 1m)**	**Month 42 (± 1m)**	**Month 48 (± 1m)**	**Month 54 (± 1m)**	**Month 60 (± 1m)**	**Month 72 (± 3m) and Annually Thereafter Up to 15 Years**
Blood draw for PBMCs for RCR[13]	X		X				X[13]		X[13]		X[13]		X[13]	X[13]
Blood draw (plasma) for MRD analysis	X		X		X		X							
Fresh tumor sample to central lab[8]	X													
Targeted AE/SAEs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted concomitant therapies[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subsequent therapy for MCL[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CBC, complete blood count; CR, complete response; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, European Quality of Life-5 Dimensions; ICE, immune effector cell-associated encephalopathy; LTFU, long-term follow-up; m, month; MCL, mantle cell lymphoma; MRD, minimal residual disease; PBMC, peripheral blood mononuclear cell; PET-CT, positron emission tomography-computed tomography; PRO, patient-reported outcome; RCR, replication-competent retrovirus; SAE, serious adverse event; w, week.

1 PROs: Both PROs will be completed by the subject at the time points specified prior to any other assessments/procedures being performed, excluding blood draws and imaging.

2 Neurological assessment: If the ICE assessments performed at Week 4 and Month 3 had not returned to baseline (± 1 point), then continue to perform the assessment at Month 6 and every 3 months until the results have returned to baseline (± 1 point) or until Month 24.

3 Physical examinations will continue through the first 24 months.

4 PET-CT 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.

5 Bone marrow assessment: As applicable, bone marrow aspirate or biopsy will be performed to confirm CR (ie, for subjects presenting with bone marrow involvement prior to therapy, for subjects without a bone marrow aspirate or biopsy at baseline, 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 aspirate or biopsy, additional bone marrow aspirates or biopsies are only required in case of clinical suspicion of disease progression in the bone marrow only.

6 Blood draw for CBC with differential:
- Local laboratory: Blood will be collected at the time points specified through Month 24 or until disease progression, whichever occurs first, and sent to the local laboratory for clinical/safety evaluation.
- Central laboratory: Subjects will continue to provide samples for central laboratory assessment of CBC with differential for pharmacokinetic assessments at the time points specified through Month 48 (these samples are distinct from samples collected and sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation).

7 PBMCs for lymphocyte subsets and anti-CD19 CAR T cells: Samples will continue to be collected at the time points specified through Month 48 even if PBMCs for RCR testing are no longer required to be collected.

8 Fresh (newly acquired) tumor sample for subjects who sign the optional portion of consent; refer to Section 7.11.1.

9 Targeted AE and SAE reporting will continue for 15 years or until disease progression or initiation of subsequent anticancer therapy (whichever occurs first). Any new/secondary malignancy, with the exception of a relapse of the primary malignancy, occurring after the administration of KTE-X19 should be reported as an SAE for up to 15 years regardless of disease progression. Refer to Section 9.

10 Targeted concomitant therapies documentation will continue for 5 years or until disease progression or subsequent therapy (whichever occurs first).

11 Subsequent therapy administered after KTE-X19 infusion for a subject's disease, such as nonstudy-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 MCL and to assess survival status.

12 After completion of at least 24 months of assessments in the KTE-C19-102 study, subjects who received an infusion of KTE-X19 will be provided an opportunity to transition to the LTFU study (KT-US-982-5968) after providing signed informed consent, to complete the remainder of the 15-year LTFU period.

13 PBMCs for RCR: In the follow-up period, samples will be collected at Months 6 and 12. Thereafter, samples will only be collected if an RCR event is clinically suspected and/or a subject's PBMC sample tested positive for RCR at any time point within the first year. If the latter, samples will continue to be collected and tested annually for up to 15 years or as clinically indicated. If a subject dies or develops a new/secondary malignancy during the study or follow-up, every effort should be made to collect blood and a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue to assay for RCR.

