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TITLE: A Phase 2 trial of anakinra for the prevention of CAR-T cell mediated neurotoxicity.

Coordinating Center: **Massachusetts General Hospital (MGH)**

***Principal Investigator (PI):** **Matthew J. Frigault, MD**
MGH Cancer Center

mfrigault@mgh.harvard.edu

IND #: 146073

IND Sponsor: **Marcela V. Maus, MD, PhD**
MGH Cancer Center

Statistician:

Nora Horick
Massachusetts General Hospital

nhorick@mgh.harvard.edu

Study Coordinator:

Jami Brown, MS, CCRP
Massachusetts General Hospital

jbrown56@mgh.harvard.edu

Responsible Research Nurse:
Betsy Valles
Massachusetts General Hospital
55 Fruit St, Boston, MA 02114
617-643-9072
617-726-0054
bvalles@mgh.harvard.edu

Responsible Data Manager:
Natascha Nolet
Massachusetts General Hospital
nnolet@mgh.harvard.edu

Other Agent(s): MGH is the sponsor of this study, working in close collaboration with Kite, a Gilead company, to fund, develop and conduct this protocol.

Protocol Type / Version # / Version Date: Original/Version #7/26AUG2021

CLINICAL STUDY PROTOCOL SYNOPSIS

Name of Sponsor/Company:
Marcela V. Maus, MD, PhD, Massachusetts General Hospital (MGH)

Name of Investigational Product:
Anakinra

Title of Study (Protocol Title):
A Phase 2 trial of anakinra for the prevention of CAR-T cell mediated neurotoxicity.

Protocol Number: 19-348

Study center(s): MGH Cancer Center

Principal Investigator: Matthew J. Frigault, MD
Investigator:

Studied period (years): 2	**Phase of development: 2**
Estimated date first patient enrolled: quarter IV, 2019 Estimated date last patient completed: quarter IV, 2021	

Objectives:

Primary Objective

- To assess the impact of anakinra as preventative management of CAR-T related neurotoxicity.

Secondary Objective:

- To assess the impact of anakinra as preventative management of CAR-T related CRS.
- To evaluate the efficacy of axicabtagene ciloleucel in combination with preventative anakinra in terms of DOR, ORR, PFS, and OS

Exploratory Objective:

- To assess the function, expansion and phenotype of axicabtagene ciloleucel in patients receiving preventative anakinra.
- To assess mechanisms of tumor resistance and escape.
- To compare CRS/Neurotox grading used in Zuma-1 to new ASBMT guidelines (Lee 2018).

Route and Regimen:

Investigational Product:

- **Anakinra** treatments consists of sub-cutaneous injection at a target weight base dose of 100mg for subjects <50kg and 200mg for subjects ≥50 kg. Refer to Section 6.4.3 for treatment details.

Bridging Therapy (in between leukapheresis and lymphodepleting chemotherapy)

- At the discretion of the investigator, bridging therapy may be considered for subjects at the investigator's discretion

- For subjects receiving bridging therapy, refer to Section 6 for bridging therapy details.

Lymphodepleting Chemotherapy

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

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

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

Subjects will have lumbar punctures performed for the collection of CSF (see Section 11.9 and SOA) before and after axicabtagene ciloleucel infusion.

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

Methodology/Study Design: This is a Phase 2 single center, open-label study evaluating the safety and efficacy of **anakinra when combined with axicabtagene ciloleucel** in subjects with refractory aggressive NHL.

Phase 2 Study

The Phase 2 study will enroll approximately **20** subjects with refractory aggressive NHL.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis period
- Bridging therapy (if applicable)
- Lymphodepleting chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long term follow-up period

For study requirements assigned to each study period, refer to Section 7 for details.

Long-term Follow-up

All subjects who complete the study, and those who withdraw from the study after receiving CAR-19 for reasons other than death, will be asked to participate in a long-term follow-up study for up to 15

years after their last CAR-19 infusion, with a focus on long-term efficacy and safety. After Month 24 patients will be followed via the CIBMTR immune effector cell therapy registry.

Diagnosis and selection criteria: CD19+ NHL

Inclusion Criteria

1. Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
2. At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma [1]. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy
3. At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy however steroids only require a 7-day washout. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).
4. Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)
5. Age 18 or older
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. ANC ≥1000/uL
8. Platelet count ≥75,000/uL
9. Absolute lymphocyte count ≥100/uL
10. Adequate renal, hepatic, pulmonary and cardiac function defined as:
    - Creatinine clearance (as estimated by Cockcroft Gault or CKD-EPI) ≥ 60 mL/min
    - Serum ALT/AST ≤2.5 ULN
    - Total bilirubin ≤1.5 mg/dl, except in subjects with Gilbert's syndrome.
    - Cardiac ejection fraction ≥ 50%, no clinically significant pericardial effusion, and no clinically significant ECG findings
    - No clinically significant pleural effusion
    - Baseline oxygen saturation >92% on room air
11. 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)
12. Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

1. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years
2. History of Richter's transformation of CLL
3. Autologous stem cell transplant within 6 weeks of planned axicabtagene ciloleucel infusion
4. History of allogeneic stem cell transplantation
5. Prior CD19 targeted therapy with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for re-treatment
6. Prior chimeric antigen receptor therapy or other genetically modified T cell therapy
7. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
8. Presence **or suspicion** of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management.
9. History of HIV infection or acute or chronic active hepatitis B or C infection. Subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines.
10. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted
11. Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases
12. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
13. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
14. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment
15. **Expected or possible** requirement for urgent therapy **within 6 weeks** due to **ongoing or impending oncologic emergency (eg,** tumor mass effect, **tumor lysis syndrome)**
16. Primary immunodeficiency
17. History of **symptomatic** deep vein thrombosis or pulmonary embolism within 6 months of enrollment
18. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
19. History of severe immediate hypersensitivity reaction to any of the agents used in this study
20. Live vaccine $\leq$ 6 weeks prior to planned start of conditioning regimen
21. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant.

Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

22. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of axicabtagene ciloleucel
23. In the investigators 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
24. History of autoimmune disease (e.g. Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

1.1 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

DSMC & SRT

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI, study team and Kite/Gilead. The DSMC will review protocols up to, but not more than four times a year with the primary focus being accrual, protocol adherence, audit results and summary of all deaths while being treated and during active follow-up. Given the collaborative nature of this protocol, there will be an additional safety review team (SRT) comprised of the study sponsor/PI and Kite/Gilead meant to review all study safety data and be the primary driver of recommendations on further study conduct as described below. .

Refer to Section 13.2 and Section 8.4.4.

Statistical methods:

The primary objective of this study is to assess the impact of prophylactic regimens on the rate and severity of neurologic toxicities. With 20 patients the study will have 86% power to detect a decrease in the grade 2+ neurotoxicity rate from 45% to 15% via a two-sided exact binomial test with a significance level of 0.05. The secondary objectives of this study inclde analyses the rate and severity of CRS as well as efficacy endpoints (ORR, DOR, PFS, OS) and levels of anti-CD19 CAR T cells and cytokines in the blood.

Study Glossary

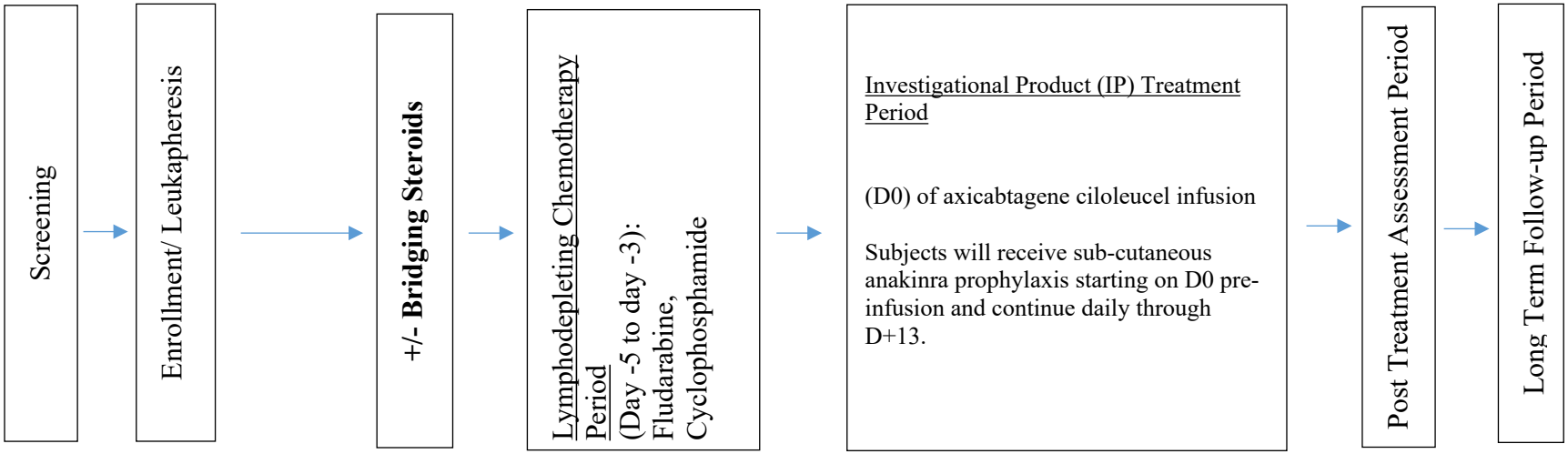
Abbreviation or Term	Definition/Explanation
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
CAR	Chimeric antigen receptor
CAR	Chimeric antigen receptor positive
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CPF	Cell processing facility
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
eACT™	Engineered autologous cell therapy
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalogram
End of Study for individual subject	Defined as when the last day that protocol specified assessments are conducted for an individual subject
End of Study (primary completion)	Defined as when the last subject is assessed or received an intervention for the purposes of final collection of data for the primary endpoint at Month 6
End of Study (end of trial)	Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments

Abbreviation or Term	Definition/Explanation
FAS	Full analysis set
FL	Follicular lymphoma
Healthcare Facility	Clinical trial site
HGBCL	High grade B-cell lymphoma
HLH	Hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICF	Informed consent form
ICU	Intensive care unit
IP	Investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRRC	Independent Radiological Review Committee
IWG	International Working Group
KTE-C19/axicabtagene ciloleucel	Autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3 zeta chimeric antigen receptor
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
mITT	Modified intent-to-treat
MMSE	Mini-Mental Status Exam
MRI	Magnetic resonance imaging
MSGV1	Murine stem cell virus-based vector
NaCl	Sodium chloride
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PET-CT	Positron emission tomography–computed tomography
PBMC	Peripheral blood mononuclear cell
PMBCL	Primary mediastinal B-cell lymphoma
PD	Progressive disease
PR	Partial response
RCR	Replication-competent retrovirus
SAE	Serious adverse event
scFv	Single chain variable fragment

Abbreviation or Term	Definition/Explanation
SD	Stable disease
SMS	Safety management study
SOA	Schedule of assessment
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
Study Day 0	Defined as the first day that axicabtagene ciloleucel is administered to the subject
TEAEs	Treatment-emergent adverse event
TFL	Transformed follicular lymphoma
ULN	Upper limit of normal
VAS	Visual analogue scale

SCHEMA

Figure 1. Study Schema



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2. OBJECTIVES

The primary objective of this study is to assess the impact of anakinra as preventative management of neurotoxicity, as measured by the incidence and maximal grade, following axicabtagene ciloleucel in subjects with aggressive refractory NHL.

The key secondary objectives include assessment of rate and severity of cytokine release syndrome and efficacy of axicabtagene ciloleucel in terms of DOR, ORR, PFS, and OS.

Exploratory objectives to include comparison of Zuma-1 CRS/NT grading criteria to new ASBMT criteria, levels of anti-CD19 CAR T cells in blood, levels of cytokines in serum and CSF, incidence of anti-axicabtagene ciloleucel antibodies and other investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product.

2.1 Study Design

Study 19-348 is a Phase 2 single center, open-label study evaluating the safety and efficacy of **anakinra when combined with axicabtagene ciloleucel** in subjects with relapsed or refractory large B cell lymphoma.

Approximately 20 subjects with aggressive refractory NHL, including DLBCL, PMBCL, high grade lymphoma or TFL will be enrolled to evaluate the safety of anakinra in combination with axicabtagene ciloleucel. If the initial regimen is determined to be safe, the study may be expanded beyond the initial 20 patient cohort. A SRT comprised of the study sponsor and Kite/Gilead, will review the safety data and make recommendations on further study conduct

For study requirements assigned to each study period, please refer to the schedule of assessments (SOA) and Section 11 for details.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis period
- Bridging therapy (if applicable)
- Lymphodepleting chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long term follow-up period

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

2.2 Protocol Objectives

Primary Objective

- To assess the impact of anakinra as preventative management of CAR-T related neurotoxicity.

