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TITLE: Radiation Therapy To Enhance CAR T Efficacy Early in Post-CAR T Cell Therapy Refractory Lymphoma: A Pilot Study

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

***Principal Investigator (PI)**

Chirayu G. Patel, MD, MPH
MGH Radiation Oncology
55 Fruit St
Cox 3
Boston, MA 02114
617-724-2340 (p)
617-726-3603 (f)
cpatel@mgh.harvard.edu

Co-PI:

Matthew J. Frigault, MD
MGH Cancer Center
MFRIGAULT@PARTNERS.ORG

Other Investigators:
Marcela Maus, MD, PhD – MGH Director of Cellular Immunotherapy Program
MVMAUS@mgh.harvard.edu

Kathleen Gallagher, PhD – Director of Immune Monitoring Lab
KGALLAGHER19@mgh.harvard.edu

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IND Sponsor: N/A

Other Agent(s): MGH is the sponsor of this study.

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CLINICAL STUDY PROTOCOL SYNOPSIS

Name of Sponsor/Company:
Department of Radiation Oncology, Massachusetts General Hospital (MGH)

Name of Investigational Product:
N/A

Title of Study (Protocol Title):
Radiation Therapy To Enhance CAR T Efficacy Early in Post-CAR T Cell Therapy Refractory Lymphoma: A Pilot Study

Protocol Number 19-861

Study center(s): MGH Cancer Center / MGH Radiation Oncology

Principal Investigator: Chirayu G. Patel, MD, MPH
Investigator: Matthew J. Frigault, MD

Studied period (years): 1	**Phase of development: Pilot**
Estimated date first patient enrolled: quarter 3, 2020 Estimated date last patient completed: quarter 1, 2022	

Objectives:

Primary Objective

- To ascertain the safety and toxicity of radiotherapy in patients with hematologic malignancies who will undergo any CD19-targeted CAR T cell therapy

Secondary Objective:

- To evaluate the efficacy of radiotherapy in the above patients
- To assess patient reported outcomes with regard to symptoms and side effects in RT following CAR T cell therapy

Exploratory Objective:

- To assess immune infiltrates into lymphoma following radiotherapy
- To evaluate mechanisms of interplay between radiotherapy and CAR T cell therapy, by examining serum cytokine levels and expression changes of key pathway mediators in lymphoma biopsy samples before and after radiotherapy

Route and Regimen:

- No investigational products are used in this trial.

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 lymphoma, physical exam including vital signs and performance status, blood draws for complete blood count (CBC), chemistry panels, cytokines, C-reactive protein, lymphocyte subsets, anti-**axicabtagene ciloleucel** antibodies, and anti-CD19 CAR T cell analysis. Women of childbearing potential will undergo a urine or serum pregnancy test prior to radiotherapy as per standard protocol.

Subjects will also undergo a biopsy (core needle biopsy, or if not possible, FNA) shortly following RT. Subjects will also undergo a PET/CT as standard of care to assess response to RT about 6 months after CAR T infusion. If there is evidence for complete response on the 6 month PET/CT scan, patients will have an additional PET/CT scan at 12 months after CAR T infusion to assess for continued complete response. Otherwise, patients will need further work-up regarding 6 month PET/CT scan.

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 pilot study evaluating the feasibility, safety, efficacy, and toxicity of radiotherapy in patients with hematologic malignancies who will undergo any CD19-targeted CAR T cell therapy

Pilot Study

The pilot study will enroll approximately **20** subjects with refractory hematologic malignancies following CAR T cell therapy.

Each subject will proceed through the following study periods:

- Screening
- Enrollment
- RT simulation, planning, and treatment
- Biopsy following RT (on protocol)
- Post treatment assessment period with a PET/CT following RT (as standard of care)
- 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 RT for reasons other than death, will be asked to participate in a long-term follow-up study for up to 6 months after their RT, with a focus on long-term efficacy and safety. These patients will also have long-term follow-up as part of CAR T cell therapy registry. After Month 24 patients will be followed via the CIBMTR immune effector cell therapy registry.

Diagnosis and selection criteria: refractory hematologic malignancy following CAR T cell therapy

Inclusion Criteria

1. Patients must be able to undergo biopsy. Biopsy will be obtained for patients to exclude possibility of false negative residual FDG avidity on PET/CT that is not substantially increased relative to pre-CAR-T PET/CT. Exceptions are allowed for patients who have clearly progressive disease for whom delaying radiation therapy to obtain a biopsy may worsen outcome (such as cases of cord compression), and for patients for whom the risks of biopsy are high (such as patients with evidence for CNS involvement).