8. SUBJECT WITHDRAWAL

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

Subjects can decline to continue to receive study required treatment and/or other protocol-required procedures at any time during the study but continue to participate in certain follow-up elements of 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 study treatment or other study-specific procedures and must discuss options for continued participation, completion of procedures, and the associated data collection as outlined in the SOA, including the following:

- Survival status, including the cause of death
- Safety reporting, including new malignancies; SAEs related to the anti-CD19 CAR T-cell product including, but not limited to, neurologic events, infections, blood, or immune disorders; and pregnancies
- Targeted concomitant therapies (until 5 years after the antiCD19 CAR T-cell infusion, PD, or subsequent therapy, whichever occurs first)
- Subsequent therapies
- Central laboratory samples (per the SOA)

The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

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

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status (eg, for subjects lost to follow-up), if available, to obtain survival data for any subject for whom the survival status is not known, per the applicable local laws. Sites may be also asked to retrieve autopsy reports to confirm status of disease at the time of death, if possible, per the local laws.

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

8.1. Reasons for Removal from Treatment

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

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

8.2. Reasons for Removal from Study

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

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death
- Termination of the study by the sponsor
- Other (eg, noncompliance, refusal to consent to the LTFU study KT-US-982-5968)

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, only targeted AEs (ie, neurological events, hematological events, infections, GVHD or aggravation of GVHD, autoimmune disorders, and new/secondary malignancies) will be monitored and reported for 15 years after the initial anti-CD19 CAR T-cell infusion or until disease progression or initiation of subsequent anticancer therapy, whichever occurs first. Any new/secondary malignancy, with the exception of a relapse of the primary malignancy, occurring after the administration of KTE-X19 should be reported as an SAE for up to 15 years after the KTE-X19 infusion for all subjects, including those whose disease progresses.

All AEs deemed related to the anti-CD19 CAR T-cell infusion should be recorded in the eCRF and reported regardless of the study period.

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 continues through 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first.

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 CTCAE version 4.03. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov). 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.

9.2.1. Grading of CRS and Neurologic Events

For all subjects, the severity of CRS events will be reported using the Lee grading scale {Lee 2014}, as outlined in Section 18.4 and the current IB. The severity of neurologic events will be

graded using CTCAE version 4.03. These grading systems will be used for toxicity management as described in the current IB.

For subjects in Cohort 3 only, in addition to the Lee criteria for CRS and CTCAE for neurologic events, CRS and ICANS will also be assessed by ASTCT grading {Lee 2019} (see Section 18.5 and Section 18.6). ASTCT grading is collected only for the purposes of comparison and will not be used for toxicity management.

9.3. Definition of SAEs

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires 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 AE according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity (ie, grade) and seriousness need to be independently assessed for each AE 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 or until initiation of subsequent anticancer therapy, whichever occurs first.

After 3 months, only targeted SAEs (ie, neurological events, hematological events, infections, GVHD or aggravation of GVHD, autoimmune disorders, and new/secondary malignancies)

observed by the investigator or reported by the subject will be reported for 15 years after the initial anti-CD19 CAR T-cell infusion or until disease progression or initiation of subsequent anticancer therapy, whichever occurs first. Any new/secondary malignancy, with the exception of a relapse of the primary malignancy, occurring after the administration of KTE-X19 should be reported as an SAE for up to 15 years after the KTE-X19 infusion for all subjects, including those whose disease progresses.

For subjects who screen fail or are enrolled but do not receive anti-CD19 CAR T cells, the reporting period for SAEs continues through 30 days after the last study-specific procedure (eg, screen procedure, leukapheresis, conditioning chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first.

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 2014} must be submitted to Kite Pharma via email to PPD within 24 hours following the investigator's knowledge of the event using a SAE Report Form for subjects in Cohorts 1 and 2. For subjects in Cohort 3, SAEs should be submitted via Safety Gateway within RAVE EDC.