Secondary Objective:

- To assess the efficacy of anakinra for prophylaxis of CRS when used in combination with axi-cel.
- To evaluate the efficacy of axicabtagene ciloleucel in combination with preventative anakinra in terms of DOR, ORR, PFS, and OS.

Exploratory Objective:

- To assess the function, expansion and phenotype of axicabtagene ciloleucel in patients receiving preventative anakinra.
- To assess mechanisms of tumor resistance and escape.
- To compare CRS/Neurotox grading used in Zuma-1 to new ASBMT guidelines

3. BACKGROUND

3.1 Disease Background and Rationale

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes or natural killer cells. In the United States, B cell lymphomas represent 80-85% of cases reported. In 2013, approximately 69,740 new cases of NHL and over 19,000 deaths related to the disease were estimated to occur. Non-Hodgkin lymphoma is the most prevalent hematological malignancy and is the seventh leading site of new cancers among men and women and account for 4% of all new cancer cases and 3% of deaths related to cancer [2]. Large B-cell lymphomas represent the most common sub-group of NHL [3].

3.1.1 Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of large B-cell lymphoma, accounting for approximately 30% of NHL cases. There are approximately 22,000 new diagnoses of DLBCL in the United States each year. In the past two decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of CHOP and immunotherapy. The addition of rituximab into combination therapies for DLBCL have greatly improved patient outcomes. However, patients with chemotherapy-refractory DLBCL following treatment under the current standards of care still have a particularly dire prognosis, with no curative treatment options [4].

The population with the highest unmet need continues to consist of patients who do not respond to first line combination chemotherapy (typically R-CHOP) or who do not respond to their last course of combination chemotherapy, as the disease is mostly insensitive to subsequent combination chemotherapy (typically R-ICE, R-ESHAP) (Table 1). In a review of 64 patients with DLBCL with disease progression during first line chemotherapy or only transient response

(≤90 days) after end of induction treatment, the response rate to second line therapy was 15% and the median overall survival (OS) was 6 months, and no patient survived more than 26 months after first diagnosis [5]. An analysis of outcome in 1126 patients with DLBCL after first line R-CHOP included 33 patients with primary refractory DLBCL who received second line therapy with curative intent. Only 3 (9%) patients were able to receive autologous stem cell transplantation (ASCT), and only 1 (3%) patient achieved long term survival [6]. Seshadri et al analyzed 120 patients who did not respond to second line platinum-based chemotherapy regimens (e.g., R-ICE) and showed that only 14% responded to their third line therapy [7]. Ardeshna et al followed 19 patients with large B-cell lymphoma, and 9 patients with TFL who did not respond to second line chemotherapy. Only 5 of the 28 total patients (18%) responded to third line chemotherapy [8].

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

Setting	Outcome to Subsequent Therapy
Refractory to 1st line	
[9] (n=28)	ORR 21%
[5] (n=64)	ORR 15%, median OS 6 mos
[8] (n=5)	ORR 0%
[6] (n=33)	Proceeded to ASCT 9%, 3% survived > 1 year
[10] (n = 111)	ORR 23%, median OS 10 mos
[11] (n=10)	ORR 10%
Refractory to 2nd line	
[12] (n=55)	Median OS 5 mos
[8] (n=28)	ORR 18%, median OS (large B-cell lympohoma) <6 mos
[7] (n=73)	ORR 14%
Relapsed post ASCT	
[13] (N=45)	Median OS 8 mos

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

3.1.2 Primary Mediastinal B-cell Lymphoma and Transformed Follicular Lymphoma

Primary mediastinal B-cell lymphoma (PMBCL) has distinct clinical, pathological, and molecular characteristics compared to DLBCL. PMBCL is thought to arise from thymic (medullary) B cells and represents approximately 3% of patients diagnosed with large B-cell lymphoma. PMBCL is typically identified in the younger adult population in the fourth decade of life with a slight female predominance [14,15]. Gene expression profiling suggests deregulated pathways in PMBCL overlap with Hodgkin lymphoma. Initial therapy of PMBCL generally includes anthracycline-containing regimens with rituximab with or without involved field radiotherapy. A recent Phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) demonstrated radiotherapy may not be required [16].

Follicular lymphoma (FL), a B cell lymphoma, is the most common indolent (slow-growing) form of NHL, accounting for approximately 20% to 30% of all NHLs. Some patients with FL will transform (TFL) histologically to DLBCL which is more aggressive and associated with a poor outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3%

for 15 years with the risk of transformation continuing to drop in subsequent years. The biologic mechanism of histologic transformation is unknown. Initial treatment of TFL is influenced by prior therapies for follicular lymphoma but generally includes anthracycline-containing regimens with rituximab to eliminate the aggressive component of the disease [17].

Treatment options for relapsed/refractory PMBCL and TFL are similar to those in DLBCL. Given the low prevalence of these diseases, no large prospective randomized studies in these patient populations have been conducted. Patients with chemotherapy refractory disease have a similar or worse prognosis [18] to those with refractory DLBCL.

In addition, the international, multicohort retrospective non-Hodgkin lymphoma research (SCHOLAR-1) study retrospectively evaluated outcomes in patients with chemorefractory DLBCL, PMBCL, and TFL. SCHOLAR-1 integrated data from two Phase 3 studies (LYSARC-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and Mayo Clinic/University of Iowa Specialized Program of Research Excellence). Among 861 patients, 635 were included based on chemorefractory search criteria. Outcomes were consistently poor, regardless of refractory subgroup and across cohorts. The results of SCHOLAR-1 indicated that patients with chemorefractory, aggressive DLBCL represent a homogenous patient population with a response rate of 26% (complete response [CR] rate of 7%) and median overall survival of 6.3 months [19].

3.1.3 **High Grade B-cell Lymphoma**

In 2016, the World Health Organization introduced a new category of large B-cell lymphomas called high grade B-cell lymphoma (HGBCL) [20]. This designation includes large B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements that are phenotypically intermediate to DLBCL or B-cell lymphoma, unclassifiable (this latter category has since been eliminated). MYC rearrangements in large B-cell lymphomas are associated with a poor prognosis that is worsened in cases of concomitant BCL2 and/or BCL6 alterations, ie, double- or triple-hit lymphomas. As such, patients with HGBCL are likely to face poor survival outcomes.

3.2 T cell Therapy for Aggressive Refractory Lymphomas

3.2.1 **Axicabtagene Ciloleucel**

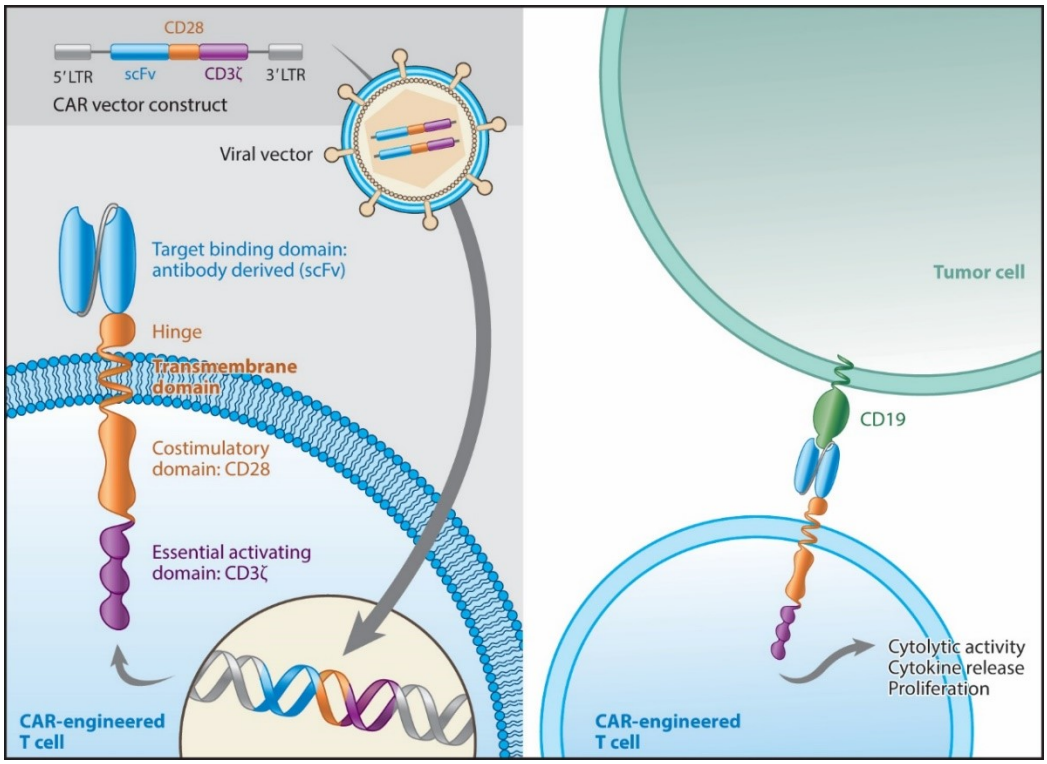
Axicabtagene ciloleucel are anti-CD19 chimeric antigen receptor (CAR) autologous human T cells that have been engineered to express an extracellular single chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem (Figure 2).

An anti-CD19 CAR vector construct was previously designed, optimized and initially tested at the Surgery Branch of the National Cancer Institute (NCI, IND 13871) (Figure 2.) [21,22]. The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 [23]. A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and persistence of anti-CD19 CAR T cells [24]. The signaling domain of the CD3-zeta

chain is essential for T cell activation. These fragments were cloned into the murine stem cell virus-based (MSGV1) vector, utilized to genetically engineer the autologous T cells.

Kite Pharma performed larger scale clinical development of autologous anti-CD19 CAR T cells, and named this therapeutic engineered cell product axicabtagene ciloleucel. Treatment with axicabtagene ciloleucel was FDA approved in 2017 based on data from the Zuma-1 study which demonstrated objective response rates upwards of 83%, with a median OS that has not been reached (Locke, Lancet Oncology 2018). Real world data of axicabtagene has demonstrated similarly robust response rates and durability, but further emphasized the need for improved toxicity management. This real world experience demonstrated cytokine release syndrome (CRS) and neurotoxicty rates of 96% and 76% with grade ≥ 3 events seen in 17% and 38% respectively (Jacobson et al, ASH 2018).

Figure 2. Axicabtagene Ciloleucel



3.3 CRS, Neurotoxicity Management and IL-1

The primary acute toxicities observed to date with CAR T cells have been CRS and neurotoxicity. CRS is defined as a constellation of symptoms which may include (but are not limited to) fever, chills, hypotension, hypoxia, and when extreme, macrophage activation syndrome. Manifestations of neurotoxicity vary and include confusion, obtundation, seizures, hallucinations, aphasia, ataxia, and more rarely, profound cerebral edema[25]. The future success and application of commercial product to a broader population of patients is limited by the frequency and severity of these

toxicities. CRS is managed in the inpatient setting with administration of the anti-IL6 receptor antibody tocilizumab, with or without steroids, only after the onset of CRS in the setting of clinical decline[25]. The CRS associated with CAR T cells shares many pathogenic features of macrophage activation syndrome[26]. CAR-T related neurotoxicity is thought to be cytokine mediated in the setting of macrophage and endothelial activation and is predominantly managed with steroids alone[27], because tocilizumab has no therapeutic efficacy against CAR T cell-related neurotoxicity. Tocilizumab has been studied in the prophylactic setting as part of the third cohort of ZUMA-1; these data showed that despite improvement in the incidence of CRS, investigators found that there was an increase in the incidence of severe neurotoxicity. This was felt to be related to the poor CNS penetration of tocilizumab, which may have led to increased intracerebral levels of IL-6.[28] Given these findings, other targets within the IL-6 inflammatory pathway have been explored for the management of macrophage activation and cytokine release syndrome. Anakinra, a human interleukin 1 receptor antagonist, has demonstrated clinical efficacy in the treatment of rheumatoid arthritis and sepsis related macrophage activation syndrome, as well as in recent mouse models of CRS and neurotoxicity in which lethal CRS and neurotoxicity were abrogated with the use of anakinra (figure 3) [29-31]. We also have anecdotal experience with the use of anakinra to treat tocilizumab-refractory cytokine release syndrome, and have noted improvements in neurologic function. These data suggest that IL-1 blockade may play a critical role in the pathophysiology of both CRS and neurotoxicity. Furthermore, it does not appear that IL-1 activity is required to maintain CAR-T cell efficacy.