2. Biopsy-confirmed refractory disease within 30-90 days following any CD19-targeted CAR T cell therapy for a hematologic malignancy (these include 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, DLBCL arising from follicular lymphoma, and mantle cell lymphoma). Of note, 'refractory' refers to patients who had early refractory disease after CAR-T cell therapy and not to patients who have received CAR-T for refractory disease, but had complete response to CAR-T cell therapy.
3. At least 1 measurable lesion according to the Lugano criteria[1]. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy
4. The following criteria pertain to pattern of progression:
    - Patients may have one refractory lesion without other residual or progressive disease as per PET/CT
    - Patients may have more than one refractory lesion, but with evidence for at least partial response of at least one other lesion as per PET/CT
    - Patients with more than one site of refractory disease without evidence for at least partial response of at least one other lesion are eligible if they are:
        - A. Symptomatic from a refractory lesion (such as cord compression or focal pain) or
        - B. Have disease that can locally affect the spinal canal or brain if left untreated.
5. Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia and prolonged cytopenias that are not expected to worsen during RT) if there is concern for overlap of anticipated radiation-related toxicity and toxicity from prior therapy due to where the RT field is located.
6. Age 18 or older
7. Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2.
8. Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

1. Any medical condition likely to interfere with assessment of safety or efficacy of RT
2. Patients with more than one site of disease without any evidence for response to CAR T cell therapy who are not focally symptomatic due to progressive disease or do not have disease that can locally affect the spinal canal or brain if left untreated
3. Women of child-bearing potential who are pregnant 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

4. 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

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 and study team. Refer to Section 13.2 and Section 8.4.4.

Statistical methods:

The primary objective of this study is to assess the safety and toxicity of RT following CAR T cell therapy. The secondary objective includes assessment of efficacy and quality of life. In terms of number of patients we anticipate to enroll, 53 patients underwent axicabtagene ciloleucel or tisagenlecleucel therapy at MGH within the past year. With a modest 30% refractory disease rate, 16 patients would have refractory disease and may be eligible for radiation therapy to achieve disease control. For the next one year, given the increasing rate of patients being referred for CAR T cell therapy, we expect that 80 patients are expected to undergo CD19-targeted CAR T cell therapy – as such, over 20 patients may be referred for RT. Univariate descriptive statistics with t-tests will be used to analyze pre- and post-RT QOL and toxicity data.

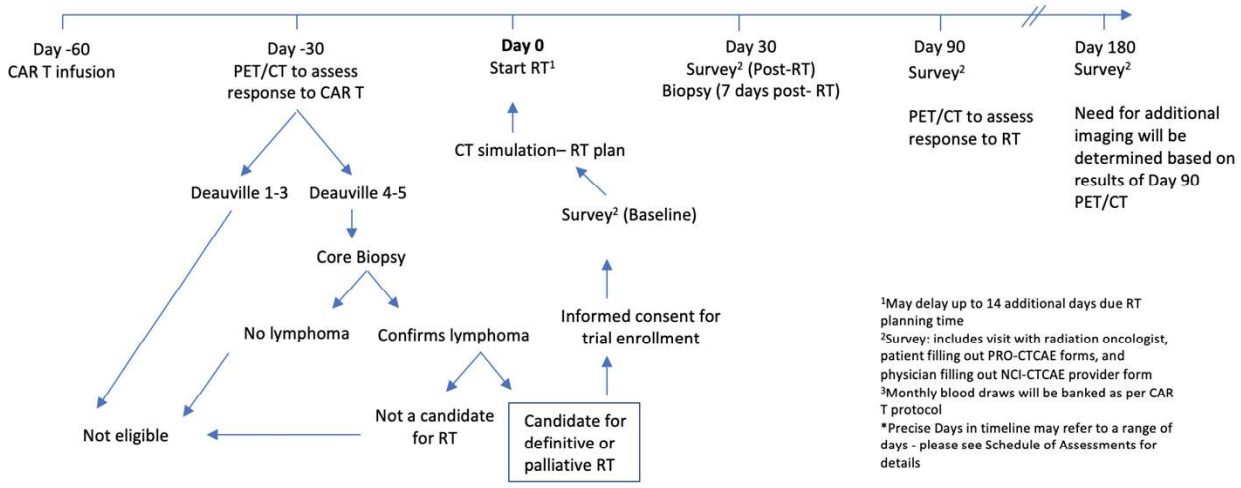
Study Glossary

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	**D**ata **S**afety **M**onitoring **B**oard
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
PRO	Patient Reported Outcome - Common Terminology Criteria for Adverse Events
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
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**

Study Schema



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2. OBJECTIVES

The primary objectives of this study are to evaluate the safety and toxicity of radiotherapy in patients with hematologic malignancies who will undergo any CD19-targeted CAR T cell therapy.

Key secondary objectives includes determination of efficacy of RT following CAR-T therapy., and assessment of patient reported outcomes with regard to symptoms and side effects in RT following CAR T cell therapy

Exploratory objectives include determination of immune infiltrates into pre- vs. post-RT biopsy samples and changes in anti-CD19 CAR T cells and cytokine profiles pre- vs. post-RT blood samples.

2.1 Study Design

Study 19-861 is a single center, pilot study evaluating the feasibility safety and efficacy of radiotherapy in patients with hematologic malignancies who will undergo any CD19-targeted CAR T cell therapy.

Approximately 20 subjects with hematologic malignancies with refractory disease following CAR-T cell therapy, including DLBCL, PMBCL, high grade lymphoma, TFL, or mantle cell lymphoma will be enrolled to evaluate the addition of radiotherapy in terms of achieving partial or complete response, and disease-free survival, as applicable. Specimens will be collected for translational analysis to study the interaction of RT and the immune microenvironment.

