CLINICAL RESEARCH PROTOCOL

DRUG:	ATLCAR.CD30
STUDY NUMBER(S):	LCCC 1524-ATL
PROTOCOL(S) TITLE:	Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)
IND NUMBER:	14688
SPONSOR:	Lineberger Comprehensive Cancer Center
ORIGINAL PROTOCOL DATE:	March 21, 2016
AMENDMENT NUMBER:	Amendment 8
VERSION NUMBER:	Version 1.0
VERSION DATE:	17 April 2023

SUMMARY OF CHANGES

Protocol Amendment #8

LCCC 1524-ATL: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

AMENDMENT INCORPORATES:

_X_ Editorial, administrative changes

_X_ Scientific changes

__ Therapy changes

_X_ Eligibility Changes

Rationale for amendment: The purpose for this amendment is to remove HTLV testing requirements from the inclusion criteria. CAR-T cells and procurement materials may also be stored for a total of 25 years (15 years + 10 years archived), and long term follow up requirements have been updated to allow for local visits. The protocol has been further reconciled so that language throughout the protocol is consistent. The Principal Investigator was also updated to Natalie Grover.

Editorial, administrative changes:

Appendix organization and numbering and other links and associated updated as appropriate

Minor mechanical and grammar edits throughout

Principal Investigator was updated to Natalie Grover, MD

Scientific changes:

Section 4.2	Time and events table footnote 6, HTLV testing removed
Section 7.2.1	HTLV testing removed from pre-procurement assessments
Section 7.5.8	Biobank repository language updated to state that CAR-T cells and material from procurement are to be stored for up to 15 years for subject treatment and

safety purposes, furthermore, samples may be archived for a total storage time of 25 years (including initial storage and archiving). Multicenter honest broker language also added.

Therapy changes:

Section 4.2 Language added to footnote 1 of the Time and Events table to allow for changes to long term follow up as follows: NOTE: Follow-up visits for month 3 and beyond can be conducted locally (i.e., by local health care provider, local treating oncologist, etc.). The study team would continue to contact the subjects at the long-term follow-up time points and request they visit their local healthcare provider to complete the follow-up test and assessments, where applicable. The study team would collect clinical information, tests and assessments results, other clinical observations from the subject's medical record and their local health care provider.

Eligibility changes:

Section 5.3 Virus testing in exclusion criteria updated to remove HTLV, language now reads: Active infection with HIV, HBV, HCV (**can be pending at the time of cell procurement; only subjects meeting the criteria as so described will be infused**). (Note: To meet eligibility subjects are required to be negative for HIV antibody, negative for Hepatitis B surface antigen, and negative for HCV antibody **or** viral load).

THE ATTACHED VERSION DATED April 17, 2023 INCORPORATES THE ABOVE REVISIONS

SUMMARY OF CHANGES

Protocol Amendment #7

LCCC 1524-ATL: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

AMENDMENT INCORPORATES:

X Editorial, administrative changes
X Scientific changes (IRB approval)
Therapy changes (IRB approval)
Eligibility Changes (IRB approval)

Rationale for amendment:

The purpose of this protocol amendment is to update correlative blood sample collection related to RCR testing, function and persistence, and clonality. In relation to RCR testing parameters are updating for collection and testing based on the development of long-term gene therapy side effects. This amendment allows for the cessation of correlative sample collection when transgene is no longer detectable. The data collection system has also been updated.

NOTE: The protocol was transitioned to an eCTD friendly protocol template. Sections of the most current protocol may be different than they were prior to the transition. Therefore, the references and/or Appendices may not be reflective of the current protocol.

Editorial, administrative changes:

	Mechanical Editing made as needed that include section and appendix reference updates.
Section 13	Data entry changed from OnCore to Advarra EDC.

Scientific Change

Section 4.2 Time and Events Table	A medical history footnote was added as #3 to detail gene therapy side effects to monitor. Footnotes 10 and 11: Information in the correlative footnotes was modified and consolidated into 1 footnote (#11). It also indicates that Correlative blood sample collection will cease if the samples are no longer required for persistence

and function or clonality analysis. Persistence and function (11a) descriptions have been modified to lower the threshold of copy number detection for sample from 1000 copies/ug to 500 copies/ug. Also, if after 1 year transgene is undetectable collections for function and persistence will discontinue. For clonality (11b), it is indicated that sample collection may cease if detection of transgene is < .5% for more than 1 consecutive testing period. For RCR (11c) it is updated to indicated that samples will be collected and stored pre-infusion AND in the event a subject develops a long-term gene therapy side effect as described in Section 7.5.2. The cytokine testing row was removed, and associated footnote contents added to the correlatives footnote as sub-bullet "11d."

As a result of the consolidation and addition of footnotes the footnotes were renumbered as needed.

Section 7.5 Updated to indicate that correlative blood sample collection will cease if the samples are no longer required for persistence and function or clonality analysis

Section 7.5.1 Function and persistence testing modified to allow testing to stop if transgene is not detected after 1 year. The level of detection was decreased to 500 copies / ug DNA from 1000 copies/ug

Section 7.5.2 Updated to identify conditions for RCR testing.in the event of long-term gene therapy side effects

Section 7.5.3 Renamed to "Clonality." Updated to indicate samples will no longer be collected if detection is < 0.5% for more than 1 testing period

Appendix III Footnote 2 for medical history is updated to include gene therapy side effects to monitor.

Abbreviated follow up table correlative sample collection footnotes 3, 4, and 5 are combined and updated similarly to the main time and events table with the exception that in the Clonality sub-bullet (b) transgene detection method is only by flow cytometry

THE ATTACHED VERSION DATED November 24, 2021 INCORPORATES THE ABOVE REVISIONS

Protocol Amendment #6

LCCC 1524-ATL: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

AMENDMENT INCORPORATES:
X Editorial, administrative changes
X Scientific changes (IRB approval)
X Therapy changes (IRB approval)
Eligibility Changes (IRB approval)
Other

Rationale for Amendment

The primary purpose of this amendment is to remove the hematologic parameters for dose limiting toxicity (DLT) based on experiences from other CAR-T cell clinical trials and discussion with experts in the field. Most of the early hematologic toxicities are likely related to lymphodepleting chemotherapy, based on prior clinical trials with fludarabine/bendamustine which found that 60% of patients experienced grade 4 neutropenia and 29% of patients experienced grade 4 thrombocytopenia [1]. Based on recently reported data, hematologic toxicity from CAR-T seems to be longer lasting and delayed more (months as opposed to weeks) in comparison to initial expectations for CAR-T cell products[2, 3]. These long-term cytopenias appear to be manageable with supportive care and do not seem to be associated with significant adverse events.

Based on the safety profile we have observed with this vector, as well as our overall experience with RCR testing in T cell products and recipient follow-up samples, the testing of transduced T cell lines and recipient follow-up samples under this protocol has been amended so that RCR testing is no longer to be routinely required. Subject blood samples will be collected pre-infusion and stored so that they are available in the event that the subject develops a new malignancy, and follow-up RCR testing is required.

This amendment also adds an exploratory objective to determine whether there are correlations [redacted]

In addition, the protocol for long term follow up has been updated to include tracking of delayed adverse events and new malignancies, and to allow for increased observation and testing in these circumstances, in keeping with best practices. The window for virus testing has also been expanded to 30 days

Finally, this amendment allows for additional analysis of collected standard of care biopsy or autopsy tissue including assessing potential causes for loss of response to therapy, including, but not limited to, the loss of CD30 expression.

Editorial, Administrative Changes

Updated the term "affiliate" to "multicenter" throughout the protocol.

Updated the name of the multicenter team from "UNCCN" to "multicenter" throughout the protocol.

Updated staff titles to current titles throughout the protocol.

Removed language related to use of other IRBs, as all sites in this study must use the UNC IRB.

Updated Section 1.5.2 Clinical Experience with CAR-T cells to indicate that as of July 2018 there are over 250 clinical trials incorporating CAR-T cells.

Clarified requirements for quantitative PCR testing in Sections 6.0 and 11.2.

Clarified the language in Section 4.2 regarding procurement.

Clarified the language in Sections 6.0 and 11.2 regarding correlative samples.

Deleted imaging language from Section 6.5, where it did not apply. This language appears where relevant, in Section 6.9.

Updated Sections 7.3.2 and 7.3.3.2 to reflect that the NIH RAC is currently no longer reviewing unexpected SAEs outside of the review conducted at the FDA. As a result, the MedWatch 3500A Form should be used instead of the GeMCRIS report form if such an event occurs.

Updated Section 7.3.3.1 IRB Reporting to include the multicenter project manager general email box.

Updated Section 7.3.3.2 FDA Expedited Reporting Requirement for Studies Conducted under an IND to remove redundant language found in section 7.1.2 Suspected Adverse Reaction (SAR) and to refer to that section for details.

.Updated Section 9.5.1, Emergency Modifications, in line with current process.

Updated Section 9.6, Amendments to the Protocol, in line with current practice.

Updated Section 9.2 Required Documentation to include financial disclosures.

Change in Principal Investigator from Thomas Shea, MD, to Marcie Riches, MD.

Corrected an inconsistency between the Table in Appendix B and its Footnote 4, which incorrectly referenced a study visit at month 9 (Note that this is the change from Version 1 to Version 1.1 of this Amendment 6).

Minor grammar and style edits throughout the document.

Scientific Changes

Added Exploratory Objective [redacted]

Clarified in Section 8.1 that subjects with insufficient cells manufactured who therefore receive a lower dose will be included in CRM calculations with a weight of 0.5, and that increasing the N of the study will be considered in the event there are more than 3 such subjects.

Therapy Changes

Section 4.4.1 was updated to indicate that subjects with insufficient cells manufactured may therefore receive a lower dose.

Section 4.4.3, Definition of DLT, was updated to remove hematologic DLT.

Updated the requirement for blood collection in Section 6.5.6 in subjects who develop symptoms of CRS, and any SAE, AE or event of clinical significance possibly related to CAR T cell administration from 10 mL to approximately 20 mL.

Updated T&E Table footnotes to include collection of an additional blood sample if any subject develops an AE or event of clinical significance that is thought to be at least possibly related to CAR T cells.

Updated the T&E table footnotes to allow a 30 day window for virus testing.

Updated Sections 6.4 regarding long term follow-up to include tracking delayed adverse events and new malignancies, and resulting investigator determination of additional observations, testing and sample collection needed.

Updated Section 6.5.2 regarding RCR testing based on the safety profile for this vector and overall experience with RCR testing. We will continue to collect subject blood samples pre-infusion and will collect a follow-up sample for RCR testing should the subject develop a new malignancy. Testing at 3, 6, and 12 months, as well as archiving annual samples for RCR testing, has been eliminated.