Following completion of KTE-C19-102, any relevant information on ongoing SAEs must be submitted to Kite Pharma within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via email to the SAE reporting mailbox: PPD, in the context of study KT-US-982-5968.

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 AE reporting period that are attributed by the investigator solely to progression of underlying lymphoma should be recorded as SAEs with the preferred term "B-cell lymphoma" and must be reported immediately to the sponsor. Death is an

outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. 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 AEs, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the AE form. The exception is for CRS where both the diagnosis and signs and symptoms will be captured on the CRF AE form. For signs and symptoms of the underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

9.7. Pregnancy and Lactation

There is no relevant clinical experience with KTE-X19 in pregnant or lactating females, and animal reproductive studies have not been performed. This experimental therapy should not be administered to pregnant females or females who are breastfeeding. Females 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. Females of childbearing potential should be monitored according to local and country-specific regulations. Refer to Section 18.7 for the definition of childbearing potential.

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 or KTE-X19 administration, whichever is longer. Male subjects are recommended to not father a child for at least 6 months after completion of conditioning chemotherapy dosing or KTE-X19 administration, whichever is longer. Refer to Section 18.7 for a complete list of highly effective contraception methods.

Pregnancy testing will occur at the time points indicated in the SOAs.

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 or the administration of KTE-X19, whichever is longer, the pregnancy must be reported to the key sponsor contact. Information regarding the pregnancy and/or the outcome may be requested by the key sponsor.

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. Any pregnancies that occur > 6 months after CAR T-cell infusion should also be reported if the investigator incidentally becomes aware of such a pregnancy.

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

The following hospitalization scenarios are not considered to be SAEs:

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

9.9. Abnormal Vital Signs Values

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

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

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

9.10. DSMB

9.10.1. Cohort 1 and Cohort 2

An independent DSMB will review safety and/or efficacy data from Cohort 1 and Cohort 2 at 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 for Cohort 1 and Cohort 2 based on an analysis of risk vs benefit. The DSMB may meet more often as needed.

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, using the criteria described in Section 9.12.

9.10.2. All Cohorts

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 quarterly. 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. Scientific Steering Committee (Cohort 3)

A scientific steering committee, comprising the study sponsor and at least 3 study investigators, will be specifically chartered to review the safety data from Cohort 3 and make recommendations on further study conduct. The scientific steering committee will meet after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days, and again after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months. The scientific steering committee may meet more often as needed.

As part of its oversight of the study, the scientific steering committee will also assess criteria to pause enrollment in Cohort 3 after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days, and again after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months, using the criteria described in Section 9.12.

The scientific steering committee may request additional analyses of safety data if a safety concern arises during the course of the trial.

9.12. Criteria to Pause Enrollment

Enrollment will be paused if any of the following criteria are met as determined by the DSMB (Cohort 1 and Cohort 2; see Section 9.10.1) or scientific steering committee (Cohort 3; see Section 9.11) at the prespecified time points:

- 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, 3-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%.

Additionally, an alternative hypothesis will be tested among Cohort 3 subjects with a target 75% ORR per independent review against a null hypothesis that the ORR is 57% or less. The hypothesis is that the ORR to KTE-X19 per independent review is significantly greater than 57% in Cohort 3 subjects.

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 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, PD, 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 2007}. For subjects enrolled in Cohort 2 and Cohort 3, ORR, as determined by investigators, is defined as the incidence of either a CR or PR per the Lugano Classification {Cheson 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 antiCD19 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

- Changes in the EORTC-QLQ-C30 score from baseline over time (Cohort 3 only)

10.2.3. Exploratory Endpoints

[redacted]

10.3. Sample Size Considerations

This study uses an open-label, 3-cohort design to test for an improvement in ORR. Up to approximately 220 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, up to 40 KTE-X19 subjects in Cohort 2, and up to approximately 90 KTE-X19 subjects in Cohort 3.

The primary analysis in Cohort 1 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 in Cohort 1, 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.