If addition of radiotherapy is safe and effective in these patients, RT may be a useful adjunct in patients with early refractory disease following CAR T cell therapy. A larger study would be done to investigate important determinants of eliciting RT response following CAR T cell therapy.

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
- RT Treatment Period
- Post treatment assessment period with a biopsy (research) and PET/CT following RT (as standard of care)
- 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 ascertain the safety and toxicity of radiotherapy in patients with hematologic malignancies who will undergo any CD19-targeted CAR T cell therapy

Secondary Objective:

- To evaluate the efficacy of radiotherapy in the above patients

Exploratory Objective:

- To assess immune infiltrates into lymphoma following radiotherapy
- To evaluate mechanisms of interplay between radiotherapy and CAR T cell therapy, by examining serum cytokine levels and expression changes of key pathway mediators in lymphoma biopsy samples before and after radiotherapy

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 Radiation Therapy for Refractory Lymphoma/Leukemia Following CAR T Cell Therapy

3.2.1 **Background and Significance**

MGH is on the forefront of academic institutions employing chimeric antigen receptor (CAR) T cell therapy, with 200+ patients already treated at MGH since the first FDA approval of axicel (axicabtagene ciloleucel; Yescarta)[1] and tisacel (tisagenlecleucel; Kimrayah)[2] in 2017. Eligible patients for these commercial CAR T cell products have ALL (acute lymphoblastic leukemia) or relapsed or refractory large B cell lymphoma after at least 2 lines of systemic therapy[1]. In addition, 30 new protocols of investigational CAR T cell therapy are underway at MGH, making it amongst the most active cellular therapy research programs across the world.

CAR T cell therapy is an exciting example of genetically modifying a patient's T cells to target tumor cells for death for patients with the above relapsed/refractory hematologic malignancies who otherwise have very limited, if any, remaining options to achieve cure. A patient first undergoes leukapheresis to collect peripheral blood mononuclear cells (PBMCs)[1]. The T cells are isolated in a manufacturing laboratory and are genetically engineered most commonly via a viral vector to target an antigen displayed by the patient's tumor cells, which thus far has been CD19. These cells are then expanded and cryopreserved, for shipment back to the hospital. The patient is

admitted for infusion of the CAR T cells, basically a re-introduction of modified T cells into the patient's body. The time from eligibility determination for CAR T cells to the infusion of the CAR T cells can take as long as 2-3 months[1].

While response rates range from 50 - 80%, durable responses are only seen in 30-40% of patients at long term time points, demonstrating that 60% of patients will eventually relapse following CAR T cell therapy[2–4]. Although, the best predictor of durable response is the ability for a patient to achieve a complete response (CR), only 40-52% of patients will achieve CR at early day 30 re-staging. Of the remaining patients with partial response, stable disease, or progressive disease, only 10-15% will subsequently convert to a CR at later timepoints without any clear predictor of later response emphasizing the need for better consolidative strategies.

The post-CAR T day 30 timepoint represents a unique opportunity to stimulate the immune system and to enhance CAR T-dependent cellular toxicity in a setting in which patients have no reliably effective therapeutic options other than local radiotherapy. These patients may have localized masses in a limited number of sites which are symptomatic or may become symptomatic. Importantly, given the sheer bulk of some of these masses, relapse after CAR T cell therapy remains a concern. Based on a recently presented multicenter retrospective study of chemorefractory high grade B cell lymphoma who underwent axicel, patients with tumor diameter < 5 cm tended to have improved outcomes [5]. In bone marrow transplant patients, for example, radiotherapy is administered for localized refractory/relapsed sites, including bulky masses, in the peritransplant setting[6] . No clinical trials on RT and CAR T cell therapy have yet been published, but Memorial Sloan Kettering[7] and University of Pennsylvania[8] are currently studying RT in the pre-CAR T cell therapy bridging setting.

In addition to potential local control benefit, even more exciting is that radiotherapy has the potential to improve immunologic response against cancer cells, to act in synergy with CAR T cell therapy, to produce long term cures. Potential mechanistic reasons for failure following CAR T cell therapy include downregulation of the tumor-associated antigen, mutation of tumor cells to a more rapidly dividing phenotype, and inability of CAR T cells to adapt to a changing tumor-associated antigen repertoire[1,9]. Low dose radiotherapy may enhance immune-directed tumor death by providing an antigen-independent mechanism of tumor cells resistant to CAR T cell due to downregulation of the receptor against which the CAR T cell are targeted to based on a murine model of pancreatic ductal adenocarcinoma[7]. Based on trials of immune checkpoint inhibitor therapy, RT contributes to immunomodulation by upregulating chemokines, which appears to help T cells locate and infiltrate the tumor, resulting in radiosensitization [10]. As such, it is conceivable that radiotherapy may help CAR T cells infiltrate into early refractory disease as at a timepoint that the CAR T cells are still very active.