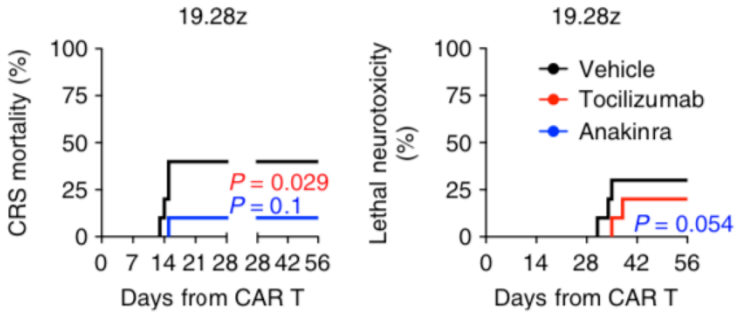


Figure 3. Anakinra, but not tocilizumab, abolishes neurotoxicity in a SGM3 mouse model of CRS and neurotoxicity. (Norelli et al. 2018)

3.3.1 **Anakinra**

Anakinra is a recombinant human IL-1 receptor antagonist (rhIL-1ra). Endogenous IL-1 is induced by inflammatory stimuli and mediates various immunological responses. Anakinra can be administered subcutaneously. Anakinra is currently FDA approved for cryopyrin-associated periodic syndromes and rheumatoid arthritis (RA).

Sub-cutaneous and intravenous administration of anakinra have been studied in multiple contexts. Anakinra was administered intravenously to patients with sepsis in several randomized controlled trials (RCTs) conducted in the 1990s[32-34]. In these trials, rhIL-1ra was administered using different regimens; all included an intravenous (IV) loading dose of 100 mg administered over about 60 seconds and followed by an IV infusion administered every 8 or 12 h by a volumetric infusion

pump at a constant rate (17-133 mg/h, n=74, or 1- 2 mg/kg/h, n=941) for 72 h. The frequencies of (serious) adverse events were not significantly different between the treatment and placebo groups. No unique clinical or laboratory adverse events were significantly more frequent in the anakinra-treated patients compared to the placebo group, and there was no evidence of delayed resolution of infection or increased frequency of secondary infections in the anakinra-treated group[34]. Before these trials of rhIL-1ra in sepsis, a phase I study of rhIL-1Ra administered intravenously at different doses had been conducted in 25 healthy individuals, generating safety and pharmacokinetic data[35]. In this study, the authors had found no clinically significant differences in clinical, hematological, biochemical, or endocrinological parameters between the groups receiving anakinra or saline. The only reaction occurred in one volunteer who developed a mild, transient case of hepatitis.

Additional placebo controlled, randomized trials have occurred designed to assess the safety of patients receiving anakinra monotherapy and combinations with other immunosuppressive agents. One such study by Fleischmann et al. included 1414 patients receiving a variety of concurrent medications for RA including some disease modifying antirheumatic drugs (DMARDs), as well as patients who were DMARD-free. Concurrent DMARDs included MTX, sulfasalazine, hydroxychloroquine, gold, penicillamine, leflunomide, and azathioprine. Although Serious infectious episodes were observed more frequently in the anakinra group (2.1% versus 0.4% in the placebo group), this was ultimately felt to be secondary to combination with other immunosuppressive agents and therefore should be monitored[36].

Several pharmacokinetic studies have been performed for subcutaneous treatment. In subjects with RA, maximum plasma concentrations of anakinra occurred 3 to 7 hours after subcutaneous administration of anakinra at clinically relevant doses (1 to 2 mg/kg; n = 18); the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of Kineret was observed after daily subcutaneous doses for up to 24 weeks. The mean plasma clearance of Kineret in subjects with mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-49 mL/min) renal insufficiency was reduced by 16% and 50%, respectively and no significant dose reduction was recommended upon FDA approval.

Refer to the most recent version of the package insert from the FDA label for additional details surrounding the anakinra.

3.4 Correlative Studies Background

Correlative studies will be performed on peripheral blood, bone marrow/tumor biopsies and, if available, CSF samples to evaluate PK/PD markers related to safety and/or efficacy. The effectiveness of axicabtagene ciloleucel T cells may depend on the expansion and persistence of CAR T cells in subjects. Therefore, the expansion and persistence will be monitored by flow cytometry and PCR analysis using peripheral blood samples as per standard SOPs. Samples will be collected per the protocol Schedule of Events (see **11.1 Schedule of Events**). Periodic monitoring of anti-inflammatory cytokines secretion will be performed to determine correlation between axicabtagene ciloleucel efficacy and/or toxicity; in addition, CD19 expression on tumor cells will be evaluated at the eligibility and in subjects failing to achieve a complete response.

Additional testing may be done depending on the clinical condition; for instance, patients with symptoms suggestive of cytokine release syndrome or with skin rash or other findings that may concern the investigators may have more frequent monitoring to enhance the safety of this trial.

If tumor tissues or bone marrow aspirates become available as part of routine clinical care, a sample will be collected for research analysis. Tissue samples will be analyzed for the presence of axicabtage ciloleucel T cells by PCR and/or flow cytometry. Additionally, different T cell subsets have demonstrated different effector function and persistence and, therefore, T cell immunophenotyping will be performed by flow cytometry. Peripheral blood samples will be analyzed for cytokine/chemokine levels by multiplex bead array technology. Tumor tissue will be analyzed for CD19 expression by immunohistochemistry and/or flow cytometry. Additional clinical samples testing may be performed based on the Exploratory Endpoints as listed in **Section 2.4.**

All research samples will be delivered, processed, and frozen as per SOP to either Kite/Gilead (for VCN and cytokine analysis) or the Maus/Immune Monitoring Laboratory at the MGH Cancer Center for storage and bulk analyses (all other correlative studies). Documentation of sample receipt, processing, and storage and primary data from the research analyses will be collected and stored by the Immune Monitoring Lab personnel. All research analyses will be performed based on assay-specific SOP using qualified assays.

4. PARTICIPANT SELECTION

All subjects must sign and date the IRB/IEC approved consent form before initiating any study specific procedures or activities that are not part of a subject's routine care. Refer to Section 10 for details.

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

4.1 Inclusion Criteria

1. Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
2. At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma [1]. Lesions that have been previously irradiated will be

considered measurable only if progression has been documented following completion of radiation therapy

3. At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy however steroids only require a 7-day washout. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).
4. Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)
5. Age 18 or older
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. ANC ≥1000/uL
8. Platelet count ≥75,000/uL
9. Absolute lymphocyte count ≥100/uL
10. Adequate renal, hepatic, pulmonary and cardiac function defined as:
    - Creatinine clearance (as estimated by Cockcroft Gault or CKD-EPI Equation)) ≥ 60 mL/min
    - Serum ALT/AST ≤2.5 ULN
    - Total bilirubin ≤1.5 mg/dl, except in subjects with Gilbert's syndrome.
    - Cardiac ejection fraction ≥ 50%, no clinically significant pericardial effusion, and no clinically significant ECG findings
    - No clinically significant pleural effusion
    - Baseline oxygen saturation >92% on room air
11. 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)
12. Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

25. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years
26. History of Richter's transformation of CLL
27. Autologous stem cell transplant within 6 weeks of planned **axicabtagene ciloleucel** infusion
28. History of allogeneic stem cell transplantation
29. Prior CD19 targeted therapy with the exception of subjects who received **axicabtagene ciloleucel** in this study and are eligible for re-treatment
30. Prior chimeric antigen receptor therapy or other genetically modified T cell therapy
31. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
32. Presence **or suspicion** of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management.

33. History of HIV infection or acute or chronic active hepatitis B or C infection. Subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines.
34. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted
35. Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases
36. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
37. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
38. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment
39. **Expected or possible** requirement for urgent therapy **within 6 weeks** due to **ongoing or impending oncologic emergency (eg,** tumor mass effect, **tumor lysis syndrome)**
40. Primary immunodeficiency
41. History of **symptomatic** deep vein thrombosis or pulmonary embolism within 6 months of enrollment
42. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
43. History of severe immediate hypersensitivity reaction to any of the agents used in this study
44. Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen
45. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential
46. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of **axicabtagene ciloleucel**
47. In the investigators 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
48. History of autoimmune disease (e.g. Crohn's, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

4.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied. The registration process includes registration of the participant for study related, as well as initiation of treatment plan related activities. An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist. This does not include registration with Kite/Gilead for manufacturing of axicabtagene ciloleucel which will be performed separately by study staff via Kite IPM.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

5.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5.3 General Guidelines for Other Investigative Sites

N/A

5.4 Registration Process for Other Investigative Sites

N/A

6. TREATMENT PLAN

6.1 Study treatment

6.1.1 **Bridging Therapy**

Bridging refers to the time in between leukapheresis and initiation of lymphodepleting chemotherapy. Bridging therapy will be allowed at the discretion of the treating investigator. Chemotherapy given after leukapheresis as bridging therapy must be stopped ≥7 days prior to lymphodepleting chemotherapy. Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis, and 5 days prior to **axicabtagene ciloleucel** administration.

6.1.2 **Lymphodepleting Chemotherapy**

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

6.1.2.1 **Fludarabine**

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

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

6.1.2.2 **Cyclophosphamide**

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

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

6.1.2.3 **Mesna**

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

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

6.1.3 **Axicabtagene Ciloleucel**

Refer to the most current Investigator's Brochure regarding axicabtagene ciloleucel and clinical experience.

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

Axicabtagene ciloleucel is a subject-specific product and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels

match the subject's information (e.g., initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of axicabtagene ciloleucel infused, the thaw start/stop time, and axicabtagene ciloleucel administration start/stop time, will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion. Refer to Section 9 for details and instruction on storage, thawing, and administration of axicabtagene ciloleucel.

6.1.4 **Anakinra**

Anakinra will be supplied by the investigative site unless otherwise noted. Anakinra is an antagonist of the interleukin-1 (IL-1) receptor. Endogenous IL-1 is induced by inflammatory stimuli and mediates various immunological responses. Anakinra will be administered subcutaneously via pre-filled syringes. The dose, schedule, and route of administration of anakinra on this protocol is described in section 6.4.3. Anakinra is currently approved for cryopyrin-associated periodic syndromes and rheumatoid arthritis. Refer to the most recent version of the package insert from the FDA label for specific details surrounding the administration of anakinra.

6.2 Treatment Regimen

6.2.1 **Chemotherapy General Instructions**

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

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

6.2.2 **Axicabtagene Ciloleucel General instructions**

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

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

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

All patients should be started on levetiracetam 750mg (PO or IV) twice daily starting day of infusion.

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

- Acetaminophen 650 mg PO
- Diphenhydramine (12.5 to 25 mg IV or 25 mg PO)

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of axicabtagene ciloleucel. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of axicabtagene ciloleucel are outlined Section 9.

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

6.2.3 **Anakinra General Instructions:**

All subjects will receive anakinra subcutaneous injections at a healthcare facility as in section 6.4.3. In brief, patients will receive their first dose 4 hours (+/- 30 min) prior to CAR-T cell infusion on day 0 and daily thereafter through D+13. Specific dosing strategy is detailed in section 6.4.3.

6.3 Rationale for Study Treatment Dosing

6.3.1 **Rationale for Lymphodepleting Chemotherapy**

Increasing levels of lymphodepleting chemotherapy correlates with clinical responses to adoptive cell therapy [38]. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T cell expansion and function in pre-clinical models. The depth and duration of the lymphodepletion in preclinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific CD8+ T cells [39]. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation [40]. Cyclophosphamide and fludarabine is a potent lymphodepleting regimen. Optimizing the doses of cyclophosphamide and fludarabine to improve the depth and duration of lymphodepletion may enhance the activity of axicabtagene ciloleucel.

As per the FDA approved label for axicabtagene ciloleucel, the lymphodepleting chemotherapy dose in will be cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days with the target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. Cyclophosphamide

(500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days has been studied and tolerated in subjects with B cell malignancies [41].

6.3.2 Rationale for Patient Population to be Included in Phase 2 Study

The proposed patient population mirrors that of Zuma-1, a multicenter phase 2 study of axicabtagene ciloleucel in relapsed/refractory large cell lymphoma that led to FDA approval. Additionally, based on real-world experience, less stringent eligibility criteria have demonstrated comparable outcomes when compared to Zuma-1.