The primary analysis in Cohort 3 will be conducted after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier. For the test of efficacy in Cohort 3, a sample size of 86 subjects will provide at least 90% power to distinguish between an active therapy with a 75% true response rate and a therapy with a response rate of 57% or less 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.

In Cohort 3, two interim analyses will be performed for safety only:

- Cohort 3 interim analysis 1 will be conducted after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days after the KTE-X19 infusion.
- Cohort 3 interim analysis 2 will be conducted after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months after the KTE-X19 infusion.

Accrual to the study will continue during all interim analyses.

Two primary analyses will be performed:

- One 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 this 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.

- The primary analysis in Cohort 3 will be conducted after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier. In this analysis, inferential testing on efficacy in Cohort 3 will be performed 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 90% power when 86 subjects are included. EAST version 6.5 was used for power calculation and evaluation of the operating characteristics of this design.

10.4. Statistical Assumptions

As described in Section 3, an open-label, 3-cohort design is used. In Cohort 1, a target response rate of 50% and a historical control rate of 25% are assumed for statistical inference. In Cohort 3, a target response rate of 75% and a historical control rate of 57% are assumed for statistical inference (see Section 2.2.1.1 for additional information about the historical control rate). 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 (ORR, best objective response, DOR, PFS, OS) for the study. This analysis set will also be used for the hypothesis testing of the primary endpoint ORR in Cohort 3.

- 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 in Cohort 1, 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 analyses 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, 3-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, scientific steering committee charter, and Trial Integrity Document.

10.7. Interim Analysis

10.7.1. Interim Analysis and Early Stopping Rules

In Cohort 1 and Cohort 2, 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.

In Cohort 3, the scientific steering committee will review safety data after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days after the KTE-X19 infusion. The scientific steering committee will also review safety data after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months after the KTE-X19 infusion.

The DSMB and scientific steering committee will also monitor safety criteria to pause enrollment in the respective cohorts (see Section 9.12).

10.7.2. Safety Interim Analysis

In Cohort 1, the DSMB will review the safety data 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.

In Cohort 3, the scientific steering committee will review the safety data twice, once after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days after the KTE-X19 infusion, and again after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months after the KTE-X19 infusion.

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 months 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.

No interim analyses for efficacy will be performed in Cohort 3.

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 analyses for regulatory interaction purposes. If conducted, no formal hypothesis testing will be performed in such analyses.

10.8. Planned Methods of Analysis

10.8.1. Primary and Additional Analyses

10.8.1.1. Cohort 1 and Cohort 2

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. A follow-up analysis of subjects treated with KTE-X19 will be performed after all subjects in the mITT set of Cohort 1 have had the opportunity to be assessed for response

18 months after the first objective response. This additional analysis will be descriptive. The final analysis of Cohort 1 and Cohort 2 will occur when all subjects in both cohorts have completed the study.

10.8.1.2. Cohort 3

The primary analysis, including inferential testing on the primary efficacy endpoint (ORR), will be conducted after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier.

A follow-up analysis will be performed after 86 subjects in Cohort 3 have had the opportunity to be assessed for response 18 months after the first objective response to further evaluate the risk-benefit profile of KTE-X19, including the durability of response. This analysis will be descriptive.

Additional descriptive analyses may occur after the primary analysis and follow-up analyses described above have been completed. The final analysis of Cohort 3 will occur when all subjects in Cohort 3 have completed the study.

10.8.2. 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, Cohort 2 subjects, and Cohort 3 subjects. An exact binomial test will be used to compare the observed ORRs per IRRC review in Cohort 1 KTE-X19 subjects and Cohort 3 subjects to response rates of 25% and 57%, respectively.

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

10.8.3. Best Objective Response

The incidence of subjects with CR, PR, SD, PD, 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, Cohort 2 subjects, and Cohort 3 subjects.

10.8.4. 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, Cohort 2 subjects, and Cohort 3 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.