3.3 Correlative Studies Background

Correlative studies will be performed on peripheral blood and tumor biopsies, before and after radiation therapy to investigate mechanisms involving potential synergy between RT and CAR T cell therapy. The effectiveness of CAR 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 when possible 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 CAR T cell effectiveness and/or toxicity and CD19 expression on tumor cells

will be evaluated at the eligibility and in subjects failing following RT.

Additional testing may be done depending on the clinical condition; for instance, patients with an atypical skin rash following RT 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 CAR-T cells by flow cytometry and/or IHC. Additionally, different T cell subsets may have demonstrated different effector function and persistence and, therefore, T cell immunophenotyping will be performed by flow cytometry. Peripheral blood samples may also be analyzed for cytokine/chemokine levels by Luminex 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 the Maus/Immune monitoring Laboratory at the MGH Cancer Center for storage and bulk analyses, and pathology samples will be delivered to MGH Pathology Department. Documentation of sample receipt, processing, and storage and primary data from the research analyses will be collected and stored in the processing 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 Diagnosis and selection criteria: refractory hematologic malignancy following any CD19-targeted CAR T cell therapy

Inclusion Criteria

1. Biopsy-confirmed refractory disease within 30 to 90 days following any CD19-targeted CAR T cell therapy for a hematologic malignancy (these include 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, DLBCL arising from follicular lymphoma, and mantle cell lymphoma)

2. At least 1 measurable lesion according to the Lugano criteria[1]. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy
3. Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia) if there is concern for overlap of anticipated radiation-related toxicity and toxicity from prior therapy due to where the radiation therapy field is located.
4. Age 18 or older
5. Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2.
6. 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)
7. Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

1. Any medical condition likely to interfere with assessment of safety or efficacy of RT
2. Women of child-bearing potential who are pregnant 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
3. 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

4.2 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.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

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.

6. TREATMENT PLAN

6.1 Study treatment

No investigational treatment is included in this study. Radiation therapy is only offered as a standard-of-care treatment.

6.2 Rationale for Study Treatment Dosing

The dose/fractionation of radiotherapy is not being experimentally studied – the radiation oncologist will follow best judgement and International Lymphoma Radiation Oncology Group (ILROG) guidelines for refractory DLBCL (if applicable) to decide on an appropriate, standard of care dose for radiation, regardless of whether or not patient decides to be on the pilot study.

The lesion receiving radiation will be a refractory site of disease following CAR T cell therapy that in most cases, has undergone biopsy, unless an exception is met as per inclusion criteria. For patients with more than one refractory lesion, radiation therapy may be provided to one site only or to a limited number of sites (with only one site getting biopsy). While there is no explicit limit on the number of sites to receive radiation therapy due to patient variety, this decision will be guided based on symptoms due to mass effect, spinal canal or brain involvement, and anticipated toxicity of providing radiation therapy to more than one site. In the vast majority of cases, radiation therapy will be limited to one or two sites.

6.3 Excluded Medications

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after CAR T cell administration, unless used to manage CAR T cell-related toxicities. Other medications that might interfere with the evaluation of the investigational product, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary. Physiologic steroids (less than or equal to 5mg/day) will be allowed on study.

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 CAR T cell infusion and radiation therapy. Patients will be allowed to remain on maintenance therapy (ibrutinib, revlimid, etc) if these medications were initiated prior to and continued during CAR-T infusion.

6.4 Subsequent Therapy

Subsequent therapy administered after the CD19-targeted CAR T cell therapy 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.

6.5 Duration of Follow Up

Long-term Follow-up Period

All subjects who complete the study, and those who withdraw from the study after receiving RT for reasons other than death, will be asked to participate in a long-term follow-up study for up to 6 months after their RT, with a focus on long-term efficacy and safety. These patients will also have long-term follow-up as part of CAR T cell therapy registry. After Month 24 patients will be followed via the CIBMTR immune effector cell therapy registry.

6.6 Criteria for Taking a Participant Off Study

6.6.1 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 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.

6.6.2 **Reasons for Removal from Study**

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

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

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. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Expected Toxicities

To date, the following important risks have been identified with axicel and tisacel: CRS, neurologic toxicities, infections, and cytopenias. Grading and management of these toxicities will be performed utilizing the recently released ASTCT CRS/ICANS grading system[21]. Please refer to the current product label for axicel,tisacel, lisocabtagene maraleucel, and brexucabtagene autoleucel for discussion of CRS and neurotoxicity (ICANS). Treatment with RT will occur after 30 day post-infusion period during which centers are FDA mandated to observe for peak toxicities. Additional information and management recommendations can also be found in appendix A. The following are important risks identified with radiation therapy but depend upon the target site for radiation therapy: dermatitis, pneumonitis, esophagitis, fatigue.

7.2 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 to treatments provided leading to study eligibility. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

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

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

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

7.2.1 **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."

7.3 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. Additionally, patients will also self-report adverse event outcomes pertaining to the region of interest as per their RT treatment field.