Updated Section 6.5.7 Other Tissue Studies to allow collection of tissue from standard of care biopsies at any time after treatment instead of only during the first year.

Updated Section 6.5.7 to allow collected tissue to also be used to assess for potential causes for loss of response to therapy, including, but not limited to, the loss of CD30 expression.

Updated Appendix F: CRS Toxicity Grading Scale and Management Guidelines to specify that the clinical grading criteria is based on NCI CTCAE v4.0.

Updated Appendix F: CRS Toxicity Grading Scale and Management Guidelines to remove the reference to the list of investigators that must approve the use of tocilizumab and/or steroids.

The attached version dated July 2, 2019 incorporates the above revisions

PROTOCOL AMENDMENT # 5

LCCC 1524-ATL: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

AMENDMENT INCORPORATES:

X Editorial, administrative changes
Scientific changes (IRB approval)
X Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)
Other

The purpose of this protocol amendment is to modify the eligibility criteria prior to cell infusion to allow for imaging results from within 60 days prior to transplant instead of from within 30 days. The eligibility criteria prior to cell infusion were also updated to require subjects to have autologous transduced activated T-cells that meet the Certificate of Analysis acceptance criteria.

The protocol has also been amended to clarify that cell procurement may occur either prior to peripheral blood stem cell (PBSC) mobilization or after PBSC mobilization. While the previous version of the protocol could be read to imply that cell procurement must occur prior to PMSC mobilization, there is no safety or manufacturing reason that it must occur in this order. As long as procurement occurs at least 7 days after ending granulocyte-colony stimulating factor (G-CSF), procurement may occur after mobilization.

Additionally, the protocol has been to clarify that the parameters of pheresis will be up to two blood volumes instead of requiring a total of two blood volumes. A total of two blood volumes may not be needed for pheresis; therefore, this change allows for less than that amount.

Finally, the protocol has been amended to include headache as an additional sign and symptom of cytokine release syndrome (CRS) and to clarify elements of the CRS grading criteria.

Summary of Changes

Section 1.1 Study Synopsis and Section 1.6 Study Rationale and Design have been amended to clarify that this is a multicenter study. The purpose of Amendment 4 was to change the study from a single center study to a multicenter study. These sections were inadvertently not updated with that amendment.

Section 1.6 Study Rationale and Design has been amended to remove the text "prior to peripheral blood mononuclear cell (PBMC) mobilization" in order to clarify that procurement may occur before or after mobilization.

Inclusion criterion prior to cell infusion 3.2.7 has been amended to allow for imaging results from within 60 days prior to transplant instead of from within 30 days

Inclusion criterion prior to cell infusion 3.2.11 has been updated from subjects being required to have autologous transduced activated T-cells with ≥15% expression of CD30CAR to being required to have autologous transduced activated T-cells that meet the Certificate of Analysis (CoA) acceptance criteria per recent guidelines from the FDA

Section 4.2 Cell Procurement has been amended to clarify that the parameters for pheresis will be "up to" 2 blood volumes instead of requiring a total of two blood volumes, as a total of two blood volumes may not be needed for pheresis.

Section 4.7 Duration of Follow Up has been updated to clarify that the abbreviated follow up procedures are required for subjects who experience disease progression and start alternative therapy

Section 6.1 Time and Events Table has been amended to remove the text "PBSC MOBILIZATION FOLLOWED BY" from the second column under "Screening" in order to clarify that procurement may occur before or after mobilization.

Footnote 6 of section 6.1 Time and Events Table has been amended to add the following text as the end of the footnote: "Procurement may occur prior to or after PBSC mobilization. If procurement occurs after PBSC mobilization, it must occur at least 7 days after ending use of G-CSF."

Footnote 8 of section 6.1 Time and Events Table has been amended to allow for imaging results at baseline from within 60 days prior to transplant instead of from within 30 days

Footnotes 10 and 13 of sections 6.1 Time and Events Table have been amended to remove the amount of blood to be taken for correlative studies and replaced with an instruction to refer to the LCCC 1524-ATL Laboratory Manual.

Section 6.1.1. Disease Assessment Guidelines for Cutaneous Lymphomas has been amended to allow for imaging to be performed within 60 days prior to transplant instead of within 30 days.

Section 6.2.1 Pre-Procurement has also been amended to allow for imaging results from within 60 days prior to transplant instead of from within 30 days. It has also been amended to clarify that procurement may occur prior to or after PBSC mobilization, and if procurement occurs after PBSC mobilization, it must occur at least 7 days after ending use of G-CSF.

Section 6.2.3 Treatment (D1 Week 0) has been updated to remove the amount of blood sample taken for correlative studies and an instruction to refer to the LCCC 1524-ATL Laboratory Manual has been added.

Section 6.9 Assessment of Efficacy has been amended to state that imaging will be performed at baseline within 60 days prior to ASCT instead of within 30 days.

Section 9.3 Registration Procedures has been updated to require registration with the LCCC CPO Multicenter Office

Section 11.2.1 Follow Up Kit Procedures has been removed as this information will now be included in the lab manual and provided separately as a handout to participants.

Section 11.5 - Appendix F: CRS Grading Criteria/Link to CRS Management Guidelines has been modified as follows:

a. Headache has been added as a sign or symptom of CRS for the constitutional organ system in Table 1: Signs and Symptoms of CRS

b. Grade 4 organ toxicity has been clarified to indicate, that Grade 4 transaminitis is characteristic of Grade 3 CRS transaminitis in Table 2: Grading Criteria. This was previously indicated in the Grade 3 CRS definition.

c. Grade 5 Death has been added to Table 2: Grading Criteria

d. To require that two doses of tocilizumab be available on site for immediate use for each patient treated with CAR-T cells. The doses must available prior to cell infusion and up to 6 weeks following cell infusion.

Minor editorial changes throughout.

The attached version dated June 15, 2018 incorporates the above revisions

PROTOCOL AMENDMENT # 4

LCCC 1524-ATL: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

AMENDMENT INCORPORATES:

X Editorial, administrative changes
Scientific changes (IRB approval)
X Therapy changes (IRB approval)
Eligibility Changes (IRB approval)
Other

The purpose of this protocol amendment is to make LCCC 1524-ATL a multi-center clinical trial. All subjects will receive their CAR T cell infusion at the lead site, the University of North Carolina, Chapel Hill.

Additionally, the protocol has been amended to include a cytokine release syndrome grading scale and guidelines for the management of cytokine release syndrome and neurotoxicity.

Summary of Changes

The list of co-investigators has now been removed from the protocol face page

Barbara Savoldo, MD, PhD has been indicated as the study's medical monitor on the protocol face page

Information in regards to neurotoxicity and macrophage activation syndrome, which have been observed for other CAR T cell products have been added to Section 1.5.2.1 Toxicities Associated with CAR-T cells

Patient reported outcome measures have been updated from a secondary to an exploratory objective/endpoint as a result of these surveys being optional to be presented to the patient and to be completed by the patient.

The primary endpoint has been updated to reference a CRS grading system provided in Section 11.6

The inclusion/exclusion criteria have been updated with a new format to divide out the different stages of eligibility determination more clearly

A history of hypersensitivity reactions to murine protein-containing products has been removed from the exclusion criteria

The study schema has been updated to indicate that LCCC 1524-ATL will now be a multi-center clinical trial where all enrolled subjects will have CAR T cell infusions at the lead site, the University of North Carolina, Chapel Hill.

Cell dose levels have been updated to include a maximum dose on each dose cohort in order to avoid excessive dosing secondary to obesity that could potentially result in toxicity. The maximum dose is calculated based on a body surface area of 2.5.

The definition of DLT has been updated to include a CRS grading system that is outlined in Appendix F.

Section 4.9, study withdrawal, was updated with new protocol template language

The T&E table and assessments were updated to indicate that infusion will occur at the lead site, the University of North Carolina, Chapel Hill

The T&E table and assessments were updated to remove the week 8 follow-up visit.

The T&E table and assessments were updated to include response assessments for patients with cutaneous T cell lymphoma

The T&E table and assessments were updated to include additional imaging at 6 months, 12 months, 18 months and 24 months (or until disease progression) (sections 6.1, 6.3.8, 6.3.10 and 6.4)

The footnotes for the T&E table were updated to clarify that the PRO questionnaires are optional

The T&E table and section 6.5.5 were updated to indicate that in the event of CRS and other SAE 10 mL blood samples should be collected once a day for the first 3 days. At the discretion of the sponsor, a daily sample may be requested for an addition 4 days.

Section 6.1.1 was added providing disease assessment guidelines for cutaneous lymphomas

Section 6.2.1 pre-procurement and section 6.2.2 pre-infusion were updated to indicate more clearly that eligibility will be checked at these time points.

Section 6.2.2 and 6.3.5 were updated to require a dermatology consult for cutaneous lymphomas and blood to be taken for leukemia profile and follow cytometry for mycosis fungiodes and Sezary syndrome patients.

Correlative studies were updated to remove the requirement for specific colored tubes

Section 6.9.1, measurement of disease, was updated to refer to response criteria for lymphomatoid papulosis and primary cutaneous ALCL included in section 11.4, Appendix D and response criteria for mycosis fungoides and Sezary syndrome included in Section 11.8 Appendix E.

Multi-center management language was added to sections 7.3.2, 7.3.3, 9.3, 9.5.1, 9.5.3

FDA expedited reporting requirements were updated to better detail 21CFR312.32.

NIH RAC and IBC reporting requirements were more clearly delineated.

Single subject exception language was updated to be consistent with LCCC's policy on SSEs.

Minor typographical errors were fixed throughout the protocol.

Updated Appendix B: Removing Week8 follow-up visits and assessments

Addition of Appendix D: Response assessment for cutaneous ALCL/Lymphomatoid papulosis in order to assess efficacy in these subjects who are eligible for the LCCC 1524-ATL protocol

Addition of Appendix E: Response assessment for mycoses fungiodes and Sezary syndrome in order to assess efficacy in these subjects who are eligible for the LCCC 1524-ATL protocol

Addition of Appendix F: CRS Toxicity Grading Scale and Management Guidelines

Addition of Appendix G: Neurotoxicity Treatment Algorithm

The attached version dated February 2, 2018 incorporates the above revisions

PROTOCOL AMENDMENT # 3

LCCC 1524-ATL: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

AMENDMENT INCORPORATES:
X Editorial, administrative changes
X Scientific changes (IRB approval)
Therapy changes (IRB approval)
Eligibility Changes (IRB approval)
Other

Summary of Changes

Subjects who experience disease progression after receiving a cell infusion(s) will still be required to complete abbreviated follow up procedures outlined in Appendix B (Section 11.2). Language added to sections 4.6 and 4.8 also clarify this point about abbreviated follow up requirements in subjects who experience disease progression.