6.3.3 Rationale for using Anakinra

Cytokine release syndrome is driven by a multitude of inflammatory cytokines culminating in varying degrees of macrophage activation syndrome and clinical CRS. Currently, IL-6R targeting therapy is the standard of care for the management of CRS[42]. Pre-clinical data suggest that while IL-6 is a primary mediator of CRS and possibly neurotoxicity, IL-6R targeting is insufficient to prevent these toxicities[29,43]. CRS and neurotoxicity prophylaxis has been attempted with tocilizumab and although lower rates of CRS were observed, high, if not higher rates of Grade 4+ neurotoxicity were seen (Locke ASH 2017). IL-1 is a pro-inflammatory cytokine that has been targeted in various inflammatory states including rheumatoid arthritis and refractory macrophage activation syndromes[30,44]. Recent animal data has demonstrated that IL-1 plays a key role in CRS and neurotoxicity and may even prime the myeloid compartment for subsequent IL-6 signaling and activation. Anakinra dosed subcutaneously can achieve 95% bioavailability with a time to peak of 3 to 7 hours, making it ideal for daily prophylactic dosing. Weight based dosing of anakinra at 100 mg (if <50kg) vs 200 mg (if ≥50kg) was selected based on currently approved dosing as well as substantial clinical data demonstrating safety at doses beyond 200mg[45]. Daily dosing was selected given the short half-life of Anakinra and ongoing cytokine production during CAR-T expansion, as seen in pre-clinical animal models and prior clinical trial experience[29].

6.4 T cell Therapy and Anakinra Administration

6.4.1 Lymphodepleting Chemotherapy

Subjects will receive the 3-day lymphodepleting chemotherapy regimen followed by 2-day rest period (48 hrs):

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

6.4.2 **Axicabtagene ciloleucel Administration**

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

As part of the FDA REMS requirement, an appropriate REMS specific medication guide and patient identification card will be supplied to the patient prior to axicabtagene infusion.

6.4.3 **Anakinra administration**

Anakinra will be administered on days 0 through D+13 as detailed below.

Anakinra dosing strategy:

- Patients will be given their first dose of Anakinra 4 hours (+/- 30 min) prior to CAR-T infusion on day 0.
- Patients will start with subcutaneous Anakinra as a weight based dose.
  - 100 mg SQ for subjects <50kg
  - 200 mg SQ for subjects ≥50 kg

Example of 80kg patient

	Day 0 (4 hrs prior to CAR-T infusion)	**Day+1**	**Day+2**	**Day+3**	**Day+4**	**Day+5**	**Day +6**
Anakinra SQ[@]	200mg	200mg	200mg	200mg	200mg	200mg	200mg
	Day+7	**Day+8**	**Day+9**	**Day+10**	**Day+11**	**Day+12**	**Day +13**
Anakinra SQ[@]	200mg	200mg	200mg	200mg	200mg	200mg	200mg

[@] Anakinra will be administered sub-cutaneously per weight based dosing (100mg SQ for subjects <50kg and 200mg SQ for subjects ≥50 kg.). Dosing allowed +/- 30 min of 4 hour window.

Additional doses of anakinra following D+13 will not be provided unless discussed with the principal investigator. It is acceptable to give tocilizumab, steroids or 3rd line agents for the management of CRS in combination with anakinra per institutional guidelines.

6.5 General Concomitant Medication and Supportive Care Guidelines

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care except those medications listed in Section 6.6. This includes following institutional guidelines for standard management of CRS and neurotoxicity, including use of tocilizumab and/or high dose steroids as per appendix A.

All concurrent therapies, including medications, intubation, dialysis, oxygen, and blood products, will be recorded from the date of the informed consent through 1 month after completing treatment with axicabtagene ciloleucel. After 1 month of follow-up, only targeted concomitant medication will be collected for 24 months after axicabtagene ciloleucel infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin,

immunosuppressive drugs, anti-infective drugs, and vaccinations.

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

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

6.6 Excluded Medications

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

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

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

6.7 Subsequent Therapy

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

6.8 Duration of Follow Up

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

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

All subjects will be consented to the CIBMTR immune effector cell therapy registry at the same time as consent for this protocol and data will be reported on standard schedules immediately following infusion as required by FDA. Following Month 24 patients, protocol long-term followup will continue through the CIBMTR immune effector cell therapy registry as part of the FDA mandated 15-year follow-up period.

6.9 Criteria for Taking a Participant Off Study

6.9.1 Subject Withdrawal

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

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

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

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

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

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

6.9.2 Reasons for Removal from Treatment

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

- Adverse Event
- Subject request
- Product not available

- Lost to Follow-up
- Death
- Decision by sponsor

6.9.3 **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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

7. DOSING DELAYS/DOSE MODIFICATIONS

In the case of medical or natural emergencies (i.e. holidays, snowstorms, acute infection) occurring after initiation of chemotherapy, the infusion of axicabtagene ciloleucel may be delayed up to one week at the investigator's discretion. Subjects who do not initiate chemotherapy within 4 weeks of enrollment will be withdrawn; however, their CAR T cell product will be stored for up to 1 year if they re-enroll at a later date. No modifications to the doses will be made at the physician level.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. CTCAE 4.03 was chosen given its utilization during the Zuma-1 study which will act as a historical control.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

8.1 Expected Toxicities

To date, the following important risks have been identified with axicabtagene ciloleucel: CRS, neurologic toxicities, infections, and cytopenias.

Anakinra has been associated with an increased incidence of serious infections (2%) vs. Placebo (< 1%) in clinical trials in RA. Treatment with anakinra should not be initiated in patients with active infections. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported with anakinra. If a severe hypersensitivity reaction occurs, administration of

anakinra should be discontinued and appropriate therapy initiated. Patients receiving anakinra may experience a decrease in neutrophil counts. Neutrophil counts should therefore be assessed prior to initiating anakinra treatment.

8.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record. AE reporting will not begin until day 0 of the cellular therapy infusion, unless felt to be directly related to a study related procedure during the leukapheresis and/or lymphodepletion period.

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

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

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

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

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

8.2.1 Definition of Serious Adverse Events

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

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

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

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

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

8.3 Adverse Event Characteristics

Adverse Event Assessment

For all AEs, the Investigator must determine both the severity of the AE and the relationship of the AE to CAR T cells treatment.

- **CTCAE term (AE description) and grade**: The descriptions and grading scales found in the revise NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting of all toxicities (including neurotoxicity) EXCEPT for cytokine release syndrome (CRS), which will use Lee 2014 [48] criteria. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **For expedited reporting purposes only:**
  - AEs for agents utilized in this study should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require reporting are outlined in the next section (Expedited Adverse Event Reporting) and under the sub-heading of Protocol-Specific Expedited Adverse Event Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

8.4 Procedures for AE and SAE Collection and Reporting

8.4.1 **Reporting of Adverse Events**

The investigator is responsible for reporting adverse events directly related to study related procedures following study registration (leukapheresis) which includes mandated biopsies, lumbar punctures and/or lab draws. Following enrollment (cellular therapy infusion and initiation of anakinra), the investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from through 3 months after treatment with axicabtagene ciloleucel infusion, and investigational product use, are monitored and reported. After 3 months, targeted adverse events including (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) will be monitored and reported for 24 months after treatment with axicabtagene ciloleucel, and investigational product use, or until disease progression, whichever occurs first.

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

The investigator must address the below for adverse events:

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

In reviewing adverse events, investigators must assess whether the adverse event is possibly related to 1) the investigational product (**anakinra),** 2) lymphodepleting chemotherapy, 3) axicabtagene ciloleucel or 4) any protocol-required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the adverse event. Additional relevant data with respect to describing the adverse event will be collected in the CRFs.

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

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

8.4.2 **Reporting of Serious Adverse Events and Non-serious CRS events Grade ≥ 3**

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

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

All serious adverse events and non-serious CRS events ≥ Grade 3 [48] must be submitted within 24 hours following the investigators knowledge of the event **using a Medwatch Report Form.** For all SAE's, submit Medwatch Report forms to the IND Sponsor, health authorities per local reporting guidelines, and Kite/Gilead (Safety_FC@gilead.com). Progression of the malignancy during the study should not be reported as a serious adverse event. Adverse events associated with disease progression may be reported as serious adverse event. If the malignancy has a fatal outcome within 3 months of the last day of the lymphodepleting therapy, axicabtagene ciloleucel, or investigational product then the event leading to death must be recorded as a serious adverse event with CTCAE Grade 5.

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

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

8.4.3 **Pregnancy and Lactation**

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

If a pregnancy occurs in a female subject enrolled into the study, or a female partner of a male subject, within 6 months of completing the axicabtagene ciloleucel and anakinra administration,

the pregnancy must be reported to Safety_FC@gilead.com within 24 hours of awareness. 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 axicabtagene ciloleucel and **anakinra** through the duration of study follow up.

The pregnancy should be reported to the key sponsor contact within 24 hours of the investigators 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 Safety_FC@gilead.com.

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.

8.4.4 Criteria to Pause Enrollment

As part of its oversight of the study, the SRT also will assess criteria to pause enrollment after 8 subjects have been treated with axicabtagene ciloleucel and anakinra and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following criteria are met during the duration of the protocol until the SRT is able to review:

1) Any fatality within the 30 day FDA risk mitigation period (REMS).

   or

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

   - Neurologic toxicities per CTCAE version 4.03
   - CRS (per Lee 2014 criteria)
   - Other non-hematological serious adverse event
   - Infection (treatment-related)

Additional stopping criteria for futility are outlined in section 14.3.

DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

8.5 Reporting to the Food and Drug Administration (FDA)

The Sponsor of this study will be responsible for all communications with the FDA. The Sponsor will report to the FDA, any serious adverse event that meets the FDA's criteria for expedited

reporting following the reporting requirements and timelines set by the FDA.

8.6 Reporting to the NIH Office of Biotechnology Activities (OBA)

The Study sponsor will be responsible for all communications with the OBA. The Sponsor will report to the OBA, any serious adverse event that meets the OBA's criteria for expedited reporting following the reporting requirements and timelines set by the OBA.

If the dosing site is a recipient of funding from the National Institutes of Health (NIH) for recombinant research, the dosing site will ensure that an Institutional Biosafety Committee (IBC) is in place that is composed of at least 5 appropriately-qualified members. The IBC will ensure that the site conforms to the requirements set forth in the Section IV-B-2 of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, promulgated by the NIH/Office of Biotechnology Activities (NIH/OBA). The Investigator will be responsible for petitioning the IBC and obtaining approval prior to enrolling any subject in the study. The Investigator will also be required to obtain and follow all biohazard safety guidelines promulgated by the IBC, and to report all findings as required to the IBC and to NIH/OBA.

This protocol and any accompanying material provided to the subject (such as subject information sheets, Informed Consent Form, or descriptions of the study used to obtain informed consent) will be submitted by the Sponsor and/or the site to the legally constituted and chartered Institutional Biosafety Committee (IBC). The clinical site will be approved by the IBC in accordance with local procedures and country specific regulatory requirements. Documentation of IBC approval must be in place prior to product shipment to the site. At the discretion of the specific IBC and within federal requirements, IBC oversight of individual sites is suggested to be terminated provided (1) all subjects at that site have completed dosing by at least 90 days, and (2) all investigational materials have been fully accounted for and either returned to the Sponsor, destroyed on site, or shipped to a duly licensed destruction facility.

8.7 Reporting to the Institutional Biosafety Committee (IBC)

Participating investigators will register and report on research protocols involving biohazards (i.e., recombinant DNA or infectious agents) according to the reporting requirements set by their respective IBC.

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC and other appropriate institutional regulatory bodies will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC and other appropriate institutional regulatory body approvals have been obtained. The protocols, informed consents, written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC and other appropriate institutional regulatory bodies by the Investigator.

8.8 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

8.9 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 8.1) and the characteristics of an observed AE (Section 8.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

9. PHARMACEUTICAL INFORMATION

9.1 *Axicabtagene ciloleucel*

9.1.1 Description

Axicabtagene ciloleucel is an autologous treatment in which the subject's own T cells, obtained by leukapheresis, are genetically engineered ex vivo, by retroviral transduction of a construct encoding an anti-C19 chimeric antigen receptor (CAR), to target CD19 expression on B-cell malignancies. The active ingredients are anti-CD19 CAR T cells. Please refer to the most recent FDA product label for additional information.

9.1.2 Storage & Stability

Each axicabtagene ciloleucel infusion bag is individually packed in a metal cassette. Axicabtagene ciloleucel is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry shipper. Axicabtagene ciloleucel must be stored at ≤ 150°C immediately after axicabtagene ciloleucel receipt and inspection until the time of thawing and infusion. The site will follow standard operating procedures and/or guidelines for logging or other documentation practices required for inventory and/or storage of cell therapy products.

- For storage in the vapor phase freezer:
    - Ensure the cassette is stored in a designated location within the chosen vapor phase freezer to prevent potential mix-up with other products.
    - Per institutional SOPs and/or guidelines, log the temperature of the vapor phase freezer at the time the axicabtagene ciloleucel is placed in the vapor phase freezer.

  - Temperature should be monitored by continuous reading of the vapor phase freezer temperature.
  - Temperature monitoring/recording should follow institutional SOPs.
- In the event that the axicabtagene ciloleucel must be temporarily stored in the LN2 dewar (eg, for transport or for immediate infusion):
  - Carefully place the cassette back into the rack after axicabtagene ciloleucel inspection.
  - Re-insert the rack containing the cassette into the LN2 dewar.
  - Close the lid over LN2 dewar ensuring that the thermocouple remains intact.
  - Check the temperature monitor per institutional procedures.