- **CTCAE term (AE description) and grade**: All non-CRS/ICANS toxicities will be graded

per CTCAE by the Investigator. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **PRO-CTCAE** – Patients will also have the opportunity to self-report adverse event outcomes. The descriptions and grading scales found in the NCI Patient Reported Outcomes. Common Terminology Criteria for Adverse Events (PRO-CTCAE) version 1.0 will be utilized. A copy of the possible items for PRO-CTCAE will can be downloaded from the NCI website. Patient will be asked to fill out the applicable section of the survey depending on their radiation treatment site, including items for pain and mood for all patients:
https://healthcaredelivery.cancer.gov/pro-ctcae/instrument.html

- **ASTCT CRS/ICANS:** Any delayed CAR-T related CRS and/or neurotoxicity (ICANS) will be graded using the ASTCT 2019 CRS/ICANS grading system (appendix A).

- **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.

7.4 Procedures for AE and SAE Collection and Reporting

7.4.1 Reporting of Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from enrollment (ie, radiation therapy consultation) through 3 months after RT 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 6 months after treatment with axicel or tisacel or until disease progression, whichever occurs first.

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 or study procedures
- Action taken

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

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. 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.

7.4.2 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 RT. 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 6 months after RT or until disease progression, whichever occurs first. For subjects who screen fail or are enrolled but do not receive RT, the reporting period for serious adverse events ends 30 days after the last procedure (e.g., biopsy).

Serious events that the investigator assesses as related to RT should be reported regardless of the study period.

All serious adverse events and non-serious CRS events ≥ Grade 3 [22] must be submitted within 24 hours following the investigators knowledge of the event **using a SAE Report Form. Refer to the SAE Report Form for instructions on how to submit the SAE report**. Subsequently, all serious adverse events will be reported to the health authorities per local reporting guidelines.

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,

CAR T infusion, or RT**,** 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 CAR T infusion or RT, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring greater than 3 months after the CAR T infusion or RT requires expedited reporting within 24 hours only if it is considered related to treatment.

7.4.3 **Pregnancy and Lactation**

There is no relevant clinical experience with CAR T cell therapy 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 RT on the fetus. RT should not be administered to pregnant women.

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 RT, the pregnancy must be reported to the PI. Information regarding the pregnancy and/or the outcome may be requested by the PI.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of axicel or tisacel through 6 months for female subjects and for 6 months for the female partner of the male subjects.

The pregnancy should be reported to the PI contact within 24 hours of the investigator knowledge of the pregnancy event.

7.4.4 **Criteria to Pause Enrollment**

Enrollment will be paused if any of the following criteria is met:

1) Any subject with grade 4+ RT-related adverse events

   or

2) Subject incidence of the following Grade 4+ CAR-T-related adverse events lasting more than 7 days is > 33%:
   Neurologic toxicities
   CRS (per ASTCT 2019)
   Other non-hematological serious adverse event
   Infection (treatment-related)

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.

7.5 Reporting to the Food and Drug Administration (FDA)

Not applicable.

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

Not applicable.

7.7 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.

7.8 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.

7.9 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.

8. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

8.1 Biomarker Studies

N/A, no biomarker studies.

8.2 Laboratory Correlative Studies

Biomarker analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for CD19-targeted CAR T cell therapy. 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 CAR T cell therapy before and after radiotherapy**. 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.

Additional translational samples of PBMC, serum cytokines, tissue, and bone marrow 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 within a local immune monitoring facility.

9. STUDY CALENDAR

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 28 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 **RT start date**. An overview of study assessments/procedures is outlined below.

9.1 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.

9.2 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.

9.3 Medical and Treatment History

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

9.4 Physical Exam, Vital Signs, Performance Status

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

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.

9.5 Laboratory

The below samples will be collected at the time points indicated in the SOA. Additional samples (eg, blood, 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.

- **Additional blood draws for PBMC and serum, as well as 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.**
- Blood draws for PBMC (lymphocyte subsets, and anti-CD19 CAR T cell levels) and cytokine analysis will be performed at intervals outlined in the SOA.
- Archived tumor tissue
    - 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.

9.6 Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for **CAR T cell therapy** and described in Section 10.1.

9.7 Description of Study Periods

9.7.1 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 4 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
    - 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

- Imaging Studies
  - PET CT post-CAR T cell therapy
    - PET-CT performed following the subject's therapy and prior to signing the consent may be used for confirmation of eligibility**.**
    - PET CT should be performed as close to enrollment as possible.
- Labs
  - Chemistry panel
  - CBC with differential
- 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 tumor sample, as well as fresh tumor sample**(s)** after RT.

9.7.2 **Enrollment Period & RT simulation/planning**

No specific restrictions are made for the use of RT after biopsy-confirmed relapse following CAR T cell therapy. Prior RT is not an exclusion criterion given the technologies available to safely deliver re-irradiation in many scenarios with modern technology. The RT simulation consists of imaging patients in the treatment position with using custom immobilization. After a planning period of 7-14 days, depending on complexity of treatment plan, patients begin radiation therapy. PET-CT imaging will be repeated if >28 days from prior imaging and enrollment.