Appendix C now describes patient reported outcome measures which will be collected via PROMIS Global Health and Physical Function and NCI PRO-CTCAE questionnaires.

Added Objective 2.2.4 and Endpoint 2.4.4 to clarify the inclusion of collection of Quality of life assessments as part of the study assessments

Added endpoint 2.4.3 to denote how persistence of T cells will be measured

The attached version dated November 10, 2016 incorporates the above revisions

PROTOCOL AMENDMENT # 2

LCCC 1524-ATL: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

AMENDMENT INCORPORATES:

X Editorial, administrative changes
X Scientific changes (IRB approval)
Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)
Other

Summary of Changes

Updated the list of Co-Investigators with the addition of Ashley Zanter, MSN, AOCNP; Megan Royall McElfresh, PA; Yara Park, MD; Christopher Dittus, DO, MPH; Natalie Grover, MD; Angela Spruill, MSN, ANP-BC, OCN; Alicia Pinto, MSN, ANP; Grace Park, PA

Minor administrative updates throughout the protocol.

Clarifying language has been added about the Study Sample Biobank Repository including storage location, storage time and storage purpose. Please refer to Section 6.7.

Clarifying language in regards to documentation of AEs or SARs. AEs and SARs collection shall begin at the time that the main study consent form is signed by the subject prior to ATLCAR.CD30 infusion. This collection should continue through the 6 week follow-up period after cellular treatment is discontinued. In addition, any AEs or SARs experienced by the subject related to the procurement procedure must also be documented. Please refer to Section 7.2.

Section 6.2.3 and the Time and Events Table footnotes #10 and #13 indicate that 10 mL of blood will be drawn at the 3-4 hour post-infusion time point. This amendment increases the amount of blood drawn to 16 mL (10 mL in a sodium heparin tube and 6 mL in an EDTA tube).

Inclusion Criterion 3.1.5 states that CD30+ disease is defined as ≥30% of the neoplastic cells stained as positive for CD30. This has been updated to indicate that CD30+ disease requires documented CD30 expression by immunohistochemistry based on the institutional hematopathology standard.

Inclusion Criterion 3.1.7 indicates that imaging results are required within 30 days prior to transplant. This protocol amendment clarifies that the results may be obtained at a time point greater than 30 days from transplant if obtained per the patient's standard of care and with prior sponsor approval.

Added Section 6.6 and Appendix B to describe the addition of patient reported outcome measures which will be collected via PROMIS Global Health and Physical Function and NCI PRO-CTCAE questionnaires. These assessments will be optional. Relevant sections of the protocol, including the time and events table and foot note #19 of the time and events table, were updated to note the inclusion of PRO assessments.

Section 4.1, Section 4.2 and footnote #6 of the time and events table of the protocol indicated that peripheral blood cells will be collected from consenting subjects who meet eligibility for cell procurement for creation of ATLCAR.CD30 cells prior to mobilization and collection of peripheral blood stem cells (PBSCs). This section was not meant to exclude patients who had previously had PBSCs collected and stored for their planned autologous stem cell transplant. Previously collected and stored PBSCs can be used as part of the autologous stem transplant therapy and blood may be procured for the creation of ATLCAR.CD30 cells any time prior to the autologous stem cell transplant even if PBSCs have already been collected and stored for transplant. These sections have been thus updated accordingly.

Section 4.2 (Cell Procurement) has been updated to indicate that a total of 300 mL of blood (in up to 3 collections) will be obtained for procurement.

Sample collection of ~1 mL of serum and ~10 mL of blood has been added in the event of cytokine release syndrome or severe toxicity (SAE resulting in hospitalization). Please refer to Section 6.5.5 and the time and events table footnote #16.

Clarified inclusion criterion prior to infusion of ATLCAR.CD30 cells to indicate that although ANC, platelet counts and Hg must be measured over 3-5 day time frames they do not need to be measured on each day of the timeframe. Instead they may be measured at the beginning and the end of the time frame.

The attached version dated October 3, 2016 incorporates the above revisions

PROTOCOL AMENDMENT # 1

LCCC 1524-ATL: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

AMENDMENT INCORPORATES:

X Editorial, administrative changes
X Scientific changes (IRB approval)
Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)
Other

Summary of Changes

Added names or corrected spelling of names of co-investigators and minor editorial changes.

Lugano Classification - Lymphoma Response Criteria provided in Appendix A to the protocol and the accompanying reference (#71) cited in Section 10 under References.

Changed eligibility criterion 3.1.2 to clarify that adults are ≥18 years of age and children eligible for enrollment are 3 to 17 years of age. Clarified language in exclusion criteria 3.2.1. and 3.2.2 to note requirement timings in relation to cell infusion

An annual physical exam will be required ONLY for the first 5 years of follow up

Children will not be allowed to enroll in a dose cohort until a minimum of 2 adult subjects are treated at that dose level and complete the follow-up for DLT .

Statistical Section 8.0 updated to include the stipulation that children are not allowed to enroll in a dose cohort until a minimum of 2 adult subjects are treated at that dose level and complete their follow-up for DLT.

Clarified that the D1/Week 3 visit will be optional. This is an optional visit that will occur if the condition of the subject is such that follow up on D1/Week 3 is considered medically necessary by the investigator. Added clinical labs to this assessment visit which can be performed as needed but are not required.

Changed DLT definition for ANC to >1,000/µl in Section 4.4.3

Modified the labs collected at each study visit to include collection of a complete metabolic panel

Added section 6.6 Biobank Repository that explains how the biological samples collected for the study will be handled and stored.

Changed platelet count in inclusion criterion 3.1.6 to 25,000 cells/mm3

The attached version dated April 29, 2016 incorporates the above revisions

LCCC1524-ATL

Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to chimeric antigen T cell receptor therapy are the confidential and proprietary information of Lineberger Comprehensive Cancer Center, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Lineberger Comprehensive Cancer Center.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Lineberger Comprehensive Cancer Center or specified designees. I will discuss the material with them to ensure that they are fully informed about ATLCAR.CD30 and the study.

Principal Investigator Name (printed) Signature

_____ _____

Date

_____

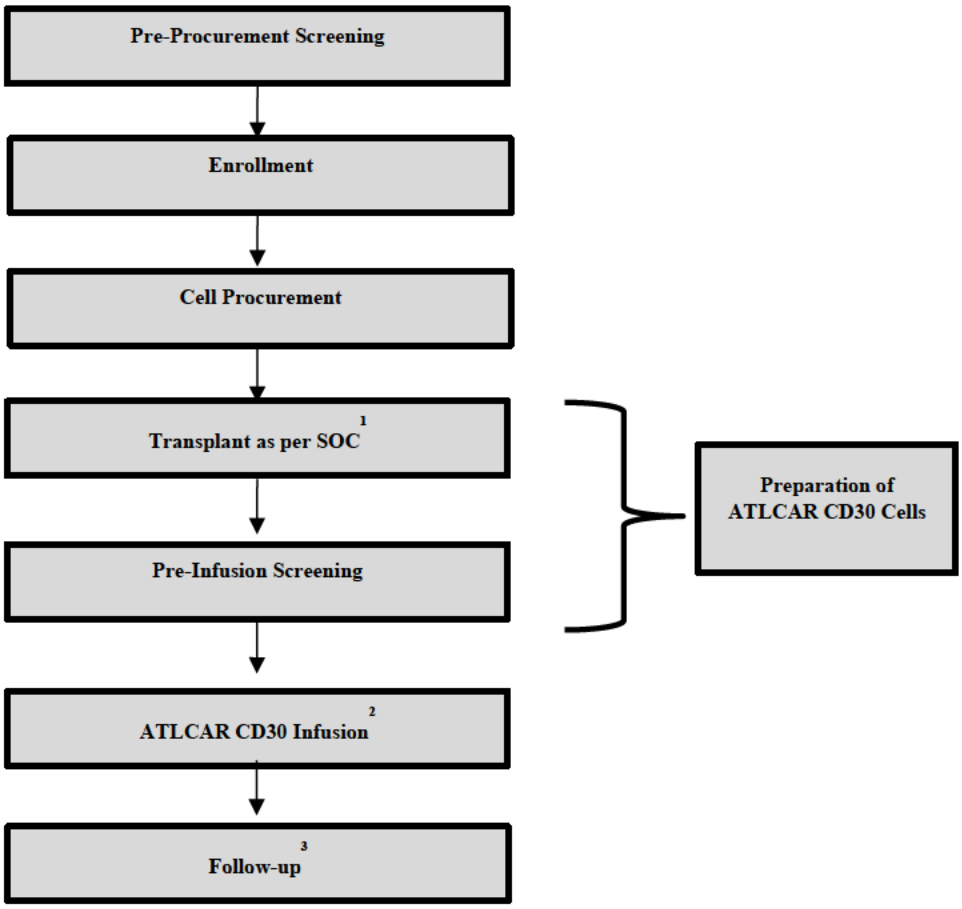
STUDY SUMMARY

Title:	Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Prevention of Relapse of CD30+ Lymphomas after High Dose Therapy and Autologous Stem Transplantation (ATLAS)
Rationale:	This open label, single-arm multicenter study is designed to identify the maximum tolerated dose (MTD) within 3 dose levels of autologous T lymphocyte chimeric antigen receptor cells (ATLCAR) targeted against the CD30 antigen (ATLCAR.CD30). the CD30 antigen is expressed on almost all Hodgkin lymphomas (HLs) at diagnosis and at relapse; and its viability as a target has been confirmed with the success of brentuximab vedotin [4], an antibody-drug conjugate that targets CD30. Brentuximab vedotin produces objective tumor responses in HL, albeit with limited durability and serious toxicities reported in 31% of subjects. The hope is that CD30-directed CAR-T therapy will provide durable responses and improve outcomes in adult and pediatric subjects with HL and other CD30+ lymphomas. Moreover, ALTCAR.CD30 therapy should reduce the risks of long-term complications that are associated with available therapies for HL, which is a special concern for pediatric subjects.
Target Population:	Adult and pediatric subjects with relapsed/refractory CD30+ peripheral T cell Hodgkin's and Non-Hodgkin's lymphoma
Number of Subjects:	40 subjects
Primary Objectives:	To determine the safety and tolerability and to estimate the MTD of ATLCAR.CD30 post ASCT in subjects with CD30+ lymphoma at high risk for relapse
Secondary Objectives:	To measure the survival of ATLCAR.CD30 in vivo To estimate PFS after infusion of ATLCAR.CD30 post ASCT in subjects with CD30+ lymphoma at high risk for relapse To determine the overall survival after infusion of ATLCAR.CD30 post ASCT in subjects with CD30+ lymphoma at high risk for relapse

Exploratory Objectives:	[redacted]
Study Design:	This study is a multicenter, Phase 1 clinical trial
Primary Endpoint:	Toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) and CRS toxicity will be graded according to the toxicity scale outlined in 18.8 (APPENDIX VII- CRS Toxicity Grading Scale and Management Guidelines). The MTD will be based on the rate of dose-limiting toxicity (DLT; see Sections 4.1.3.2 and 4.1.3.3).
Secondary Endpoints:	PFS is defined from day of ASCT to relapse (in subjects with a documented complete response after ASCT) or progression (in subjects with documented stable disease or partial response after ASCT), or death as a result of any cause as per the Revised Response Criteria for Malignant Lymphoma (see APPENDIX II- Revised Response Criteria for Lymphoma) [74].[5]. Overall survival will be measured from the date of administration of CAR.CD30 transduced ATL to date of death Persistence of CAR.CD30 T cells in vivo will be determined by quantitative PCR and flow cytometry in peripheral blood samples
Exploratory Endpoints:	[redacted]

STUDY SCHEMA

Figure 1 Study Schema



[1] SOC = standard of care.