The axicabtagene ciloleucel must remain stored in the vapor phase freezer, or within the LN2 dewar if infusing immediately, until the time of thawing and infusion.

Axicabtagene ciloleucel is stable at room temperature for up to 3 hours after thaw.

Please refer to the most recent FDA product label for additional information.

9.1.3 **Compatibility**

The bag of axicabtagene ciloleucel T cells is compatible for infusion with normal saline. No other medications should be administered in the same tubing through the same intravenous access line during axicabtagene ciloleucel T cell infusion. Please refer to the most recent FDA product label for additional information.

9.1.4 **Handling**

Axicabtagene ciloleucel must be maintained at ≤ –150°C until ready to thaw. The axicabtagene ciloleucel must be thawed prior to infusion. Thawing will be done in accordance to SOPs and/or other institutional guidelines but must be done at the location specified on the Chain of Custody Site Questionnaire.

Thawing of axicabtagene ciloleucel should not start until the subject and site staff are prepared for infusion. Frozen cells will be thawed at the bedside using a water bath maintained at 36°C to 38°C or dry warming device. The bag will be gently massaged until the cells have just thawed. There should be no frozen clumps left in the container. If the axicabtagene ciloleucel cell product appears to have a damaged or leaking bag, or otherwise appears to be compromised, it should not be infused, and should be returned to the GMP Facility as specified below.

Thawed axicabtagene ciloleucel CAR T cells should be administered to the subject at the bedside within 60 min of thaw following GCP specific procedures.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the biotherapeutic agent in a self-contained and protective environment.

Please refer to the most recent FDA product label for additional information.

9.1.5 **Availability**

The product is commercially available and will be provided by Kite/Gilead.

9.1.6 **Preparation**

Axicabtagene ciloleucel is supplied in an infusion bag containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% DMSO and 2.5% albumin (human). Axicabtagene ciloleucel comprises a suspension of 2×10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL. Please refer to the most recent FDA product label for additional information.

9.1.7 **Administration**

Axicabtagene is for autologous use only. Infusions should be performed per institutional guidelines and SOPs for the infusion of IEC products, of note:

- Do NOT use a leukodepleting filter.
- Central venous access is recommended for the infusion of axicabtagene ciloleucel.
- Confirm the patient's identity matches the patient identifiers on the axicabtagene ciloleucel product bag.
- Prime the tubing with normal saline prior to infusion.
- Infuse the entire contents of the axicabtagene ciloleucel bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the product bag during axicabtagene ciloleucel infusion to prevent cell clumping.
- After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered.
- Prior in infusion, confirm that two doses of tocilizumab are available for the patient during the recovery period.

Axicabtagene ciloleucel contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Please refer to axicabtagene ciloleucel IB label and institutional protocols for additional information.

9.1.8 Ordering

Ordering refers to the physician order for initiation of lymphodepleting chemotherapy and infusion of manufactured cellular therapy product. The physician investigator will provide such order through their protocol specific order set in their standard electronic ordering system. Drug ordering for manufacturing is initiating through the use of the Kite Clinical system during the enrollment (screening) portion of the study. This will provide the subject ID, registration (triggering the drug order) and oversight and management of the study from a cell journey perspective.

9.1.9 Accountability

Axicabtagene ciloleucel accountability and traceability is ultimately the responsibility of the Investigator and Sponsor. However, this responsibility may be delegated to suitably qualified personnel listed on Food and Drug Administration (FDA) Form 1572 who has had appropriate study-specific training and whose name has been appropriately listed on the Delegation of Responsibility Log for this task.

Detailed records will be maintained to allow for accurate accountability of the axicabtagene ciloleucel as per applicable sponsor and clinical site procedures. These records will include details of storage of axicabtagene ciloleucel; transfer axicabtagene ciloleucel from the transduction facility, administration to subjects, and disposal of remaining materials.

For any remaining drug product after infusion or drug product that cannot be administered due to triggering of stopping rules or other reasons, drug product will be kept cryopreserved in the vapor phase of liquid nitrogen until further instruction by the sponsor.

9.1.10 Destruction and Return

All material containing axicabtagene ciloleucel will be treated and disposed of as hazardous waste in accordance with governing regulations and clinical site procedures.

9.2 *Anakinra*

9.2.1 Description

Anakinra is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). Anakinra differs from native human IL-1Ra in that it has the addition of a single methionine residue at its amino terminus. Anakinra consists of 153 amino acids and has a molecular weight of 17.3 kilodaltons. It is produced by recombinant DNA technology using an *E coli* bacterial expression system. Please refer to the most recent FDA product label for additional information.

9.2.2 **Storage, Stability & Handling**

Anakinra should be stored in the refrigerator at 2° to 8°C (36° to 46°F). **DO NOT FREEZE OR SHAKE.** Protect from light. Please refer to the most recent FDA product label for additional information.

9.2.3 **Preparation**

Anakinra is supplied in single-use preservative free, prefilled glass syringes with 27 gauge needles. Each prefilled glass syringe contains 100 mg of anakinra per 0.67 mL. The full syringe contains 100 mg anakinra. Please refer to the most recent FDA product label for additional information.

9.2.4 **Administration**

Anakinra should be injected subcutaneously 4 hours (+/- 30 mins) prior to T cell infusion.

The prescribed dose of Anakinra should be administered according to the instructions for use and any unused portions discarded. After administration of Anakinra it is essential to follow the proper procedure for disposal of syringes and any residual drug. See the "Information for Patients" insert for detailed instructions on the handling and injection of Anakinra.

Do not use Anakinra beyond the expiration date shown on the carton. Visually inspect the solution for particulate matter and discoloration before administration. There may be trace amounts of small, translucent-to-white amorphous particles of protein in the solution. The prefilled syringe should not be used if the solution is discolored or cloudy, or if foreign particulate matter is present. If the number of translucent-to-white amorphous particles in a given syringe appears excessive, do not use this syringe. Please refer to the most recent FDA product label for additional information.

9.2.5 **Ordering**

Anakinra will be provided free of charge to patients. Pharmacy should place the order using the MGH -supplied cost center number.

9.2.6 **Accountability**

Anakinra accountability and traceability is ultimately the responsibility of the Investigator and Sponsor. However, this responsibility may be delegated to suitably qualified personnel listed on Food and Drug Administration (FDA) Form 1572 who has had appropriate study-specific training and whose name has been appropriately listed on the Delegation of Responsibility Log for this task.

Detailed records will be maintained to allow for accurate accountability of the anakinra as per applicable sponsor and clinical site procedures. These records will include details of

storage of anakinra; transfer anakinra from the transduction facility, administration to subjects, and disposal of remaining materials.

For any remaining drug product after infusion or drug product that cannot be administered due to triggering of stopping rules or other reasons, drug product will be kept cryopreserved in the vapor phase of liquid nitrogen until further instruction by the sponsor.

9.2.7 **Destruction and Return**

Unused/expired doses of anakinra will be destroyed per pharmacy institutional standards. Please refer to the most recent FDA product label for additional information.

10. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

10.1 Biomarker Studies

N/A, no biomarker studies.

10.2 Laboratory Correlative Studies

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

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

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

Lumbar punctures for collection of CSF samples will be performed at the following time points: after eligibility is confirmed and prior to start of lymphodepleting chemotherapy, after axicabtagene ciloleucel infusion on Day 5 ($\pm$ 3 days), and at the Week 4 visit ($\pm$ 3 days). Collection of CSF samples will enable measurement of baseline cytokine levels prior to axicabtagene ciloleucel infusion. Changes in levels of cytokines after axicabtagene ciloleucel infusion will be measured at the time of peak CAR T-cell expansion (Day 5) and at Week 4 when it is anticipated that cytokine levels would return to baseline levels. Infiltration of CAR T cells will also be

assessed by flow cytometry in post-axicabtagene ciloleucel infusion CSF samples. Exploratory analysis of cells, analytes, or immune cell markers within the CSF will be analyzed in conjunction with the clinical data to better understand the pathogenesis of **neurologic toxicities.**

Additional translational samples of PBMC, serum cytokines, tissue, bone marrow, and CSF may be taken for additional genomics sequencing, RNA expression profiling, cytokine/biomarker analysis and flow cytometry, and tumor profiling. This may also include tumor samples for genomic, transcriptional and protein expression analysis. Samples will be analyzed at the MGH Immuno Monitoring Laboratory.

11. STUDY CALENDAR

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Research staff should refer to the SOAs for an outline of the procedures required. The visit schedule is calculated from **axicabtagene ciloleucel** infusion on Day 0. An overview of study assessments/procedures is outlined below.

11.1 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.

11.2 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.

11.3 Medical and Treatment History

Relevant medical history prior to the start of adverse event reporting will be collected. Relevant

medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.
In addition to the medical history, all history related to the subject's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.
For subjects who are being referred from another clinic or institution to the participating research center, copies from the subjects chart should be obtained.

11.4 Physical Exam, Vital Signs, Performance Status

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

Vital signs including blood pressure, heart rate, oxygen saturation, and temperature will be monitored before and after the axicabtagene ciloleucel infusion and then routinely **per institutional guidelines**. If the subject has a fever (temperature 38.0^{o}C or greater), vital signs will be monitored more frequently as clinically indicated.

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

11.5 Neurological Assessment

Neurological assessments will include ICE scores as per the schedule of assessments. In addition, standardized assessments using IPCG guidelines will be used in collaboration with neuro-oncology. A full neurological assessment will be completed during screening to establish a baseline. Subsequent assessments will be performed before axicabtagene ciloleucel administration at screening, Month 1 and Month 3 visits.

11.6 Cardiac Function

Each subject's cardiac function, as measured by ECHO will be assessed during the screening period to confirm study eligibility. Both LVEF and pericardial effusion will be assessed prior to study entrance by ECHO. An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility. To establish a baseline, an ECG will also be performed during the screening period.

11.7 Magnetic Resonance Imaging

Each subject will undergo a screening brain MRI to rule out CNS metastasis during the screening period of the study. Evaluation of any new onset of ≥ Grade 2 **neurologic toxicities** should include a brain MRI as described in Section 6.4.

11.8 Bone Marrow Biopsy

Bone marrow aspirate/biopsy may be performed at screening if not previously performed to assess

bone marrow involvement. For subjects with a potential complete response to axicabtagene ciloleucel, a follow-up bone marrow aspirate/biopsy will be performed in subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. To confirm a complete response, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. Refer to Section 12 and Appendix B for treatment response assessment requirements per the revised IWG Response Criteria for Malignant Lymphoma [1]. Bone marrow aspirate/biopsy should also be considered to evaluate HLH. 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.

11.9 Lumbar Puncture

Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture performed at the screening visit for examination of cerebral spinal fluid. In addition, lumbar puncture may be performed as applicable for subjects with new onset of ≥ Grade 2 neurologic toxicities after axicabtagene ciloleucel infusion (see Section 8).

Lumbar punctures for the collection of CSF samples will be performed pre- and post-axicabtagene ciloleucel infusion at times outlined in the SOA. Samples will be submitted to the central laboratory as outlined in the central laboratory manual. Adequate platelet support should be provided prior to performing a lumbar puncture (e.g. platelet >50,000/mm^3). Lumbar punctures will only be performed when felt to be clinically safe by investigator.

11.10 Laboratory

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

Local lab analysis:

- Sodium (Na), potassium (K), chloride (Cl), total CO_2 (bicarbonate), creatinine, glucose, blood urea nitrogen (BUN) or urea (if BUN test cannot be analyzed by the local lab), albumin, calcium total, magnesium total (Mg), inorganic phosphorus, alkaline phosphatase, ALT/GPT, AST/GOT, total bilirubin, direct bilirubin, LDH, uric acid
- C-reactive protein (CRP)
- Complete Blood Count (CBC) with Differential
- A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma medical monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma Medical Monitor for instructions.