10.8.5. 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, Cohort 2 subjects, and Cohort 3 subjects. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided.

10.8.6. 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, Cohort 2 subjects, and Cohort 3 subjects. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

10.8.7. Safety

Subject incidence rates of AEs, including all, serious, fatal, CTCAE version 4.03 Grade 3 or higher, and treatment-emergent AEs (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.

10.8.8. Long-term Data Analysis

All subjects will be followed for survival status for up to 15 years after receiving KTE-X19 or axicabtagene ciloleucel infusion. LTFU data analysis will be performed on subjects in this study and after transition to the KT-US-982-5968 LTFU study. No formal hypothesis testing will be performed based on data obtained after the primary analysis in each cohort. 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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use/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

11.4. Ethics

Study KTE-C19-102 will be conducted under a US IND application or equivalent and in accordance with recognized international scientific and ethical standards, including but not limited to the ICH guideline for GCP, and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations Title 21, Part 312, and the European Community Directive 2001/20/EC, as well as other local legislation.

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 filing system of all subject records that are readily retrieved to be monitored and/or audited at any time by the key sponsor contact (or delegate), regulatory authorities, and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject ID lists
- Essential documents for the conduct of this clinical study
- 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 shipping the documents.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject ID
- Documentation that subject meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number/name)
- Study discussed and date of informed consent
- Dates of all visits

- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of IP, including start and stop times of axicabtagene ciloleucel or KTE-X19 administration
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end date, dose if relevant, and dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

Traceability records for the product, from procurement through manufacture to the administration of the product, should be kept by each relevant party (eg, the sponsor, the investigator/institution) for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by agreement with the sponsor. Before, during, and after completion or termination of the trial, each party should hold the necessary information available at all times to ensure bidirectional traceability, linking the subject information at the procurement site to the product and the subject information at the clinical trial site to the product, while ensuring the data protection legally required for the subject.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Kite to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

If a subject transfers to another study site, the investigator must notify Kite in advance before assigning the subject's study records to another party or moving them to another location.

14. STUDY MONITORING AND DATA COLLECTION

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

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

By signing the Investigator'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 Kite Quality Assurance site audit. A Kite Quality Assurance 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. Investigators will provide Kite Quality Assurance auditors access to subject records.

Representatives of regulatory authorities may conduct inspections of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Kite medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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 has insurance that provides compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Kite will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal or travel expenses or reimbursements, consulting fees, and any other transfer of value.

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18. APPENDIX

18.1. Appendix 1: Revised International Working Group Response Criteria for Malignant Lymphoma

Information in this section has been taken from {Cheson 2007}. These criteria will be used for disease assessments by the site investigators for subjects in Cohort 1 only.

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, 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

18.2.1. Disease Staging

Subjects in Cohort 3 will have disease staging at study entry performed per the Lugano Classification {Cheson 2014}. This staging system is a modification of the Ann Arbor classification and is presented in Table 11.

Table 11. Disease Staging System per Cheson, 2014

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Note: Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
a Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and prognostic factors.

18.2.2. Disease Response Assessment

Refer to imaging manual and {Cheson 2014} for details of assessment. These criteria will be used for disease assessments by the site investigators for subjects in Cohort 2 and Cohort 3.

Table 12. 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 2014}

18.2.2.1. Complete Response

18.2.2.1.1. 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.

18.2.2.1.2. 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

18.2.2.2. Partial Response

18.2.2.2.1. 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.

18.2.2.2.2. 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.

18.2.2.3. Stable Disease

18.2.2.3.1. 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.

18.2.2.3.2. 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.

18.2.2.4. PD

18.2.2.4.1. 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.

18.2.2.4.2. 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, France, and United Kingdom:

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 7 or Table 9, 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.

18.4. Appendix 4: Cytokine Release Syndrome Grading per Lee, 2014

For all subjects, the severity of cytokine release syndrome (CRS) will be graded according to the grading system proposed by Lee and colleagues {Lee 2014} (Table 13). Guidelines for management of CRS are provided in the current Investigator's Brochure (IB).