[2] See dose levels table for doses to be administered within each cohort.

3 See Time & Events Table for schedule of blood draws post-infusion. Dose limiting toxicity (DLT) will be monitored for up to 6 weeks post infusion. Short-term follow-up will begin after the 6-week safety evaluation and continue for up to 1 year post infusion. See section 7.4 for schedule of long-term follow-up

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALCL	Anaplastic large cell lymphoma
ALK-1	Anaplastic lymphoma kinase 1
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
ASCT	Autologous stem cell transplant
AST	Aspartate Aminotransferase
ATL	Autologous T Lymphocytes
ATLCAR	Autologous T Lymphocyte – Chimeric Antigen Receptor
β-HCG	Beta-Human Chorionic Gonadotropin
BOR	Best Overall Response
BSA	Body surface area
BUN	Blood Urea Nitrogen
CAP	College of American Pathologists
CAR-T	Chimeric Antigen Receptor T Cell
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CLIA	Clinical Laboratory Improvement Amendments
CLL	Chronic lymphocytic leukemia

CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CoA	Certificate of Analysis
CTO	Clinical Trials Office
CR	Complete Response
CRM	Continual Reassessment Method
CRS	Cytokine Release Syndrome
CT	Computer Tomography
CTLs	Cytotoxic T-lymphocytes
DCR	Disease Control Rate
DL	Dose Level
DLBCL	Diffuse large B- cell lymphomas
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
EBV-CTL	Epstein-Barr Virus-Specific Cytotoxic T Lymphocytes
ECHO	Echocardiography
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
FDA	Food and Drug Administration
FL	Follicular lymphoma
GCP	Good Clinical Practice

g-CSF	Granulocyte-colony stimulating factor
HAMA	Human Anti-Mouse Antibodies
HER2	Human epidermal growth factor receptor 2
HL	Hodgkin's Lymphoma
HLA	Human leukocyte antigen
HLH	Hemophagocytic lymphohistiocytosis
LDH	Lactate dehydrogenase
LMP-1	Latent membrane protein (LMP-)
mAB	Monoclonal antibodies
MAS	Macrophage activation syndrome
MTD	Maximum tolerated dose
MHC	Major histocompatibility complex
NHL	Non-Hodgkin's Lymphoma
ORR	Overall response rate
PBMCs	Peripheral blood mononuclear cells
PFS	Progression-free survival
PT	Prothrombin time
PTCL	Peripheral T-cell lymphoma
Q-PCR	Quantitative polymerase chain reaction
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCR	Replication competent retrovirus
SAE	Serious Adverse Event
SCT	Stem cell transplant

TNF	Tumor necrosis factor
TNF-R	Tumor necrosis factor receptor
TRAIL	TNF-α-related apoptosis-inducing ligand
WOCBP	Women of childbearing potential

1.0 INTRODUCTION AND RATIONALE

1.1 Study Synopsis

This open label, single-arm multicenter study is designed to identify the maximum tolerated dose (MTD) within 3 dose levels of autologous T lymphocyte chimeric antigen receptor cells (ATLCAR) targeted against the CD30 antigen (ATLCAR.CD30). This phase I design uses the continual reassessment method (CRM), a Bayesian adaptive method for estimating the MTD. Subjects with CD30+ lymphoma at high risk of relapse will receive one infusion of ATLCAR.CD30 after undergoing an autologous stem cell transplant (ASCT) for treatment of recurrent disease. The study will enroll up to a maximum of 18 subjects. Secondary endpoints include evaluation of persistence of ATLCAR.CD30 cells in vivo, and progression free survival (PFS). Study participants may be given the option to complete patient reported outcomes (PRO) questionnaires during the study.

LCCC1524-ATL builds on the prior clinical trial experience of UNC investigators Drs. Dotti and Savoldo during their time at Baylor College of Medicine in Houston Texas. Reference in this protocol to their previous related trial experience is referring to work done at Baylor College of Medicine Cell and Gene Therapy Program (BCM-CAGT).

1.2 Hodgkin's Lymphoma (HL) Overview

HL, a malignant neoplasm of immature B cell origin, has an incidence of about 2.4 per 100,000 per year [6]. Modern radiotherapy and/or chemotherapy regimens have dramatically improved the cure rate of subjects with HL. However, despite the identification of clinical prognostic factors, and the optimal use of primary and secondary treatments, HL remains fatal for more than 15% of subjects [6]. Even in subjects who are cured, the morbidity of therapy is substantial and long lasting. New therapeutic agents are required therefore not only to further reduce mortality but also to alleviate morbidity [7].

The commonly accepted standard of care for HL that has relapsed after initial treatment with standard chemotherapy is high dose chemotherapy followed by ASCT. While this approach is thought to provide better disease free survival than conventional second line chemotherapy alone, the relapse rate is over 40% [8]. Therefore, strategies to improve outcomes are needed, in particular for subjects at higher risk of relapse (i.e., subjects: with failure to achieve complete response post initial treatment **OR**; who relapse within 12 months of initial complete response **OR** with extranodal involvement at time of pre-transplant salvage therapy) [4]..

In about 40% of cases of HL, tumor cells express viral latency proteins of Epstein Barr Virus (EBV) such as LMP-1 and 2 [9]. However, the great majority of HL does not

express viral proteins, while they almost invariably express the CD30 protein [10]. CD30 expression is routinely used for the diagnosis of HL.

1.3 CD30+ Non-Hodgkin's Lymphoma (NHL) Overview

Other types of lymphoma also express the CD30 antigen. Anaplastic large cell lymphoma (ALCL) is a subtype of peripheral T-cell lymphoma (PTCL) first described in 1985. ALCL represents a distinct category of large cell lymphomas defined by a strong expression of CD30 on all or most neoplastic cells [11]. It represents <5% of all cases of NHL [12]. Three subtypes of ALCL exist including systemic (s) ALK-1 positive ALCL, ALK-1 negative, and primary cutaneous ALCL. The majority of subjects present in an advanced stage, and CHOP chemotherapy represents the most commonly used front-line regimen. Unfortunately, particularly for the ALK-1 negative and primary cutaneous ALCL, outcomes are poor. Treatment with conventional dose chemotherapy following relapse is often not curative. High dose chemo-radiotherapy followed by hematopoietic stem cell transplantation, however, may represent an effective therapy in these subjects [12, 13]

CD30+ lymphoproliferative disorders (LPD) of the skin (CD30+ LPD) represent a well-defined spectrum of primary cutaneous T-cell lymphomas that have been recognized as distinct entities in recent lymphoma classifications [14]. Lympho-matoid papulosis and ALCL share the expression of CD30 antigen as a common phenotypic hallmark but differ in regard to their clinical and histological features as well as their biologic behavior [14].

CD30+ B-cell lymphomas have been observed and they are most commonly diffuse large B-cell lymphomas (DLBCL). In addition, occasional to numerous CD30+ B cells have been described in sporadic cases of follicular lymphoma (FL), resembling the pattern seen in reactive tonsils and lymph nodes [10].

CD30 may be present on activated B or T cells, but not resting mature or precursor B or T cells. Benign reactive CD30+ cells tend to be large, immunoblastic-appearing cells located at the periphery of germinal centers [10].

1.4 CD30 as a Target Antigen

CD30 is a transmembrane glycoprotein and is a member of the tumor necrosis factor receptor superfamily [10]. CD30 plays a role in regulating the function or proliferation of normal lymphoid cells. Members of the tumor necrosis factor (TNF)/TNF-receptor (TNF-R) superfamily coordinate the immune response at multiple levels. For example, TNF, LTα, LTβ and RANKL provide signals required for lymphoid neogenesis; CD27, OX-40, 4-1BB and CD30 deliver costimulatory signals to augment immune responses, while pro-apoptotic members such as TNF, CD95L and TRAIL may contribute to the

termination of the response [10]. CD30 plays a role in regulating the function or proliferation of normal lymphoid cells. Ki-1 (CD30) antigen expression has been used to identify ALCL and Reed-Sternberg (RS) cells in Hodgkin's disease [10]. Indeed, CD30 is expressed on virtually all Hodgkin's RS cells, and is therefore a target for both antibody based immunotherapy and cellular therapies in almost all subjects with HL and in a proportion of those with NHL [10].

Initial approaches used an anti-CD30 mAb without a payload in the treatment of subjects with Hodgkin's lymphoma. While this approach was reasonably well tolerated, the overall response rate and durability of those responses was quite poor [15, 16]. As a result a CD30 monoclonal antibody (MAb) drug conjugate, brentuximab vedotin (anti-CD30 mAb linked to monomethyl auristatin E) was generated. This drug conjugate is FDA approved for use in subjects with HL after failure of ASCT or in those who are not candidates for ASCT after failing at least two prior chemotherapy regimens, and in subjects with systemic ALCL who have failed at least one prior regimen. FDA granted accelerated approval for these indications in 2011 based on the rate of overall response reported in separate single arm phase II trials (n=102 in the HL trial; 75% overall response rate (ORR) and 34% complete remission (CR), and n=58 in the systemic ALCL trial; 86% ORR, 57% CR). In this latter study, duration of overall response was 12.6 months, and duration of CR 13.2 months [17]. Long-term data from the HL trial (after median of ~3 years), published in July 2015, reported a median overall survival of 40.5 months and PFS of 9.3 months [18].