- **Additional blood draws for PBMC and serum, as well as CSF, bodily fluids and tissue may be collected and stored locally for subsequent translational research studies to include, but not limited to, cytokine analysis, FLOW and expression phenotyping, DNA/RNA sequencing, IHC/RNA ISH, and/or correlative studies.**

Central lab analysis:

- Blood draws for PBMC (lymphocyte subsets, RCR, and axicabtagene ciloleucel levels) and cytokine analysis will be performed at intervals outlined in the SOA.
- Serum samples may also be evaluated centrally for anti-axicabtagene ciloleucel antibodies.
    - Anti-axi-cel antibodies will be examined at baseline, days 7-14, 28, 60, and 90 after the first administration of the drug and 4 weeks post study. If any anti-drug antibodies are detected in patients, monitoring should continue until patient antibody levels return to the baseline.
- Archived tumor tissue
    - If possible, fresh tumor samples will be collected for central pathology review and evaluation of prognostic markers specific for large B-cell lymphoma and pertaining to the tumor immune environment. Additional analysis may include CD19 expression, gene expression profiling, and analysis of tumor-specific DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations), RNA, or protein markers. In the event that a fresh biopsy is not possible, or would significantly delay treatment, archival tissue is acceptable. If no archival tissue is available and it is not clinically safe to get a fresh biopsy, biopsy will be deferred.
- CSF and possibly bone marrow samples will also be collected and analyzed at the central laboratory as outlined in the schedule of assessments and per Section 10.
- See central laboratory manual for details on sample collection, processing, and shipping instructions.

11.11 Biomarkers and Correlative Analyses

Laboratory Correlative analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for **axicabtagene ciloleucel** and described in Section 10.2

11.12 Description of Study Periods

11.12.1 Screening

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

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 3 and who commence leukapheresis will be enrolled in the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

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

- Medical history and disease assessment
- Physical examination including height and weight
    - Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Neurocognitive function post infusion per standard IPCG guidelines.
- ECG
- ECHO/MUGA for LVEF and pericardial effusion assessment
    - An ECHO/MUGA performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility
- Imaging Studies
    - Brain MRI
    - Baseline PET CT of the neck, chest, abdomen and pelvis
        - PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility**.**
        - If PET CT is performed > 28 days prior to the initiation of lymphodepleting chemotherapy or if subject receives any anti-cancer therapy between screening and lymphodepleting chemotherapy, the scans must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible.
- Bone marrow aspirate/biopsy as needed (if not done at initial diagnosis or between diagnosis and screening)
- Labs
    - Chemistry panel
    - CBC with differential
    - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Serious Adverse Event reporting (refer to Section 8 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- Once eligibility confirmed, collection of archived or fresh tumor sample, as well as CSF samples.
- Lumbar puncture for collection of CSF samples to be performed after eligibility confirmed and prior to start of lymphodepleting chemotherapy

11.12.2 **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 identification number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, only the procedure(s)/assessment(s) that did not originally meet the eligibility criteria needs to be repeated; all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs, or leukapheresis is delayed, more than 28 days from the signing of the original informed consent, subjects must be reconsented and repeat all screening procedures/assessments.**

11.12.3 **Enrollment/Leukapheresis**

Before leukapheresis commences, the following criteria must be met. If criteria are not met, leukapheresis must be delayed until the event resolves.

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

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

The following procedures/requirements will occur within 24hrs of leukapheresis collection day and as outlined in the SOA:

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

11.12.4 Bridging Therapy

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

11.12.5 Lymphodepleting Chemotherapy Period

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

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

No evidence or suspicion of infection

No clinically evident changes in bone marrow, renal, hepatic, pulmonary, or cardiac function since date of informed consent

No acute neurologic toxicity > Grade 1 (with the exception of peripheral neuropathy)

In addition, if any of the following are known to occur, a delay in lymphodepleting chemotherapy may be required. Contact the Kite Pharma medical monitor before lymphodepleting chemotherapy commences for guidance.

Temperature is ≥ 38.0ºC within 48 hours prior to lymphodepleting chemotherapy. Unexplained fever requires pan-culture, respiratory viral panel, chest computed tomography (CT), and any additional symptom-directed workup to rule out occult infection.

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

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

11.12.6 **Treatment Period**

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 5 days prior to axicabtagene ciloleucel administration.

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

- No evidence or suspicion of infection. Subject must not be receiving systemic anti-microbials for the treatment of an active infection within 48 hours prior to axicabtagene ciloleucel infusion (prophylactic use of anti-microbials is allowed).
- No clinically evident changes in bone marrow, renal, hepatic, pulmonary, or cardiac function since screening
- Serum creatinine < 2 x ULN
- No acute neurologic toxicity > Grade 1 (with the exception of peripheral neuropathy)

In addition, if any of the following are known to occur, a delay in axicabtagene ciloleucel infusion may be required. Contact the Kite medical monitor before axicabtagene ciloleucel infusion commences for guidance.

- Temperature is ≥ 38.0ºC within 48 hours prior to axicabtagene ciloleucel infusion. Unexplained fever requires pan-culture, respiratory panel, chest X-ray, and any additional symptom-directed workup to rule out occult infection.
- If any screening assessments or procedures are repeated between leukapheresis and the axicabtagene ciloleucel infusion and results are outside the eligibility criteria (Section 3; with the exception of lymphodepleting chemotherapy-induced cytopenias)

Should an event not meet these criteria immediately prior to receiving axicabtagene ciloleucel, the axicabtagene ciloleucel infusion must be delayed until the event resolves. If the axicabtagene ciloleucel infusion is delayed > 2 weeks, lymphodepleting chemotherapy must be repeated.

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

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

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

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

- **Neurological assessment for subjects to include ICANS consensus criteria (ICE scores).**
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature, daily at a health care facility for at least 7 days
- Labs (before axicabtagene ciloleucel infusion, as described in the SOA)
  - Chemistry Panel
  - CBC with differential
  - Lymphocyte subsets
  - Cytokine levels
  - Anti-CD19 CAR T cells
  - RCR analysis
- Infusion of axicabtagene ciloleucel
- Administration of weight based anakinra (<50kg = 100mg, ≥50kg =200mg) as detailed in section 6.4.3.
- Lumbar puncture as described in the SOA when clinically appropriate.
- Concomitant medications documentation

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

11.12.7 Post-treatment Assessment Period

After completing **axicabtagene ciloleucel** infusion and completing the **minimum 7-day observation period**, all subjects will be followed in the post-treatment assessment period.

Counting from Day 0 (**axicabtagene ciloleucel** infusion), subjects will return to the clinic at the following intervals.

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

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

- **Neurological assessment for subjects to include ICANS consensus criteria (ICE scoring).**
- PET-CT for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated. Refer to the imaging charter for detailed instructions.
- As applicable, bone marrow aspirate/biopsy to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment)
- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs
    - Chemistry Panel
    - CBC with differential
    - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
    - Cytokine levels
    - Lymphocyte subsets
    - Anti-CD19 CAR T cells
    - RCR analysis
    - Translational lab collection
- Discontinue levetiracetam as clinically indicated.
- Lumbar puncture for collection of CSF samples at Week 4 (± 3 days)
- Adverse/Serious Adverse Event reporting (refer to Section 8 for safety reporting guidelines)
- Concomitant medications documentation

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

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

- Cytokines

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

11.12.8 Long-term Follow-up Period

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

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

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

- Physical exam
- PET-CT/ Disease assessment through 24 months or until disease progression, whichever occurs first. If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per institutional standard of care.
- Survival status
- Labs
  - CBC with differential
  - Anti-axicabtagene ciloleucel antibodies **(**refer to Section 10.10)
  - Lymphocyte subsets
  - Anti-CD19 CART-cell levels
  - Replication-competent retrovirus (RCR) analysis
  - Immune Monitoring Laboraotory collections
- Subsequent therapy for the treatment of NHL
- **Refer to Sections 8.4 for** targeted adverse/serious adverse event reporting
  - Including neurological, hematological, infections, autoimmune disorders, and secondary malignancies
- Targeted concomitant medication documentation (for 24 months or until disease progression, whichever occurs first)
  - Including gammaglobulins, immunosuppressive drugs, anti-infectives, and vaccinations

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

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

The following procedures/assessments will be completed for subjects who are enrolled, but do not receive axicabtagene ciloleucel or anakinra, at the time points outlined in the SOA:

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

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

All subjects will be consented to the CIBMTR immune effector cell therapy registry at the same time as consent for this protocol and data will be reported on standard schedules immediately following infusion as required by FDA. Following Month 24 patients, protocol long-term followup will continue through the CIBMTR immune effector cell therapy registry as part of the FDA mandated 15-year follow-up period.

11.12.9 **Retreatment**

Subjects may have an option to receive a second course of lymphodepleting chemotherapy and **axicabtagene ciloleucel without administration of anakinra prophylaxis** under the following conditions:

- Subject had no better than a PR
- Subjects disease subsequently progresses
- CD19 tumor expression confirmed locally by biopsy after disease progression and prior to re-treatment**. A portion of the biopsy should be sent to the central laboratory.**
- Subject continues to meet the original study eligibility criteria with exception of prior axicabtagene ciloleucel use in this study**. Screening assessments should be repeated if clinically indicated, as determined by the investigator, to confirm eligibility.**
- Subject has not received subsequent therapy for the treatment of lymphoma
- Toxicities related to lymphodepleting chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to re-treatment
- There is a second infusion available from the patient's original manufacturing.

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

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

Allowance for retreatment is based on clinical experience reported in the 2 studies conducted at the pediatric [49] and Surgery Branch [50] of the NCI where 6 subjects in total have been re-treated upon progression. Three of the re-treated subjects (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression. Given limited experience with re-treatment, re-infusions will be censored from the primary end-point and efficacy outcomes will be analyzed separately.

Table 2. Schedule of Assessments

Procedures	**Screening**	**Enrollment/ Leukapheresis**	**Lymphodepleting Chemotherapy Period**					**IP Administration Period**		**Post Treatment Follow-up (each visit calculated from Day 0)**				
Day	Within 28 days of enrollment	Within approx. 5 days of eligibility confirmation	-5	-4	-3	-2	-1	0	+1 -+13	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Medical history	X													
ECOG Performance Status	X		X					X						
Neurological assessment per standard IPCG guidelines	X							X				X		X
Neurotoxicity assessment per CTCAE v4.03 [11,12]								X	X	X	X	X	X	X
ICANS Consensuses grading of neurotox (ICE score required)[11]								X	X	X	X	X	X	X
ECG	X													
ECHO	X													
Archival/Fresh tumor[1]	X													
Brain MRI	X													
PET-CT/ disease assessment [2, 14]	X											X		X
Physical exam	X									X		X	X	X
Vital signs (BP, HR, O_2 sat, temp)	X	X	X	X	X			X	X	X		X	X	X
Weight **(**plus Height at screening**)**	X	X												
Pregnancy test (serum or urine)	X													X
Lumbar Puncture[6]	X								X			X		
Blood draw for Chemistry panel	X	X	X	X	X			X	X	X		X	X	X
Blood draw for CBC w/differential	X	X	X	X	X			X	X	X		X	X	X
Blood draw for C-reactive protein (CRP)		X												
Blood draw for Anti-**axicabtagene ciloleucel** antibodies [3]		X										X		X
Blood draw for Lymphocyte subsets		X						X				X		X
Blood draw for Cytokines [7, 10, 13]		X						X	QOD [10]	X		X		
Blood draw for Anti-CD19 CAR T cells[7, 13]		X						X	Day +3, +7	X	X	X		X
Blood draw for RCR analysis [4]								X						X
Blood draw for translational lab collection[13]			X					X	QOD	X	X	X	X	X
Blood draw for minimial residual disease testing												X		X

Procedures	**Screening**	**Enrollment/ Leukapheresis**	**Lymphodepleting Chemotherapy Period**					**IP Administration Period**		**Post Treatment Follow-up (each visit calculated from Day 0)**				
Day	Within 28 days of enrollment	Within approx. 5 days of eligibility confirmation	-5	-4	-3	-2	-1	0	+1 -+13	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Leukapheresis		X												
Fludarabine/Cyclophosphamide			X	X	X									
Axicabtagene ciloleucel infusion IV								X						
Anakinra[8]								Day 0 through day +13 .						
Levetiracetam[9]								**Starting on Day 0**						
Adverse events/ Concomitant medication	X	X												

[1] Archival/Fresh tumor sample: Either FFPE tumor block or up to 20 unstained slides. Either archived or a fresh tumor samples (either will suffice) will be submitted to central laboratory after eligibility has been confirmed and prior to start of lymphodepleting chemotherapy. **See 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 lymphodepleting chemotherapy or if subject receives any anti-cancer therapy between screening and lymphodepleting chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. **As applicable, bone marrow aspirate/biopsy will be performed to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). Bone marrow samples may also be collected and analyzed centrally for subjects who develop toxicities post axicabtagene ciloleucel.**

[3] Blood draw for Anti-**axicabtagene ciloleucel** antibodies: Baseline antibody sample to be collected prior to start of leukapheresis. Anti-axi-cel antibodies will be examined at baseline, days 28 and 90 after the first administration of the drug and 4 weeks post study. If any anti-drug antibodies are detected in patients, monitoring should continue until patient antibody levels return to the baseline.

[4] Blood draw for RCR: on Day 0 prior to administration of **axicabtagene ciloleucel** and at Month 3, 6 and 12; then **collect** yearly for up to 15 years. Yearly **samples will only be analyzed** if positive at Month 3, 6, or 12.