Table 13. CRS Grading Scale (Excluding Neurologic Events) per Lee, 2014

Grade	Symptoms
Grade 1	Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement < 40% FiO_2 or Hypotension responsive to fluids or low dose of 1 vasopressor[a] or Grade 2 organ toxicity[b]
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO_2 or Hypotension requiring high-dose or multiple vasopressors[a] or Grade 3 organ toxicity or Grade 4 transaminitis[b]
Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)[b]
Grade 5	Death

Abbreviations: CRS, cytokine release syndrome; FiO_2, fraction of inspired oxygen.
a High-dose vasopressor doses shown in Table 14.
b Severity based on Common Terminology Criteria for Adverse Events.

Table 14. Definitions of High-dose Vasopressors in Adults

Vasopressor	Dose[a]
Norepinephrine monotherapy	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥ 10 µg/min[b]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 µg/min[b]

a All doses are required for ≥ 3 hours.
b VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10]

18.5. Appendix 5: Cytokine Release Syndrome Grading per American Society for Transplantation and Cellular Therapy

In 2018, the American Society for Transplantation and Cellular Therapy (ASTCT) published a grading system for cytokine release syndrome (CRS) {Lee 2019}. For subjects in Cohort 3 only, in addition to the modified Lee criteria (Section 18.4), CRS will also be assessed by ASTCT grading, as shown in Table 15. Importantly, toxicity management will only be based on Kite grading and management criteria as described in the current Investigator's Brochure (IB).

Table 15. ASTCT CRS Consensus Grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or[b]				
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome.
Notes: Organ toxicities associated with CRS may be graded according to the Common Terminology Criteria for Adverse Events but they do not influence CRS grading.

a Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or corticosteroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b The CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

c Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

18.6. Appendix 6: Neurologic Event Grading per American Society for Transplantation and Cellular Therapy

In 2018, the American Society for Transplantation and Cellular Therapy (ASTCT) published a grading system for immune effector cell-associated neurotoxicity syndrome (ICANS) {Lee 2019}. For subjects in Cohort 3 only, ICANS will be assessed by the ASTCT grading, as shown in Table 16 (using immune effector cell-associated encephalopathy [ICE] scores as determined by Table 17). However, neurotoxicity management will only be based on the Common Terminology Criteria for Adverse Events (CTCAE) grading as described in the current Investigator's Brochure (IB).

Table 16. ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7 to 9	3 to 6	0 to 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolved rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviation: ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; N/A, not applicable.
Notes: The ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, and raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified with Grade 3 ICANS.

a A patient with an ICE score of 0 may be classified with Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified with Grade 4 ICANS if unarousable.
b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE, but they do not influence the ICANS grading.
d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE.

Table 17. Immune Effector Cell-associated Encephalopathy Score[a]

Task		Score
Orientation:	Orientation to year, month, city, hospital	4 points
Naming:	Ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following commands:	Ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing:	Ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1 point
Attention:	Ability to count backwards from 100 by 10	1 point

a Immune effector cell-associated encephalopathy (ICE) score as developed by the American Society for Transplantation and Cellular Therapy consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells {Lee 2019}.

18.7. Appendix 7: Childbearing Potential and Birth Control

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

18.7.1. Definition of Childbearing Potential

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

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

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

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

Methods that can achieve a failure rate of < 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation[a]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - Oral
  - Injectable
  - Implantable[b]
- Intrauterine device (IUD)[b]

[a] Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method.
[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

- Intrauterine hormone-releasing system (IUS)[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[b,c]
- Sexual abstinence[d]

18.7.3. Unacceptable Birth Control Methods

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

[c] A vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the female of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and preferred and usual lifestyle of the subject.

amd-9-protocol KTE-C19-102

ELECTRONIC SIGNATURES

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