While these data are promising, and support CD30 as a target for treatment, toxicity associated with brentixumab vedotin is not insignificant (see brentuximab vedotin (Adcetris®) prescribing information November 2014) and substantially due to toxicity mediated by the chemotherapic moiety, monomethyl auristatin E. Across both trials, the most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting. Serious adverse reactions, regardless of causality, were reported in 31% of subjects. The most common serious adverse reactions experienced by subjects with HL included peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%). The most common serious adverse reactions experienced by subjects with systemic ALCL were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection. Other important serious adverse reactions reported include progressive multifocal leukoencephalopathy (PML), Stevens-Johnson syndrome, and tumor lysis syndrome. Infusion related reactions including anaphylaxis have occurred with brentuximab vedotin.

Based on these data, prescribing information for brentuximab vedotin include warnings and precautions on peripheral neuropathy, anaphylaxis and infusion reactions,

hematologic toxicities, serious and opportunistic infections, tumor lysis syndrome, hepatotoxicity, pulmonary toxicity, serious dermatologic reactions and embryofetal toxicity. In addition, the prescribing information includes a black box warning for PML.

Brentuximab vedotin has also been evaluated for use as consolidation therapy post ASCT in HL subjects at high risk of relapse in a randomized (1:1) placebo controlled phase 3 trial (n=329) [4]. The toxicity profile of brentuximab vedotin was similar to that reported in the earlier trial; 67% of subjects in the brentuximab vedotin arm experienced peripheral neuropathy (13% experienced grade 3 peripheral neuropathy). Brentuximab vedotin significantly improved median PFS as compared to placebo (42.9 months versus 24.1 months). FDA approval for this indication was recently granted.

Data from brentuximab vedotin trials support CD30 as a therapeutically relevant target for the treatment of CD30+ lymphoma, although toxicities associated with its use are of concern. Studies evaluating alternative ways to target CD30 that may lead to options with reduced toxicity and improved efficacy are warranted.

1.5 Chimeric Antigen Receptor (CAR) Redirected T (CAR-T) Cells

Since HL and NHL are both apparently sensitive to the cellular immune response (graft versus lymphoma effect) and antibody treatment, there is interest in combining both approaches through the generation of artificial CARs. Chimeric receptors are usually generated by joining the heavy and light chain variable regions of a MAb with a linker to form a single-chain Fv (scFv) molecule [19]. This scFv is then attached to the transmembrane and cytoplasmic portion of T Cell Receptors (TCR) ζ chain via a flexible hinge region. Engagement of the extracellular scFv of the chimeric receptor results in tyrosine phosphorylation of immune-receptor activation motifs present in the cytoplasmic domain, initiating T cell signaling to the nucleus. Human T lymphocytes genetically engineered to express these recombinant receptor genes have exhibited specific lysis via the perforin/granzyme pathways, as well as cytokine secretion upon exposure to tumor cells expressing the cognate target antigen [19]. The advantages of CARs over the native antibodies or ligands from which they derive are a consequence of their physical association with effector T cells [19-21]. Thus, CAR-T cells can have an active biodistribution, with migration through multiple tissue planes along chemokine gradients, and can recruit the multiple cytotoxic effector mechanisms available to a T cell, rather than the more restricted cytotoxic machinery associated with, for example, the Fc component of an antibody. CARs also offer advantages over transfer of native αβTCRs of T lymphocytes. Target cell recognition by αβTCRs is MHC restricted, precluding the design of a “universal” receptor for the treatment of subjects with different HLA polymorphisms. By contrast, CARs, like MAbs, are essentially universal as their cytotoxic activity is MHC- unrestricted [20]. Moreover, many tumors down-regulate expression of MHC molecules and/or have dysfunctional antigen processing machinery, so that the target antigenic epitopes for αβTCR are

simply not present. Since CAR-modified T cells bind directly to native proteins expressed on the surface of target cells without the need for antigen processing or MHC- restricted presentation, they are unaffected by this immune evasion strategy. Moreover, CARs can recognize non-protein antigens, unlike conventional αβTCRs [21].

1.5.1 Extending the Survival of CAR-T Cells

Despite consistent and robust expression of CAR molecules in T cells, early clinical studies of the approach were disappointing. A major problem of CAR-T cells is their lack of expansion and persistence *in vivo* [21]. A number of factors likely contribute to these differences but a major contribution is the inability of CAR-engagement alone to recapitulate the co-stimulatory events that follow the physiologic engagement of the native αβTCR. Full activation and proliferation of T cells requires not only TCR engagement (first signal) but also co-stimulation provided by antigen presenting cells (APCs, second signal) and cytokines (third signal) [21, 22]. A multiplicity of these costimulatory receptor-ligand and cytokine signals is required, in an optimal temporal and spatial sequence. CAR-T cells lack any such costimulation when they engage tumor cells, since these target cells are deficient in costimulatory molecule expression (e.g. CD8 0 and CD86) and do not release helper cytokines. CAR-T cells cannot receive activation through stimulation provided by professional APCs in secondary lymphoid organs since the native receptors on CAR-T cells are not specifically directed towards antigens on the hosts' APCs. To compensate for the lack of costimulation following CAR engagement [21, 22], costimulatory signaling domains (CD28, OX40, 4-1BB, etc.) have been incorporated as part of the CAR itself. Studies using polyclonally activated T lymphocytes expressing these novel "second generation" CARs are currently open at several institutions [23-32].

At the Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX, Dr. Savoldo and Dr. Dotti were Principal Investigators (PIs) on a clinical study in which subjects with CD19+ B-cell lymphomas were infused simultaneously with two autologous T-cell products [26]. Each product contained cells expressing the identical CAR exodomain specific for the CD19 antigen (CD19-specific scFv) present on many B-cell derived malignancies. In one product the CAR was coupled to the ζ endodomain (first generation) while in the second product the CAR was coupled to the CD28 and ζ endodomains (second generation). With this study design, each subject acted as "a self-control", allowing us to directly discover, even in a small study with heterogeneous subjects, the consequences of incorporating a co-stimulatory endodomain on the fate of engineered T cells *in vivo*. Six subjects with B-cell lymphomas relapsed after multiple cycles of therapy using conventional treatments were enrolled into the study. For each subject, two T-cell products expressing either CAR.CD19ζ (first generation) or CAR.CD19-28ζ (second

generation) were generated. Both cell products were similar by functional and phenotypic analyses. Two subjects for each dose level ($2x10^7$, $1x10^8$ and $2x10^8$ cells/m^2 dose level 1, 2 and 3, respectively) were infused with both sets of CAR.CD19 modified T cells. Infusions were well tolerated without any immediate side effects. Expansion and persistence of CAR-T cells *in vivo* were assessed in the peripheral blood by quantitative PCR (Q-PCR) assays specific for CAR.19ζ and CAR.19-28ζ transgenes, respectively. Molecular signals for CAR.19-28ζ^+ T cells increased from 3 hours after infusion to 1-2 weeks post infusion (representing a 2 to 59 fold expansion). Molecular signals then declined by 6 weeks follow up and did not further expand *in vivo*. By contrast, molecular signals derived from CAR.19ζ^+ T cells that were detected 3 hours after infusion did not show significant expansion thereafter (from 0 to 1 fold expansion), and had become almost undetectable by 6 weeks. These data indicate that the infusion of second generation CD19- specific CAR-T cells is safe at the doses so far tested and that CD28 does indeed provide a co-stimulatory signal *in vivo* in subjects with B-cell lymphoma [26].

1.5.2 Clinical Experience with CAR-T Cells

As of July 2018, there are over 250 clinical trials incorporating CAR-T cells registered as being open in clinicaltrials.gov, across all malignances. In April 2014, a review of CAR-T cell trials in hematologic malignancies was published, and included a summary of 12 published and 35 ongoing trials (including 3 targeting CD30). The majority of published and ongoing trials summarized in this review utilized CAR-T targeting CD19. Doses were expressed per m^2 or per kg, with doses/m^2 ranging in trials from $1.5 x10^7$ to $3.3 x10^9/m^2$ [33-35]. Overall, as reported in the published trials, treatment with CAR-T cells was very well tolerated, and evidence of clinical benefits observed [36].

Toxicities Associated with CAR-T Cells

Potential toxicities may be categorized as those related to infusion of T-cells; transduction; cross-reactivity with normal tissues; cytokine release syndrome (CRS); neurotoxicity; macrophage activation syndrome (MAS) and tumor lysis syndrome.

Infusion of T Cells

Regarding infusion of T cells, in this study we will be administering transduced autologous peripheral blood ATL so there will no risk of alloreactivity. Many previous studies have infused much larger numbers of autologous T cells that have been activated *ex vivo* with no adverse effects [37, 38].

Retroviral Transduction

Retroviral transduction, discussed in more detail in section 8.3, results in new random integrations in host cell DNA, which rarely may cause abnormal or uncontrolled proliferation [39]. This effect is much more common with replication-competent retrovirus (RCR) where each cell receives multiple integrants [40]. We will test the producer line and all batches of supernatant with biological assays of RCR to exclude this possibility.

Cross-Reactivity with Normal Tissues

In terms of cross-reactivity (also described in more detail in Section 8.3), we chose to target CD30 since this antigen is only expressed on cells of hematopoietic origin. It is not detected on cells of the peripheral blood or on resting lymphocytes, but it is only present on a subpopulation of physiologically activated T-cells and on thymic medulla[10]. The CD30 knock out mouse shows impaired thymic negative selection of T lymphocytes but this does not compromise the development of efficient immune responses[41]. We previously showed that CAR.CD30-redirected T-cells did not impair the generation of virus specific cytotoxic T-lymphocytes (CTLs) ex vivo[42] and CD30 is not expressed in normal tissues like lung and fibroblasts (RAC#1003-1034).

CRS/Tumor Lysis Syndrome

CRS is a potential major side effect of CAR-T cell therapy and results from the release of inflammatory cytokines secondary to T-cell activation. The severity of CRS may be related to tumor burden, particularly for therapy involving CAR-T cells [36, 43]. CRS may correlate with anticancer activity (although whether the severity correlates as well is an outstanding question), and CRS is often accompanied by high levels of IL-6 [36]. Symptoms of CRS vary greatly, and may

include (but are not limited to) fever, rash, hypoxemia, delirium, hypotension, nausea and diarrhea [43]. When associated with CAR-T therapy, symptom onset can occur days to weeks after the infusion, perhaps associated with maximal in vivo expansion of T cells. Very high doses of T cells may result in early more severe reactions, although a clear dose response relationship has not yet been defined [43]. Strategies to minimize this syndrome include lowering the dose of CAR T cells and treatment with an anti-IL6 receptor antibody, or in severe cases, corticosteroids.