9.7.3 **RT Treatment**

Patients are seen weekly during RT as per standard of care to monitor toxicities of RT. Subject will allow study personnel 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:

- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs
  - Chemistry Panel
  - CBC with differential
  - Cytokine levels
  - Lymphocyte subsets
  - Translational lab collection.
- Adverse/Serious Adverse Event reporting (refer to Section 8 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is admitted to the hospital with any **RT, CAR T-** 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**:

- Translational labs (two 10cc purple top tubes)
- Cytokines (one 10cc red top tube)

9.7.4 **Post RT Period**

Patients are seen weekly for one month following RT. Subject will allow study personnel 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:

Seven to fourteen days after beginning RT, patients will undergo a core-needle biopsy (FNA acceptable if core-needle unable to be done for any reason). This biopsy will allow a direct comparison of inflammatory cytokine and T cell infiltration into the tumor in comparison to pre-RT biopsy that confirmed refractory disease. If it is deemed unsafe to proceed biopsy may be deferred as other immune correlates will be collected from peripheral blood and serum.

- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs
    - Chemistry Panel
    - CBC with differential
    - Cytokine levels
    - Lymphocyte subsets
    - Translational lab collection.
- Adverse/Serious Adverse Event reporting (refer to Section 8 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is admitted to the hospital with any **RT, CAR T-** 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**:

- Translational labs (two 10cc purple top tubes)
- Cytokines (one 10cc red top tube)

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 translational lab set **and serum** sample **(for cytokine evaluation)** should be collected at the time of progression, prior to starting any subsequent anti-cancer therapy.

9.7.5 **Long-term Follow-up Period**

All subjects who complete the study, and those who withdraw from the study after receiving RT for reasons other than death, will be asked to participate in the long-term follow-up portion of this study up to 12 months from CAR-T infusion, with a focus on long-term efficacy and safety. These patients will also have long-term follow-up as part of the FDA mandated CIBMTR CAR T cell therapy registry.

The following procedures will be completed for subjects who are enrolled at the time points of 6, 9, and 12 months following CAR-T infusion, as outlined in the SOA (Long-term Follow-up Period) Table 3:

- Physical exam
- CTCAE/PRO-CTCAE Surveys
- PET-CT/ Disease assessment at 6 and 12 months per standard of care
- Survival status
- Labs
  - CBC with differential
  - Cytokine levels
  - Lymphocyte subsets
  - Translational lab collection.
- 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 12 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 translational lab sample and **serum (for cytokine evaluation**) should be collected at the time of progression as part of CAR T cell therapy protocol, prior to starting any subsequent anti-cancer therapy.

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.

As patients will be receiving commercial product, patients will also have long-term follow-up as part of FDA mandated CAR T cell therapy registry.

Table 2. Schedule of Assessments

Procedures	Screening	Enrollment & RT Planning	Radiotherapy		Post Radiotherapy Period			
Day	No longer than 14 days from biopsy and within 28 days of enrollment	Within 14 days of Initiation of Radiotherapy	Day 0	Weekly through completion (± 7 days)	Week 1 Post-Treatment (± 7 days)	Week 2 Post-Treatment (± 7 days)	Week 3 Post-Treatment (± 7 days)	Week 4 Post-Treatment (± 7 days)
Informed consent	X							
Medical history	X							
ECOG Performance Status	X		X	X	X			
CRS/ICANS Consensus Grading	X		X	X				
CTCAE/PRO-CTCAE Surveys		X			X			
Tumor Biopsy	X[1,2] (w/in 90 days of CAR T infusion)				X[2]			
PET-CT/ disease assessment	X[3]							
RT Planning		X						
Physical exam	X			X				
Vital signs (BP, HR, O_2 sat, temp)	X			X				
Weight (plus Height at screening)	X							
Blood draw for Chemistry panel	X		X	X	X	X	X	X
Blood draw for CBC w/differential	X		X	X	X	X	X	X
Blood draw for C-reactive protein (CRP)	X		X	X	X	X	X	X
Blood draw for Lymphocyte subsets[3]			X	X	X	X	X	X
Blood draw for Cytokines[4,5]			X	X	X	X	X	X
Blood draw for translational lab collection[4, 6]			X	X	X	X	X	X
Radiotherapy[7]			X					
Adverse events/ Concomitant medication	X	X	X	X	X	X	X	X

[1] Tumor biopsy: Either FFPE tumor block or up to 20 unstained slides. Fresh tumor biopsies are preferred however archival tissue is acceptable if obtained prior to screening period but following CAR-T infusion without intervening therapy.

[2] Tumor biopsy may be deferred if not deemed clinically appropriate and safe.

[3] PET-CT (Neck-Chest-Abdomen-Pelvis)/disease assessment: If recent PET-CT performed > 45 days from enrollment, baseline scans must be repeated.

[4] Prior to radiotherapy on Day 0, then weekly through 4 weeks post radiotherapy.
[5] Cytokines: 5cc red top tubes
[6] Translational Labs: Two 10cc purple top tubes
[7] Radiotherapy: Individual patient course may vary depending on optimal treatment strategy.
[8] Tumor biopsy: Either FFPE tumor block or up to 20 unstained slides. If possible, repeat tumor biopsy to be obtained in the event of disease progression.