[5] Cytokines: prior to **axicabtagene ciloleucel** infusion on Day 0, then on Day 1 and then every other day **during the 7 day post infusion monitoring period.**

[6] Lumbar Puncture: subjects with symptoms of CNS malignancy (e.g., new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects will have lumbar puncture for the collection of CSF performed at baseline prior to **axicabtagene ciloleucel** infusion (if not already performed as part of screening and within 28 days of axicabtagene infusion), post **axicabtagene ciloleucel** infusion (Day 5 ± 3 days) and at week 4 visit (±3 days).

[7] If a subject is admitted to the hospital within the 7-day observation period is discharged and then subsequently re-admitted to the hospital with any **axicabtagene ciloleucel** related adverse events, blood samples for anti-CD19 CAR T cells and cytokines will be collected on day of **hospital re-**admission and then weekly **through and including the** day of discharge. **Blood samples for anti-CD19 CAR T cells and cytokines should also be collected at the time of disease progression prior to starting any subsequent anticancer therapy.**

[8] Anakinra, weight-based dosing (100mg for subjects <50kg, 200mg for subjects ≥ 50kg). Anakinra will be given subQ for prophylactic dosing on days 0 through day +13 per section 6.4.3. The first dose of anakinra should be given 4 hours (+/- 30 min) prior to planned axicabtagene ciloleucel infusion.

[9] Levetiracetam at a dose of 750mg (PO or IV) twice daily starting day of infusion (Day 0) See Sections 5.1 and 7 for further details.

[10] **Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1, and then every other day during the 7 day post infusion monitoring period.**

[11] In the event of hospitalization, ICANS neurotoxicity assessments (including ICE scores) will be obtained daily until discharge.

[12] Specific grading based on CTCAE 4.03 can be found in appendix A "Grading and Management of Neurologic Toxicities" for grading of nervous system disorders involving somnolence, confusion, memory impairment, encephalopathy, dysphagia, seizures, and cerebral edema.

[13]For weekend/holiday sample collections following axicabtagene infusion, allow for +/- 24hr window.

[14] While PET-CT is preferred, CT assessment may be used in place of PET-CT in the event of failure to obtain insurance coverage. Baseline, month 1, 6 and 12 should be assessed via PET/CT.

Table 3. Schedule of Assessments (Long-term Follow-up Period)

Procedure	**Long Term Follow-up Period (Each visit calculated from Day 0)**					
Visit Frequency	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24
Physical exam[1]	X	X	X	X	X	X
PET-CT/disease assessment[2,9]	X	X	X		X	X
Survival Status	X	X	X	X	X	X
Blood draw for CBC w/differential [3]	X	X	X	X	X	X
Blood draw for Anti-**axicabtagene ciloleucel** antibodies [4]	X	X	X			
Blood draw for Lymphocyte subsets [3]	X	X	X	X	X	X
Blood draw for anti-CD19 CAR T cells[3]	X		X			X
Blood draw for RCR analysis [5]	X		X			X
Targeted AE/SAEs [6]	X	X	X	X	X	X
Targeted concomitant medication [7]	X	X	X	X	X	X
Subsequent therapy for NHL[8]	X	X	X	X	X	X
Blood draw for minimial residual disease testing	X					

[1] Physical exams will continue through Month 24

[2] PET-CTs/disease assessments will continue through Month 24 or until disease progression, whichever comes first**.** If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per standard of care.

[3] Subjects will continue to provide samples for CBC w/diffs, lymphocyte subsets and anti-CD19 CAR T cells through Month 24

[4] Anti-**axicabtagene ciloleucel** antibody samples.

[5] RCR samples: collect and measured at Month 3, 6 and 12, then collect yearly for up to 15 years. Yearly samples will only be analyzed if positive at Month 3, 6, or 12.

[6] Targeted AEs/SAEs will be collected for 24 months or until disease progression (whichever occurs first)

[7] Targeted concomitant medications will be collected for 24 months or until disease progression (whichever occurs first)

[8] Subsequent therapy administered after **axicabtagene ciloleucel** infusion for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy must be collected until subject completes the long term follow up period, is considered lost to follow up, withdraws consent, or dies. Subjects may be contacted by telephone to collect information about subsequent therapy for NHL and to assess survival status.

[9] While PET-CT is preferred, CT assessment may be used in place of PET-CT in the event of failure to obtain insurance coverage. Month 1, 6 and 12 should be assessed via PET/CT.

12. MEASUREMENT OF EFFECT

12.1 Neurotox Response Assessment

Neurotox will be graded using CTCAE 4.03 as was done for Zuma-1 which will act as a historical control. Specific grading based on CTCAE 4.03 can be found in appendix A "Grading and Management of Neurologic Toxicities" for grading of nervous system disorders involving somnolence, confusion, memory impairment, encephalopathy, dysphagia, seizures, and cerebral edema. Additionally, information required for Neurotox grading per ASTCT consensus criteria will also be collected as an exploratory endpoint. Specific ICANS related ASTCT grading requirements, including ICE scores, can be found in appendix A "ASBMT Grading of ICANS."

12.2 Disease Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the revised IWG Response Criteria for Malignant Lymphoma [1]. Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Baseline PET-CT scans of the neck, chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. **Subjects will undergo additional PET-CT or CT tumor assessments after their axicabtagene ciloleucel infusion. While PET-CT is preferred, CT assessment may be used in place of PET-CT in the event of failure to obtain insurance coverage. Baseline, month 1, 6 and 12 should be assessed via PET/CT. The first of these post-treatment PET-CT tumor assessments will occur 4 weeks after infusion; subsequent assessments will occur at regular intervals throughout the post-treatment and long-term follow-up portions of the study, as highlighted in the SOA.**

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

A bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR. Per the revised IWG Response Criteria for Malignant Lymphoma [1], a bone marrow aspirate and biopsy should be performed only when the subject had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology, or if indeterminate by morphology, it must be negative by immunohistochemistry to assign a CR to treatment.

For subjects who discontinue the study due to an assessment of progressive disease which was not subsequently confirmed by a central radiology reviewer, any additional imaging data, subsequent to the image in question will be submitted to the central reviewer to confirm disease response.

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

13.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

13.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

13.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI, study team and Kite/Gilead. The DSMC will review protocols up to, but not more than four times a year with the primary focus being accrual, protocol adherence, audit results and summary of all deaths while being treated and during active follow-up. Given the collaborative nature of this protocol, there will be an an additional safety review team (SRT) comprised of the study sponsor/PI and Kite/Gilead meant to review all study safety data and make recommendations on further study conduct as described below. As both axicabtagene ciloleucel and anakinra are FDA approved therapies with known toxicity profiles, the goal of the SRT will be to observe for unforeseen toxicities not previously observed in the initial phase I/II studies that led to FDA approval of both agents. Specific guidance as outlined in section 8.4.4.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

14. STATISTICAL CONSIDERATIONS

The primary objective of the study is to assess the impact of anakinra as preventative management of neurotoxicity. Secondary objectives will include evaluate the impact of anakinra as preventative management of CAR-T related CRS, to evaluate the efficacy of axicabtagene ciloleucel in combination with preventative anakinra in terms of DOR, ORR, PFS, and OS in comparison to the pivotal Zuma-1 study.

14.1 Study Endpoints

Primary Endpoint:

- Rate and severity of neurotoxicity as per CTCAE v4.03 criteria within the first 30 days of infusion.

Secondary Endpoints:

- Rate and severity of CRS as per Lee 2014 criteria within the first 30 days of infusion in comparison to the pivotal Zuma-1 study.

- **Duration of response (DOR)**: Among subjects who experience an objective response, DOR is defined as the date of their first objective response to disease progression per the revised IWG Response Criteria for Malignant Lymphoma [1] or death regardless of cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing.

- **Objective response rate (ORR)**: **ORR** is defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma [1]. All subjects that do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders.

- **Progression-free Survival (PFS)**: PFS is defined as the time from the **axicabtagene ciloleucel** infusion date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma [1] or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

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

Exploratory Endpoints:

- Levels of anti-CD19 CAR T cells in blood
- Levels of cytokines in serum and CSF
- Incidence of anti-axicabtagene ciloleucel antibodies
- Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product.

- Rates of CRS/NT based on grading used in Zuma-1 (i.e. Lee 2014 for CRS, and CTCAE version 4.03 for neurotoxicity) vs ASTCT consensus guidelines

The primary objective of this study is to assess the impact of prophylactic regimens or earlier interventions on the rate and severity of CRS and neurologic toxicities. The assessment of ORR is a secondary objective, and the analysis will be descriptive.

14.2 Sample Size, Accrual Rate and Study Duration

The anticipated enrollment in this study is approximately **20 patients over a 2-year period. The goal is to accrue one patient/month to the study protocol over this period.**

With 20 patients the study will have 86% power to detect a decrease in the neurotoxicity rate from 45% to 15% via a two-sided exact binomial test with a significance level of 0.05. The secondary objectives of this study include analyses the rate and severity of CRS as well as efficacy endpoints (ORR, DOR, PFS, OS) and levels of anti-CD19 CAR T cells and cytokines in the blood.

All subjects will be followed for survival for up to approximately 15 years after the last subject receives **axicabtagene ciloleucel per FDA requirements** and data will be collected through the CIBMTR data registry starting at Month 24.

14.3 Interim Monitoring Plan

Interim Analysis and Early Stopping Rules

The SRT will review safety data when 8 subjects treated have had the opportunity to be followed for 30 days, respectively**.**

The rate of grade 2+ neurotoxicity will be evaluated using a Simon's two-stage design. Initially, 8 patients will be enrolled. If 3 or more of the initial 8 patients experience grade 2+ neurotoxicity, enrollment will be terminated early or dosing modification discussed. The probability of early termination is 0.78 if the true rate of grade 2+ neurotoxicity is 45% or higher. Otherwise, enrollment will continue to a total of 20 patients. The treatment will be considered promising if 5 or fewer of 20 patients experience grade 2+ neurotoxicity. The two-stage design provides 86% power to demonstrate that the treatment is associated with a favorable neurotoxicity rate if the true rate is 15%. In contrast, there is a 4% (alpha) probability of concluding that the treatment has a favorable neurotoxicity rate if the true rate is 45% or higher.

Safety Interim Analysis

The SRT will review AE and SAE information on a regular basis throughout subject treatment in Phase 2 of the study. AE and SAE information will be collected to assure no unforeseen toxicities are noted with this combination. The SRT may request additional safety data or modify the study conduct. The sponsor may request additional reviews by the SRT if safety concerns are identified.

Data submitted to the SRT may be monitored or unmonitored to facilitate timely review. Additional stopping rules per section 8.4.4.

Efficacy Interim Analysis

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

14.4 Analysis of Primary and Secondary Endpoints

Planned Method of Analysis
The primary analysis of all treated subjects have had the opportunity to be followed for 8 weeks and 6 months for primary and secondary endpoints respectively. No central radiologic review of disease assessment will be performed for these cohorts.

Descriptive analyses may occur at any time.

Neurotoxicity Rate
The incidence of grade 2+ neurotoxicity will be assessed in comparison to a historical rate of 45% via a two-sided exact binomial test with significant level of 0.05. Exact 2-sided 95% confidence intervals for the neurotoxicity rate will be generated.

Objective Response Rate
The incidence of objective response and exact 2-sided 95% confidence intervals will be generated.

Duration of Response

The Kaplan-Meier survival method will be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence of non-disease related mortality (Kaplan-Meier method) will be estimated along with 2-sided 95% confidence intervals at 3-month intervals.

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

Overall Survival

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

Safety
Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4.03 Grade 3 or higher and treatment related AEs reported throughout the conduct of the study will be tabulated by preferred term and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths though the long-term follow-up and treatment related SAEs will be provided.

In the event of changes in the safety management using steroids, sensitivity analyses will explore the effect of these changes on outcomes via stratification and/or adjustment for use of steroids in multivariable models.

14.5 Reporting and Exclusions

The statistical reporting of the safety and efficacy endpoints will be compared to historical controls from the Zuma-1 study. Subject incidence rates of treatment-emergent CRS, neurologic toxicities, axicabtagene ciloleucel-related adverse events, and ORRs will be summarized. DOR, PFS, and OS will also be summarized.

Analysis Subsets

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

Modified Intent to Treat Set (mITT): the modified intent to treat set will consist of all subjects enrolled and treated with the target dose of axicabtagene ciloleucel, 2 x 10^6 CAR T cells/kg (range 1 x 10^6 to 2.4 x 10^6 CAR T cells/kg) and at least one dose of anakinra. This analysis set will be used for all efficacy analyses.