SAEs resulting from CRS have been reported in subjects receiving CAR-based T cell therapies [44, 45]. Morgan and colleagues at the NIH reported a subject with widely metastatic colon cancer who received over 10^{10} T cells modified with a CAR targeting HER2 containing two costimulatory moieties (CD28 and 4-1BB) after intensive lymphodepletion. This subject developed pulmonary toxicity within 15 minutes in association with very high cytokine levels followed by cardiac arrest and death 4 days later [45]. After extensive investigation and analysis of autopsy specimens the investigators concluded that the toxicity may have been due to effects of the transgene on pulmonary endothelium. This protocol is very different from the current study in that (1) a much higher dose of T cells was given, (2) the target was HER-2/neu which has different tissue expression than CD30, and (3) the construct contained two costimulatory domains.

Brentjens and colleagues from Memorial Sloan Kettering Cancer Center reported a subject with bulky CLL and extensive previous treatment who received autologous T cells transduced with a CD19-28ζ CAR in a dose of 3 x 10^7/kg after lymphodepletion with cyclophosphamide [44]. This subject developed fever, hypotension and dyspnea 6 hours post infusion that rapidly progressed. In this subject elevated cytokine levels were also seen and an autopsy failed to reveal an obvious cause of death. The investigators concluded that sepsis was the most likely cause in this heavily pre-treated immunosuppressed subject but could not exclude the possibility that a cyclophosphamide induced “cytokine storm” may have enhanced modified T cell *in vivo* activation, and led to tumor lysis syndrome.

Investigators at the CAGT program at Baylor have given T cells expressing CD19-specific CAR with or without CD28 co-stimulatory endodomain to 12 subjects with B-cell malignancies ($2x10^7$ cells/m^2, $1x10^8$ cells/m^2 or $2x10^8$ cells/m^2) and T cells expressing Kappa-Light-Chain -specific CAR with CD28 co-stimulatory endodomain to 16 subjects with B-cell malignancies or Multiple Myeloma ($2x10^7$ cells/m^2, $1x10^8$ cells/m^2 or $2x10^8$ cells/m^2) with no adverse effects [26] [46]. In addition, Dr. Dotti and Dr. Savoldo have recently completed a phase I trial of CAR.CD30 in relapsed/refractory CD30+ lymphoma, described in section 1.5.5, and did not observe any CRS or other toxicities.

Neurotoxicity

Neurotoxicity from CAR-T cell therapy can occur as part of cytokine release syndrome or as an independent process. The underlying pathophysiology for neurologic toxicity from CAR-T therapy is not fully understood. CAR-T cells in the central nervous system (CNS) may play a role. However, the heightened systemic inflammatory and cytokine state resulting from CAR-T therapy may also be a factor.

The symptoms and manifestations of neurotoxicity are broad and range from confusion/altered mental status to seizure to cerebral edema. Routine monitoring is critical in patients receiving CAR-T therapy to identify neurologic symptoms early and neurology should be consulted for any subjects who exhibit early signs/symptoms of neurotoxicity. Early interventions should be employed to prevent worsening, especially if therapies are already indicated such as corticosteroids.

Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) has been found previously in patients with acute lymphoblastic leukemia receiving CAR T cell therapy. MAS is characterized by pancytopenia, liver insufficiency, coagulopathy and neurological symptoms and is thought to be mediated by uncontrolled proliferation and activation of T cells leading to macrophage activation and differentiation and cytokine production with hemophagocytosis. The pathophysiology of MAS is complex, but appears to have some similarities to hemophagocytic lymphohistiocytosis (HLH). Correlative evaluations have shown that hepatic biopsy samples in patients with hemophagocytic lymphohistiocytosis including a subgroup with macrophage activation syndrome demonstrated the presence of CD8+ T cells generating IFN- γ with macrophages generating IL-6 and TNF. There was overproduction of IL-18, which may play a role in the polarization of T cells.

Diagnosis of macrophage activation syndrome is based on pancytopenia, fever, elevated AST, ALT, triglycerides and LDH, increased prothrombin time (PT) and activated partial thromboplastin time (aPTT) associated with increased number of fibrin split products and decreased fibrinogen. Additionally, splenomegaly, hepatomegaly and CNS dysfunction characterized by lethargy, irritability, disorientation, headache, seizures and coma can be found.

1.5.3 Rationale for ATLCAR.CD30 in Pediatric Subjects with CD30+ Lymphoma

HL occurs in both children and adults; the American Cancer Society projects that 8,500 new cases of HL will be diagnosed in the US in 2016 (3,710 in females and 4,790 in males). HL is a common malignancy in young adults [47] (ages 15 to 40),

peaking in incidence in persons in their 20s [http://www.cancer.org/cancer/hodgkindisease/detailedguide/hodgkin-disease-key-statistics]. Although rare in children less than 5 years of age, approximately 10-15% of HL cases are diagnosed in children and teenagers. The long term impact of therapy for HL on quality of life is of special concern given that this disease often impacts a much younger cohort of subjects than the typical malignancy. Thus, treatment of HL requires a careful balance between providing effective therapy to cure the disease while minimizing the toxic effect of therapy that could result in excessive long-term treatment-related complications [47].

Although approximately 90% of limited stage HL subjects are projected to be cured with standard of care therapy (i.e., multi-agent chemotherapy ± radiation), many do not live their expected life span due to delayed treatment–related toxicities that include secondary malignancies and cardiovascular disease [48, 49]. For example, the preferred treatment option for early stage I or II non-bulky HL with favorable prognosis is the use of chemotherapy (e.g., doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVD) with or without involved-field radiation therapy [50-52]. In a recent retrospective study, survivors of HL treated with chemotherapy alone had a lower incidence of secondary malignancies with a 30-year cumulative incidence of 5.8%, compared to 24.7% in HL subjects who received consolidative radiation [53]. Given the unclear overall survival advantage, and the long-term toxicities associated with consolidative radiation, the use of this modality remains controversial in the treatment of HL. In addition, both an increased dose of radiation and anthracycline exposure were associated with significantly increased risk of cardiovascular complications [54]. While the use of interim PET/CT to guide treatment of limited stage disease can identify subjects who need less intensive therapy, treatment for those with high-risk disease is more intensive and acute, and long-term complications of therapy remain a concern. Furthermore, salvage chemotherapy for subjects who relapse includes high-dose chemotherapy followed by a stem cell transplant [52]. While effective, the intensity of this approach also leads to long-term treatment-related comorbidities such as secondary acute myeloid leukemia and myelodysplastic syndrome [55, 56]. Although the two leading causes of death in HL survivors are second malignancies and cardiovascular disease, other key late complications include atherosclerotic disease, pulmonary disease, and endocrine dysfunction such as hypothyroidism and infertility [57].

In addition to the risks associated with therapies for HL, current thinking is that the success of traditional chemotherapy and radiation-based strategies for the treatment of pediatric malignancies has reached a plateau, especially in subjects with relapsing or refractory disease [58]. The additive toxicities and limited efficacy of conventional regimens in achieving a cure has led to Phase I studies in pediatric cancers of immune-based or molecularly targeted therapies to prevent relapse or treat minimal disease.

As noted in section 1.5.2, of the over 250 trials incorporating CAR-T cells registered on the https://clinicaltrials.gov/ website, there are currently at least 30 studies that have allowed for pediatric enrollment with the majority of these trials being conducted in CD19+ hematologic malignancies [36, 58]; moreover, these approaches are showing promise. For example, a CD19-directed CAR therapy study conducted at the Children's Hospital of Philadelphia reported outcomes in 25 children with ALL, the majority of whom had received prior SCT [31]. Complete remissions were achieved in up to 90% of these subjects, which included 2 children previously treated with blinatumomab. In addition, event-free and overall survival at 6 months in these subjects were 67% and 78%, respectively and durable remissions of up to 24 months have been observed. Other CD19 CARs studies enrolling pediatric subjects are also reporting promising outcomes in ALL with manageable toxicity [28, 59]. Moreover, CARs are in development targeting other lymphoid and myeloid antigens such as CD13, CD20, CD30 and CD33 [58]. Clinical trials targeting these antigens are currently ongoing, with promising preliminary data reported for ATLCAR.CD30 therapy in relapsed/refractory CD30+ lymphomas as discussed in the next section.

As noted in section 1.4 above, the CD30 antigen is expressed on almost all HLs at diagnosis and at relapse; and its viability as a target has been confirmed with the success of brentuximab vedotin [4], an antibody-drug conjugate that targets CD30. Brentuximab vedotin produces objective tumor responses in HL, albeit with limited durability and serious toxicities reported in 31% of subjects. The hope is that CD30-directed CAR-T therapy, which appears safe thus far (see section 1.5.5), will provide durable responses and improve outcomes in adult and pediatric subjects with HL and other CD30+ lymphomas. Moreover, ALTCAR.CD30 therapy should reduce the risks of long-term complications that are associated with available therapies for HL, which is a special concern for pediatric subjects.

1.5.4 ATLCAR.CD30

After constructing a CAR targeting CD30 [60, 61], Drs. Savoldo and Dotti demonstrated in preclinical studies that T-lymphocytes engineered to express this receptor are redirected to kill CD30+ HL cell lines [42, 62].

The success rate for manufacturing of cells is 100%. At Baylor College of Medicine, cell lines have been manufactured for 18 subjects starting from a median of 2.4×10^7 PBMCs (range 3.6×10^6 to 4.9×10^7). During cell manufacture, 3 subjects became ineligible due to rapid worsening of their performance status and 1 subject was not infused because his tumor was subsequently shown to be CD30-negative. One subject was still in remission and without evidence of disease post SCT and 1 subject went on to another phase I study. At the time of protocol submission, 3 subjects were awaiting assessment of eligibility for ATLCAR.CD30 treatment. We

therefore consider the number of subjects accrued but unable to receive ATLCAR.CD30 cells as limited. Subjects who did not receive treatment were ineligible to receive cells post SCT for clinical or other reasons. No subjects were unable to receive ATLCAR.CD30 treatment due to issues related to manufacturing failure.

1.5.5 Phase I Trial of ATLCAR.CD30 for Relapsed/Refractory CD30+ Lymphoma

At Baylor Drs. Savoldo and Dotti recently completed dose escalation in a phase I trial designed to determine if ATLCAR.CD30 was safe for therapy of CD30+ HL and CD30+ NHL and would persist in these subjects long enough to potentially control disease.

ATLCAR.CD30 were given to 9 subjects (7 with HL and 2 with CD30 + ALCL) with relapsed/refractory HL or CD30+ NHL. Eight of the 9 subjects had relapsed or progressed after treatment with brentuximab vedotin. Two were treated on dose level (DL) 1 (2×10^7 CAR-T/m^2), two on DL2 (1×10^8) and five on DL3 (2×10^8), without any conditioning regimen before T cell infusion, as mandated by FDA to exclude occurrence of "on target-off tumor" toxicities. CAR-T cell infusions produced no attributable adverse events, and none of the subjects developed a CRS. Nine subjects were evaluable for antitumor responses. At 6 weeks after treatment, 4 subjects had stable disease, 1 had PR and 1 had a CR, while 3 subjects (1 of whom with ALCL) had disease progression [63].