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

Procedure	**Long Term Follow-up Period (Each visit calculated from CAR-T infusion)**		
Visit Frequency	Month 6	Month 9	Month 12
Physical exam	X	X	X
CTCAE/PRO-CTCAE Surveys	X	X	X
PET-CT/disease assessment[1]	X		X
Survival Status	X	X	X
Blood draw for CBC w/differential [3]	X	X	X
Blood draw for Lymphocyte subsets [3]	X	X	X
Blood draw for Cytokines[4,5]	X	X	X
Blood draw for translational lab collection [4, 6]	X	X	X
Targeted AE/SAEs 7	X	X	X
Targeted concomitant medication [8]	X	X	X
Subsequent therapy for NHL[9]	X	X	X

[1] PET-CTs/disease assessments will continue through Month 12 or until disease progression, whichever comes first, as is 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 12 as per standard of care
[4] Monthly starting 6 months from CAR-T infusion
[5] Cytokines: 5cc red top tubes
[6] Translational Labs: Two 10cc purple top tubes
[7] Targeted AEs/SAEs will be collected for 24 months or until disease progression (whichever occurs first)
[8] Targeted concomitant medications will be collected for 24 months or until disease progression (whichever occurs first)
[9] Subsequent therapy administered after **CAR-T** infusion for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant 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.

10. MEASUREMENT OF EFFECT

10.1 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 Lugano Criteria[1] for Malignant Lymphoma [23]as applicable (appendix B). Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Pre-RT PET-CT scans of the neck, chest, abdomen and pelvis is required. **Subjects will undergo additional PET-CT tumor assessment as part of standard of care.**

After RT, 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.

11. 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).

11.1 Data Reporting

11.1.1 Method

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

11.1.2 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.

11.2 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 and study team. In additional to the DF/HCC DSMC, a safety review team (SRT) comprised of the study sponsor and Kite/Gilead, will review the safety data and make recommendations on further study conduct as described below.

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.

12. STATISTICAL CONSIDERATIONS

The primary objective is to ascertain the safety and toxicity of radiotherapy in patients with hematologic malignancies who will undergo CD19-targeted CAR T cell therapy. The secondary objectives are to evaluate the efficacy of radiotherapy in these patients. Exploratory objectives include assessing T cell infiltration, including CAR T cells, into lymphoma following radiotherapy and evaluating mechanisms of interplay between radiotherapy and CAR T cell therapy, by examining serum cytokine levels and expression changes of key pathway mediators in lymphoma biopsy samples before and after radiotherapy

This protocol is designed to **assess the impact of radiation therapy.**

12.1 Study Endpoints

Primary Endpoint:

- Rate and severity of RT-related toxicity as per CTCAE v5.0 criteria during RT or within the first 30 days of completing RT.

Secondary Endpoints:

- **Duration of response (DOR)**: Among subjects who experience an objective response, DOR is defined as the date of their first objective response (which is subsequently confirmed) to disease progression per Lugano criteria[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)** per IRRC: **ORR** per IRRC is defined as the incidence of either a complete response or a partial response by Lugano criteria[1] as determined by the IRRC. 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 RT completion date to the date of disease progression per Lugano criteria[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 RT completion 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
- 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.
  External collaboration with BostonGene, a biotechnology company: anonymized tumor samples from core-needle biopsy and blood (paired pre-RT and post-RT samples for each patient) will be made available for Next-Generation Sequencing (NGS) and analysis following sample collection from all enrolled patients. BostonGene will perform NGS and analysis. In order to assist with clinical correlation of NGS data, BostonGene will be provided with anonymized data for each sample with regard to clinical characteristics (age, diagnosis, prior therapies, response on imaging, pathology results, blood counts, and cytokine profiles). Anonymized patient samples will be delivered by secure courier. All data will be anonymized (free from any patient identifiers) and securely transmitted with approved methods as per MGH IS.

The primary objective of this study is to assess safety and toxicity of RT following CAR T cell therapy. The assessment of ORR is a secondary objective, and the analysis will be descriptive.

12.2 Sample Size, Accrual Rate and Study Duration

In terms of number of patients we anticipate to enroll, 53 patients underwent axicel or tisacel therapy at MGH within the past year. With a modest 30% refractory disease rate, 16 patients would have refractory disease and may be eligible for radiation therapy to achieve disease control. For the next one year, given the increasing rate of patients being referred for CAR T cell therapy, we expect that 80 patients are expected to undergo axicel or tisacel therapy – as such, **we modestly anticipate enrolling 20 patients who are candidates for RT on this study**. In terms of sample size calculation, with a 95% confidence level and a confidence interval of 10, with 0.3 (refractory disease rate) * 80 patients = 24 eligible in the population, the required sample size is 19 patients. It is noted that this is a **pilot** study, where the primary objective is assessing safety and toxicity, within the limits of what a pilot study can establish. Typically recommended ranges for pilot study sample sizes tend to range from 10 – 30. The number 20 is based primarily on how many patients can be accrued within a year and how many patients there is funding for. We are most concerned about Grade 4 or higher toxicity within RT field. Patients will have many different anatomic sites in terms of radiation treatment. Inherently, while a sample size calculation can be done as an exercise, the validity of it is highly questionable given the multiple anatomic sites to which patients may receive RT and no published data of patients who undergo RT following CAR T cell therapy. Results from this pilot study will be used to design a larger study, and for that, sample size can be computed based on what safety and

toxicity-related events are seen in the pilot study. Univariate descriptive statistics with t-tests will be used to analyze pre- and post-RT QOL and toxicity data.