Safety Analysis Subset: The safety analysis subset is defined as all subjects treated with any dose of axicabtagene ciloleucel and at least one dose of anakinra. For retreated subjects, only the initial treatment will contribute to the safety analyses while events following retreatment will not be included in the safety analysis.

Retreatment Subset: Separate safety and efficacy analyses will be conducted in subjects who are retreated. These analyses will include data from non-initial treatments and follow the inclusion criteria specified above for safety and efficacy analysis.

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

15. ETHICAL AND REGULATORY REQUIREMENTS

15.1 Independent Review Board/Independent Ethics Committee

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

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

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

15.2 Subject Confidentiality

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

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

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

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

15.3 Investigator Signatory Obligations

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

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

15.4 Protocol Amendments and Termination

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

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

15.5 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. Case report form entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

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

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

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

15.6 Study Monitoring and Data Collection

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

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with

respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 14.5.

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

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

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

16. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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

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

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 the Sponsor for review and approval. The study contract between the institution, principal investigation and Sponsor or its delegate will outline the requirements for publication review in collaboration with Kite/Gilead.

REFERENCES

1 Cheson, B. D. *et al.* Revised response criteria for malignant lymphoma. *J Clin Oncol* **25**, 579-586, doi:10.1200/jco.2006.09.2403 (2007).
2 Howlader, N. *et al.* SEER Cancer Statistics Review, 1975-2014. *National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017* (2017).
3 Rodriguez-Abreu, D., Bordoni, A. & Zucca, E. Epidemiology of hematological malignancies. *Ann Oncol* **18 Suppl 1**, i3-i8, doi:10.1093/annonc/mdl443 (2007).
4 Flowers, C. R., Sinha, R. & Vose, J. M. Improving outcomes for patients with diffuse large B-cell lymphoma. *CA: A Cancer Journal for Clinicians* **60**, 393-408 (2010).
5 Josting, A. *et al.* Prognostic factors and treatment outcome in primary progressive Hodgkin lymphoma: a report from the German Hodgkin Lymphoma Study Group. *Blood* **96**, 1280-1286 (2000).
6 Hitz, F. *et al.* Outcome of Patients with Chemotherapy Refractory and Early Progressive Diffuse Large B Cell Lymphoma After R-CHOP Treatment. *Blood (ASH Annual Meeting Abstracts, Poster Session)* **116 (Abstract #1751)** (2010).
7 Seshadri, T., Kuruvilla, J., Crump, M. & Keating, A. Salvage Therapy for Relapsed/Refractory Diffuse Large B Cell Lymphoma. *Biology of Blood and Marrow Transplantation* **14**, 259-267 (2008).
8 Ardeshna, K. M. *et al.* Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol* **130**, 363-372, doi:10.1111/j.1365-2141.2005.05603.x (2005).
9 Philip, T. *et al.* Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* **333**, 1540-1545, doi:10.1056/nejm199512073332305 (1995).
10 Telio, D. *et al.* Salvage chemotherapy and autologous stem cell transplant in primary refractory diffuse large B-cell lymphoma: outcomes and prognostic factors. *Leukemia & Lymphoma* **53**, 836-841 (2012).
11 Matasar, M. J. *et al.* Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. *Blood* **122**, 499-506, doi:10.1182/blood-2012-12-472027 (2013).
12 Moskowitz, C. H. *et al.* Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. *J Clin Oncol* **17**, 3776-3785 (1999).
13 Nagle, S. J. *et al.* Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *American Journal of Hematology* **88**, 890-894 (2013).
14 Sehn, L. H. *et al.* Primary diffuse large B-cell lymphoma of the mediastinum: outcome following high-dose chemotherapy and autologous hematopoietic cell transplantation. *Blood* **91**, 717-723 (1998).
15 Savage, K. J. *et al.* Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* **17**, 123-130,

doi:10.1093/annonc/mdj030 (2006).

16 Dunleavy, K. *et al.* Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med* **368**, 1408-1416, doi:10.1056/NEJMoa1214561 (2013).

17 National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology; Non-Hodkin's Lymphomas, Version 1.* , <http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#nhl> (2014).

18 Kuruvilla, J. *et al.* Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma. *Leuk Lymphoma* **49**, 1329-1336, doi:10.1080/10428190802108870 (2008).

19 Crump, M. *et al.* Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* **130**, 1800-1808, doi:10.1182/blood-2017-03-769620 (2017).

20 Swerdlow, S. H. *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* **127**, 2375-2390, doi:10.1182/blood-2016-01-643569 (2016).

21 Kochenderfer, J. N. *et al.* Construction and preclinical evaluation of an anti-CD19 chimeric antigen receptor. *J Immunother* **32**, 689-702 (2009).

22 Kochenderfer, J. N., Yu, Z., Frasheri, D., Restifo, N. P. & Rosenberg, S. A. Adoptive transfer of syngeneic T cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells. *Blood* **116**, 3875-3886, doi:10.1182/blood-2010-01-265041 (2010).

23 Nicholson, I. C. *et al.* Construction and characterisation of A functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. *Molecular Immunology* **34**, 1157-1165 (1997).

24 Kowolik, C. M. *et al.* CD28 costimulation provided through a CD19-specific chimeric antigen receptor enhances in vivo persistence and antitumor efficacy of adoptively transferred T cells. *Cancer Res* **66**, 10995-11004, doi:10.1158/0008-5472.can-06-0160 (2006).

25 Bedoya, F., Frigault, M. J. & Maus, M. V. The Flipside of the Power of Engineered T Cells: Observed and Potential Toxicities of Genetically Modified T Cells as Therapy. *Mol Ther* **25**, 314-320, doi:10.1016/j.ymthe.2016.11.011 (2017).

26 Neelapu, S. S. *et al.* Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*, doi:10.1038/nrclinonc.2017.148 (2017).

27 Gust, J. *et al.* Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. *Cancer Discov* **7**, 1404-1419, doi:10.1158/2159-8290.CD-17-0698 (2017).

28 Locke, F. L., et al. Preliminary Results of Prophylactic Tocilizumab after Axicabtageneciloleucel (axi-cel; KTE-C19) Treatment for Patients with Refractory,Aggressive Non-Hodgkin Lymphoma (NHL). ASH Abstract 1547. *Blood* (2017).

29 Giavridis, T. *et al.* CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat Med* **24**, 731-738, doi:10.1038/s41591-018-0041-7 (2018).

30 Sonmez, H. E., Demir, S., Bilginer, Y. & Ozen, S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. *Clin*

Rheumatol, doi:10.1007/s10067-018-4095-1 (2018).

31 Shakoory, B. *et al.* Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. *Crit Care Med* **44**, 275-281, doi:10.1097/CCM.0000000000001402 (2016).

32 Fisher, C. J., Jr. *et al.* Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA* **271**, 1836-1843 (1994).

33 Fisher, C. J., Jr. *et al.* Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med* **22**, 12-21, doi:10.1097/00003246-199401000-00008 (1994).

34 Opal, S. M. *et al.* Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* **25**, 1115-1124, doi:10.1097/00003246-199707000-00010 (1997).

35 Granowitz, E. V. *et al.* Pharmacokinetics, safety and immunomodulatory effects of human recombinant interleukin-1 receptor antagonist in healthy humans. *Cytokine* **4**, 353-360 (1992).

36 Fleischmann, R. M. *et al.* Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* **48**, 927-934, doi:10.1002/art.10870 (2003).

37 Yang, B. B., Baughman, S. & Sullivan, J. T. Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther* **74**, 85-94, doi:10.1016/S0009-9236(03)00094-8 (2003).

38 Dudley, M. E. *et al.* Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. *J Clin Oncol* **26**, 5233-5239, doi:10.1200/jco.2008.16.5449 (2008).

39 Gattinoni, L. *et al.* Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. *J Exp Med* **202**, 907-912, doi:10.1084/jem.20050732 (2005).

40 Klebanoff, C. A., Khong, H. T., Antony, P. A., Palmer, D. C. & Restifo, N. P. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. *Trends in Immunology* **26**, 111-117 (2005).

41 O'Brien, S. M. *et al.* Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. *J Clin Oncol* **19**, 1414-1420, doi:10.1200/jco.2001.19.5.1414 (2001).

42 Thompson, J. A. New NCCN Guidelines: Recognition and Management of Immunotherapy-Related Toxicity. *J Natl Compr Canc Netw* **16**, 594-596, doi:10.6004/jnccn.2018.0047 (2018).

43 Norelli, M. *et al.* Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat Med* **24**, 739-748, doi:10.1038/s41591-018-0036-4 (2018).

44 Sota, J. *et al.* Safety profile of the interleukin-1 inhibitors anakinra and canakinumab in

real-life clinical practice: a nationwide multicenter retrospective observational study. *Clin Rheumatol*, doi:10.1007/s10067-018-4119-x (2018).

45 Emsley, H. C. *et al.* A randomised phase II study of interleukin-1 receptor antagonist in acute stroke patients. *J Neurol Neurosurg Psychiatry* **76**, 1366-1372, doi:10.1136/jnnp.2004.054882 (2005).

46 Galea, J. *et al.* Intravenous anakinra can achieve experimentally effective concentrations in the central nervous system within a therapeutic time window: results of a dose-ranging study. *J Cereb Blood Flow Metab* **31**, 439-447, doi:10.1038/jcbfm.2010.103 (2011).

47 Yang, B. B., Baughman, S. & Sullivan, J. T. Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clinical Pharmacology & Therapeutics* **74**, 85-94 (2003).

48 Lee, D. W. *et al.* Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* **124**, 188-195, doi:10.1182/blood-2014-05-552729 (2014).

49 Lee, D. W. *et al.* T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet* **385**, 517-528, doi:10.1016/S0140-6736(14)61403-3 (2015).

50 Kochenderfer, J. N. *et al.* Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol* **33**, 540-549, doi:10.1200/JCO.2014.56.2025 (2015).

51 Pepe, M. S. Inference for Events With Dependent Risks in Multiple Endpoint Studies. *Journal of the American Statistical Association* **86**, 770-778, doi:10.2307/2290411 (1991).

52 Fine, J. P. & Gray, R. J. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* **94**, 496-509 (1999).

APPENDIX A

Grading and Management of CRS – Lee 2014

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

[a]High-dose vasopressor doses

[b]Severity based on CTCAE

[c] or equivalent dexamethasone

Grading and Management of Neurologic Toxicities

Neurologic Toxicities	Supportive Care	Tocilizumab	Corticosteroids	Follow up
Grade 1 examples include: • Somnolence-mild drowsiness or sleepiness • Confusion-mild disorientation • Encephalopathy-mild limiting of ADLs • Dysphagia-not impairing ability to communicate	• Supportive care per institutional standard of care • Closely monitor neurologic status • Consider prophylactic levetiracetam • Continuous cardiac telemetry and pulse oximetry as indicated	N/A	N/A	Continue supportive care
Grade 2 examples include: • Somnolence-moderate, limiting instrumental ADLs • Confusion-moderate disorientation • Encephalopathy-limiting instrumental ADLs • Dysphagia-moderate impairing ability to communicate spontaneously • Seizure(s)	• Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Levetiracetam/ antiepileptics if subject has seizures	N/A	• Dexamethasone 10mg intravenously every 6 hours	Improving: • Taper corticosteroids Not improving: • Manage as Grade 3 (below)
Grade 3 examples include: • Somnolence-obtundation or stupor • Confusion-severe disorientation • Encephalopathy-limiting self-care ADLs • Dysphagia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	• Management in monitored care of intensive care unit	N/A	• Dexamethasone 10mg intravenously every 6 hours	Improving: • Taper corticosteroids Not improving: • Manage as Grade 4 (below)
Grade 4 examples include: • Life-threatening consequences • Urgent intervention indicated • Requirement for mechanical ventilation • Consider cerebral edema	• Per Grade 3 • Mechanical ventilation, may be required	N/A	• Methylprednisolone 1 gram daily for 3 days	Improving: • Taper corticosteroids Not improving: • Consider 1 gram of methylprednisolone TID, alternative immunsuppressive (e.g. siltuximab) and anti-thymocyte globulin (ATG 2mg/kg x 1 and reassess)

ASBMT Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	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 resolves 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‡	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§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, 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 as grade 3 ICANS.
N/A indicates not applicable.
* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ 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 v5.0.

ICE Score

ICE
• **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

Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

APPENDIX B

Revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007)

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

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

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

- ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible and should include mediastinal and retroperitoneal nodes if possible.
- No increase in size of nodes, liver or spleen and no new sites of disease.
- If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for single nodules.
- Bone marrow is irrelevant for determination of a PR. If patient has persistent bone marrow involvement and otherwise meets criteria for CR the patient will be considered a PR.
- Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site. Note: in subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated in subjects with one or at most two residual masses that have regressed by 50% on CT scan.

Stable Disease (SD):

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

Progressive Disease:
Defined by at least one of the following:

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