After establishing the safety and persistence of ATLCAR.CD30 in the non-transplant setting, LCCC1524-ATL is designed to determine if these cells are safe for consolidation therapy following autologous transplant and will persist in subjects with CD30+ HL or NHL long enough to potentially control or prevent disease after high dose therapy and ASCT.

1.6 Study Design and Rationale

ASCT may be the only curative option for subjects with refractory/relapsed hematological malignancies. Despite ASCT, disease recurrence remains the major cause of treatment failure. Hence development of non-toxic consolidation treatments after transplant remains a highly desirable objective, and the adoptive transfer of CTLs is one promising approach [64-67].

In this Phase I multicenter study, peripheral blood will be collected for production of ATLCAR.CD30 cells in subjects with $CD30^+$ lymphoma at high risk of relapse post-transplant, and scheduled to undergo ASCT. Three dose levels will be evaluated to identify the MTD in this population: Level 1 = 2×10^7 CAR^+ T cells/m^2; Level 2 = 1×10^8/m^2; Level 3 = 2×10^8/m^2. The total number of cells infused will be calculated on the number of CAR-T cells as requested by the FDA. Similar to the prior phase I

summarized in section 1.5.5, we will monitor the persistence of these infused cells in the peripheral blood of the subjects and whenever lymph nodes are biopsied as per routine clinical care during the first year after treatment at the tumor site by measuring the level of the transgene by both phenotypic and molecular analyses. Currently, we can regularly detect a single transduced cell in 50,000 peripheral blood mononuclear cells by real-time PCR amplification. Moreover, because gene persistence and expression may not correlate with antitumor effector function, we will also determine the functionality of the peripheral blood T cells *ex vivo*.

Ex vivo expanded, polyclonally activated T cells have been infused as early as two days after stem cell transplant in myeloma subjects without significant side effects [68]. However, since the study we propose will be the "first in man" application of ATLCAR.CD30^{+} T cells after ASCT, we will infuse these cells after ASCT once hematologic recovery is evident (see section 4.1.2 for this definition). By using this conservative approach, we believe we will be able to infuse T cells in an environment in which homeostatic mechanisms favor lymphoid expansion [69] without interfering with stem cell engraftment. It is now evident that non-myeloablative conditioning is required to allow high level expansion of CAR-T cells and obtain optimal anti-tumor efficacy [70, 71]. ASCT creates a lymphodepleted environment, with production of high levels of homeostatic cytokines such as IL-7 and IL-15 that induce expansion of the infused CAR-T cells in the absence of competing endogenous lymphoid cells for the homeostatic cytokines [69].

The ability to combine CAR-based therapies with ASCT will reduce tumor immune evasion of this cell therapy. Tumor cells use several mechanisms to evade immune responses, by generating hostile chemokine and cytokine milieus or by recruiting inhibitory cells such as Tregs and Th2 cells. This may limit the benefits of CAR-based therapies [72]. ASCT depletes Tregs and disrupts the tumor microenvironment improving the prospects for CAR^{+} T cell persistence, expansion and anti-tumor activity. HL and ALCL in particular will provide a useful model for studying this postulate since HL and ALCL cells release inhibitory molecules and ligands (TGFβ, IL-10, Fas-L) and attract suppressive T-cell subsets including Th2 and Tregs [73, 74].

As outlined above, toxicities and even deaths [45, 69] due to "tumor lysis syndrome" and "cytokine storms" have occurred in subjects with high tumor burden when they received CAR-T cells. This is likely the result of rapid and massive T-cell activation through their CAR/costimulatory molecule complex followed by the release of cytokines (IFNγ, TNFα, IL-6 etc.). These potentially lethal toxicities should be limited if CAR- T cells are infused after ASCT, since the burden of targeted tumor will be minimized. [44, 45]. We will collect serum before and after infusion for cytokine monitoring, and continue to monitor subjects for 4 hours after infusion.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To determine the safety and tolerability and to estimate the MTD of ATLCAR.CD30 post ASCT in subjects with CD30+ lymphoma at high risk for relapse.

2.2 Secondary

2.2.1 To measure the survival of ATLCAR.CD30 in vivo

2.2.2 To estimate PFS after infusion of ATLCAR.CD30 post ASCT in subjects with CD30+ lymphoma at high risk for relapse

2.2.3 To determine the overall survival after infusion of ATLCAR.CD30 post ASCT in subjects with CD30+ lymphoma at high risk for relapse

2.3 Exploratory

2.3.1 [redacted]

3.0 STUDY ENDPOINTS

3.1 Primary

3.1.1 Toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) and CRS toxicity will be graded according to the toxicity scale outlined in 18.8 (APPENDIX VII- CRS Toxicity Grading Scale and Management Guidelines). The MTD will be based on the rate of dose-limiting toxicity (DLT; see Sections 4.1.3.2 and 4.1.3.3).

3.2 Secondary

3.2.1 PFS is defined from day of ASCT to relapse (in subjects with a documented complete response after ASCT) or progression (in subjects with documented stable disease or partial response after ASCT), or death as a result of any cause as per the Revised Response Criteria for Malignant Lymphoma (see APPENDIX II- Revised Response Criteria for Lymphoma) [74].

3.2.2 Overall survival will be measured from the date of administration of CAR.CD30 transduced ATL to date of death.

3.2.3 Persistence of CAR.CD30 T cells in vivo will be determined by quantitative PCR and flow cytometry in peripheral blood samples.

3.3 Exploratory

3.3.1 [redacted]

3.3.2 [redacted]

4.0 **STUDY PLAN**

This study is a multicenter, open-label phase I clinical trial testing the hypothesis that the administration of ATLCAR.CD30 to subjects with CD30+ lymphoma post autologous transplant is safe as evidenced by the rate of DLT. The rate of DLT will be used to determine the MTD; see section 4.1.3.2**.** Three dose levels of ATLCAR.CD30 will be evaluated to determine a recommended dose in adult and pediatric subjects. Initially, only adults will be enrolled during the dose escalation phase of the study. Once a dose level has been tested in at least 2 adults without the occurrence of DLTs during the assessment period, children may then be enrolled on that dose level according to the CRM. Each subject will receive one injection followed by close monitoring over the subsequent 6 weeks. See section 7.4 for schedule of longer term follow-up.

Subjects scheduled to undergo an ASCT at one of the protocol sites for treatment of lymphoma will be approached for consent to screening and potential enrollment into LCCC1524-ATL. Peripheral blood cells will be collected from consenting subjects who meet eligibility for cell procurement for creation of ATLCAR.CD30 cells (see section 4.1.1) prior to ASCT. The ASCT, including mobilization and collection of PBSCs, administration of myeloablative therapy, reinfusion of PBSCs and supportive care following transplant will be as per routine standard of care, and not expected to be impacted by enrollment into LCCC1524-ATL. Post ASCT, subjects who meet eligibility criteria for treatment will receive one infusion of ATLCAR.CD30 cells once there is evidence of hematologic recovery as defined in section 4.1.2. Research personnel will keep track of any subjects who undergo procurement but do not undergo treatment with ATLCAR.CD30 cells, and the reason for withholding treatment.

4.1 Study Treatment

4.1.1 Cell Procurement

In adult subjects, up to 300 mL total of peripheral blood will be obtained (in up to 3 collections) for cell procurement. In pediatric subjects, up to 3 mL/kg of peripheral blood will be obtained (in up to 3 collections) for cell procurement Additionally, leukopheresis leukapheresis may be performed to isolate sufficient cells in subjects with a low absolute lymphocyte count or who had inadequate peripheral blood collection.

For pediatric patients (patients under 18 years of age), the total amount of blood drawn will not be more than 3 mL (less than 1 teaspoon) per 2.2 lbs. that the child weighs.

4.1.2 ATLCAR.CD30 Cells Administration

Post ASCT, once the subject has started to experience hematologic recovery (defined as ANC ≥500 cells/mm3 for 3 consecutive days, AND platelet count ≥25 cells/mm3 without transfusion over the preceding 5 days, AND Hg ≥8g/dL without transfusion support over preceding 5 days), ATLCAR.CD30 cells will be administered as described below. The dose of cells and exact day of cell infusion will vary, depending on the cohort enrolled. See section 4.1.3 for dose levels and dose escalation rules. This will generally occur between 14 and 20 days following infusion of autologous stem cells following high-dose chemotherapy.

Premedication

Subjects may be pre-medicated with Benadryl (diphenhydramine) up to 1 mg/kg IV (max 50mg) and Tylenol (acetaminophen) 10 mg/kg oral (max 650mg). Alternative antihistamines or anti-pyretics can be used in the case of diphenhydramine or acetaminophen hypersensitivity. We will premedicate subjects who have a history of reactions to blood products. Steroids should be avoided given their detrimental effect on the survival of the infused T cells (see exclusion criteria 5). Anti-emetics in appropriate dosage for each subject will be prescribed as necessary.

Cell Administration

ATLCAR.CD30 cells will be given by a licensed provider via intravenous injection over 1-10 minutes through either a peripheral or a central line. The expected volume will be 1-50cc.

Monitoring

Monitoring will be undertaken according to institutional standards for administration of blood products. Subjects will be monitored for at least 4 hours post infusion.

4.1.3 Dose Escalation Rules

Three dose levels will be evaluated. Using the continual reassessment method (CRM), initial cohort of size two will be enrolled at each dose level (see section 11.), after that subjects are enrolled one at a time until a minimum of 12 subjects is treated. Each subject will receive one injection according to the dosing schedules listed below. We will start with the lowest cell dose (2×10^7 cells/m^2) given to subjects in one of our previous trials employing CAR-T cells including the CD28 costimulatory endodomain [26], and we will escalate the cell dose to the highest cell dose (2×10^8/m^2) given in the same trial [26]. These are also the doses utilized in the phase I trial using ATLCAR.CD30 and described in section 1.5.5. All those

cell doses were safe. A maximum dose is included for each dose cohort in order to avoid excessive dosing secondary to obesity and potentially resulting in toxicity. The maximum dose is calculated based on a body surface area of 2.5 m^2.

Note: Initially, only adults will be enrolled during the dose escalation phase of the study. Once a dose level has been tested in at least 2 adults without the occurrence of DLTs, children may then be enrolled on that dose level according to the CRM.