All subjects will be followed for survival for up to approximately 15 years after the last subject receives CAR T cell therapy, with data collected through the CIBMTR data registry starting at Month 24.

12.3 Interim Monitoring Plan

Interim Analysis and Early Stopping Rules

The SRT will review safety data when 3 and 10 subjects treated have had the opportunity to be followed for 30 days, respectively**.** The study will be stopped if any patients develop grade 4 or higher toxicity attributed to RT rather than to lymphoma progression or other cause as per SRT.

Safety Interim Analysis

The SRT will review AE and SAE information on a regular basis throughout subject treatment in Phase 2 of the study. The SRT may request additional safety data or modifying 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.

Efficacy Interim Analysis

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

12.4 Analysis of Primary and Secondary Endpoints

Planned Method of Analysis
The primary analysis of all treated subjects will take place once they have had the opportunity to be followed for 6 months.

Descriptive analyses may occur at any time.

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

Duration of Response

The competing-risk analysis method [24,25] will be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence of non-disease related mortality (the competing risk) 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 5.0 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.

12.5 Reporting and Exclusions

The statistical reporting of the safety and efficacy endpoints will be compared to historical controls of patients with refractory disease following CAR T cell therapy who did not undergo RT. Subject incidence rates of axicel or tisacel-related adverse events, and ORRs will be summarized. DOR, PFS, and OS will also be summarized.

Analysis Subsets

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.

13. ETHICAL AND REGULATORY REQUIREMENTS

13.1 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.

13.2 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.

13.3 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

13.4 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.

13.5 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.

13.6 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

14. 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.

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APPENDIX A

CYTOKINE RELEASE SYNDROME (CRS) AND NEUROTOXICITY MANAGEMENT

Table 1. CRS Grading System – ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever†	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or‡				
Hypoxia	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

CPAP: Continuous positive airway pressure; BiPAP: Bilevel positive airway pressure

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

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

#Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

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

Table 2. Management of CRS by Grade

CRS Grade	Anti-IL-6 Therapy	Corticosteroids	Additional Supportive Care
Grade 1	For prolonged CRS (>3 days) in patients with significant symptoms and/or comorbidities, consider tocilizumab as per Grade 2	N/A	• Empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Dexamethasone 10 mg IV every 6 hours (or equivalent)	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to intensive care unit (ICU), consider echocardiogram, and initiate other methods of hemodynamic monitoring • Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy • Symptomatic management of organ toxicities
Grade 3	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, manage as grade 4	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen including high-flow oxygen delivery and noninvasive positive pressure ventilation • IV fluid bolus and vasopressors as needed. • Symptomatic management of organ toxicities
Grade 4	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, consider methylprednisolone 1000 mg/day IV	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

Table 3. Anti-IL6 Therapy and Dosing Recommendations

DRUG	RECOMMENDED DOSE FOR CRS AND/OR NEUROTOXICITY	MAXIMUM DOSE	MECHANISM OF ACTION	COMMENTS
TOCILIZUMAB	8 mg/kg IV for up to three doses in a 24-hour period (Maximum 4 doses total)	Maximum 800 mg per dose	IL-6 receptor antagonist	First line agent Doses can be given 8 hours apart

Table 4. Grading of Neurotoxicity (Lee et al., 2018)

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 Non-convulsive 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
Raised 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 having Grade 3 ICANS.
^A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with

global aphasia. But a patient with an ICE score of 0 may be classified as having Grade 4 ICANS if the patient is unarousable.
Depressed level of consciousness should be attributable to no other cause (e.g. 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: Immune effector Cell-associated Encephalopathy; ICP: Intracranial pressure; EEG: electroencephalogram.

Table 5. Encephalopathy assessment tools for grading of Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS).

Immune effector Cell-associated Encephalopathy (ICE)
• **Orientation:** Orientation to year, month, city, hospital: 4 points • **Naming:** Name 3 objects (e.g., point to clock, pen, button): 3 points • **Following commands:** (e.g., Show me 2 fingers or Close your eyes and stick out your tongue): 1 point • **Writing:** Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point • **Attention:** Count backwards from 100 by ten: 1 point

Score 10: No impairment
Score 7-9: Grade 1 ICANS
Score 3-6: Grade 2 ICANS
Score 0-2: Grade 3 ICANS
Score 0 due to patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

Table 6. Management of ICANS

Treatment by Grade	
Grade 1	• Supportive care
Grade 2	• Supportive care • Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen.
Grade 3	• ICU care is recommended. • Dexamethasone, 10 mg IV every 6 h • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.
Grade 4	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids, methylprednisolone 1000 mg/day IV x3 days • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

APPENDIX B
Lugano criteria for response assessment in lymphoma (Cheson 2014)

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

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Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.