Cell dose Levels

Table 1 Group One

Schedule	ATLCAR.CD30[2]	Maximum Dose
Week 0 Day 11	$2x10^7$ cells/m^2	$5x10^7$ cells

Table 2 Group Two

Schedule	ATLCAR.CD30[2]	Maximum Dose
Week 0 Day 11	$1x10^8$ cells/m^2	$2.5x10^8$ cells

Table 3 Group Three

Schedule	ATLCAR.CD30[2]	Maximum Dose
Week 0 Day 11	$2x10^8$ cells/m^2	$5x10^8$ cells

The dose is based on the CAR.CD30 expressing cell. With a lower limit of CAR positivity at 15%, even a larger subject (2.0 m^2) would receive 2.66 x 10^9 total cells which would still be in the lower range of infused cells as reported by Johnson *et al*. [75].

1. Only one infusion will be administered, and will be given after stem cell transplantation and engraftment as defined in section 4.1.2.

2. If there are insufficient cells manufactured for a subject to receive their proposed dose level, the subject may be infused with a quantity of cells consistent with one of the previously cleared dose levels.

Definition of MTD

For this study, MTD is defined as the dose that causes DLT (see section 4.1.3.3) in 10% of eligible cases. The trial will continue until a minimum of 12 subjects is treated. Six additional subjects might be accrued to obtain more data at the current MTD. The final MTD will be the dose with estimated probability of the DLT closest to the target toxicity rate of 10%.

Definition of a DLT

The timeframe for DLT evaluation is from day of infusion through 6 weeks post infusion.

Except as noted below, DLT will be defined as any of the following that may, after consultation with the FDA, be considered possibly, probably, or definitely related to the study cellular products:

- Grade 3 and 4 cytokine release syndrome (CRS*) that persists beyond 72 hours, or any Grade 5 CRS
- Any other ≥ Grade 3 non- hematologic toxicity, including allergic reactions to T cell infusions

*Grade 3 and 4 expected CRS reactions seen with the use of CAR-based immunotherapy such as (but not limited to) fever and hypotension requiring pressor support will not be considered a DLT unless it persists beyond 72 hours.

CRS toxicity will be graded according to the toxicity scale outlined in section 18.8 (APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines).

Supportive Care

Subjects will receive supportive care for acute or chronic toxicity, including blood components or antibiotics, and other intervention as appropriate.

4.1.4 Concomitant Medications/Treatments

Ideally, subjects should not receive other antineoplastic agents for at least 6 weeks post T cells (for purposes of evaluation) however, subjects with progressive disease may receive other therapy if needed at the discretion of their attending physician. If subjects receive other therapy adverse event reporting will cease after the initial 6-week assessments outlined in section 4.2 are completed. These subjects will continue to be monitored after PD according to the Time and Events Table in APPENDIX IV - Abbreviated Follow Up Required After Initiating Alternative Therapy (section 18.4).

If subjects experience PD after the initial 6-week assessment period following the cell infusion has been completed, they should be followed according to the Time and Events Table in APPENDIX IV - Abbreviated Follow Up Required After Initiating Alternative Therapy(section 18.4).

4.2 Time & Events Table

Table 4 Time and Events Table

Study Assessments	Screening[1]			ATLCAR Treatment [2]	Follow-up										
	Pre-procurement	ASCT AS PER STANDARD OF CARE	Pre-infusion of ATLCAR.CD30 cells	Wk 0 D1[1]	Wk 1 D1[1]	Wk 2 D1[1]	(Optional) Wk 3 D1[1]	Wk 4 D1[1]	Wk 6 D1[1]	Mth 3 D1[1]	Mth 6 D1[1]	Mth 9 D1[1]	Mth 12 D1[1]	Every 6mths x 4 yrs[1]	Yearly[1,17]
History[3]	X		X		X	X	X	X	X	X	X	X	X		X
Physical exam			X		X	X	X	X	X	X	X	X	X		X[1*]
Check Eligibility	X		X												
Performance status[1]	X		X			X				X	X	X	X		
Pregnancy test[2]	X		X												
PFTs and EF[4]	X														
Pulse oximetry			X												
CBC with diff [5, 19]	X[5]		X		X	X	X	X	X	X	X	X	X		
Virus testing[6]	X[6]														
Procurement of cells	After screening [7]														
Complete metabolic panel[7]	X[7]*		X		X	X	X	X	X	X	X	X	X		
Tumor Imaging[9]	X								X		X		X	X[9]	
Thyroid function[10]			X							X			X		

Correlative Samples[11]			X	X	X	X	X	X	X	X	X	X	X	X[11]	X[11,17]
HAMA testing[12]			X[12]						X[12]						
Toxicity[13]			X	X	X	X	X	X	X						
CoA			X[14]												
Infusion of ATL CAR.CD30				X[15]											
PRO Questionnaires (optional)[16]	X		X		X	X	X	X	X	X	X	X	X	X	X
Tissue Studies	See Section 7.5.7														

Key to Time and Events Table Footnotes

1. Screening includes tests to confirm eligibility for both procurement and treatment; NOTE: some pre-infusion screening tests may not be performed until the day of infusion. A window of +/-3 days will apply to all study visits for the first 8 weeks unless otherwise noted below. A window of +/-10 days will apply to every 3 months study visits, and a window of +/-30 days will apply to visits separated by ≥ 6 months. Yearly follow-up visits during long-term follow-up for a total of 15 years. *An annual physical exam will be required ONLY for the first 5 years of follow up. NOTE: Follow-up visits for month 3 and beyond can be conducted locally (i.e., by local health care provider, local oncologist, etc.). The study team would continue to contact the subjects at the long-term follow-up points and request they visit their local healthcare provider to complete the follow-up test and assessments, where applicable. The study team would collect clinical information, tests and assessments results, other clinical observations from the subject's medical record and their local health care provider.

2. Serum pregnancy testing will be done in female subjects of childbearing potential within 72 hours prior to procurement and repeated 72 hours prior to infusion.

3. Medical history must include collecting the following information: 1. New malignancy(ies) 2. New incidence or exacerbation of pre-existing neurologic disorder 3. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder 4. New incidence of a hematologic disorder and 5. New incidence of infection (potentially product related).

4. PFTs = pulmonary function tests and includes forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and diffusing capacity (DLCO); EF=ejection fraction evaluated via MUGA or ECHO. These will be evaluated within 3 months prior to transplant.

5. CBC includes complete blood count with diff and platelets. *NOTE: Pre-procurement, only Hg is necessary, and if a serum Hg has already been performed within 7 days of procurement as part of SOC pre-transplant work-up, it does not need to be repeated. Prior to ATLCAR.CD30 treatment, CBC with diff and platelets must be performed within 24 hours prior to infusion. CBC with diff and platelets performed as needed on D1/Week 3.

6. HIV, HBV, HCV testing required for confirmation that no active infection exists; results can be pending at the time of cell procurement; only those samples confirming lack of active infection will be used to generate transduced cells. Virus testing may be performed up to 30 days prior to procurement.

7. See section 8.2, procurement happens after pre-procurement screening and prior to ASCT. Procurement may occur prior to or after PBSC mobilization. If procurement occurs after PBSC mobilization, it must occur at least 7 days after ending use of G-CSF

8. Complete Metabolic Panel (CMP): includes BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, and alkaline phosphatase. NOTE: *Pre-procurement, only creatinine, bilirubin, and AST is necessary, and if these tests have already been performed within 7 days of procurement as part of SOC pre-transplant work-up (i.e. as part of CMP), they do not need to be repeated. Prior to ATLCAR.CD30 treatment, a CMP must be performed within 24 hours prior to infusion. CMP performed as needed on D1/Week 3.

9. To assess disease status, imaging will be performed at baseline (within 60 days prior to ASCT) and at 6-8 weeks following the infusion. The choice of imaging will depend on what studies have been most informative in following the subject's disease (i.e., PET, CT scans, MRI, nuclear imaging). In subjects who do not have documented disease progression at the 6 weeks scan, another scan will occur at 6 months, 12 months, 18 months and 24 months (with a +/- 1 month window), until documentation of disease progression. If imaging studies are performed at other times after treatment on this study; that data will be collected, and information gained will be used for this study.

Response assessment for subjects with cutaneous T cell lymphoma

a. Will be performed at the same time point outlined above in the Time and Events Table and by the few exceptions outlined in section 7.1.1.

b. Notable differences in the follow up for these subjects are outlined in section 7.1.1 based on consensus guidelines.

c. Consult with a dermatologist will be required within 14 days prior to transplant.

10. Thyroid function (T3, Free T4 and TSH) will be monitored in view of changes seen in subjects receiving CD30 antibody.

11. Correlative analysis will include the following. Correlative blood sample collection will cease if the samples are no longer required for persistence and function or clonality analysis.

a. **Persistence and Function:** The analyses will be used to monitor persistence and function (if applicable) in peripheral blood and will include immunophenotyping as well as quantitative polymerase chain reaction (qPCR) to detect transgene persistence and

functional assays such as in vitro reactivation of PBMCs in subjects for whom the appropriate reagents are available. Quantitative real-time PCR to detect the transgenes will be collected pre-lymphodepletion, pre-dosing (approximately 19 mL of blood), at 3 – 4 hours post infusion (approximately 16 mL of blood), 1, 2-, 3-, 4- and 6-weeks visits post each T-cell infusion and then at the 3-, 6-, 9-, and 12-months visits. Persistence and function will be continued for up to one-year post-CAR T cell infusion. If a transgene copy number is > 500 copies/µg DNA, then samples to determine transgene copy numbers will be collected every 6 months after the first year until transgene copy number is < 500 copies/µg DNA at which time samples will then be collected yearly for up to a total of 15 years. If transgene is no longer detectable by PCR after 1-year post-final CAR T infusion, then collection for function and persistence will discontinue. See Section 7.5.1 and the Laboratory Manual for the amount of blood collected/type of tube used for all of the correlative studies.

b. **Clonality:** If the transgene is detected at > 0.5% either flow cytometry (if feasible) or by qPCR at the 6-month sample collection timepoint, then PCR to detect retroviral integrant clonality and integrant locus will be performed. This analysis will continue every 6 months until detection is < 0.5% for up to 5 years. After this time, it will be collected annually. If the level of detection is < 0.5% at 6-months, samples will be collected annually and may be archived. Samples will no longer be collected if detection is < 0.5% for more than 1 consecutive testing period. See Section 7.5.3.

c. **RCR:** For replication competent retrovirus (RCR) testing, subject blood samples will be collected and stored pre-infusion. The pre-infusion sample will only be tested if the subject develops a long-term gene therapy side effect as described in Section 7.5.2. Additional samples for RCR testing will only be collected and subsequently analyzed in the event that the subject develops a long-term gene therapy side effect as described in Section 7.5.2.

d. **Cytokine Testing:** Serum collected before and 3-4 hours after infusion for cytokine testing.

12. Serum from blood drawn for functional studies at baseline and week 6 will be stored for measurement of human anti-mouse antibodies (HAMA). These studies will be performed in the event of a suspected immunologic reaction. See section 7.5.4 for additional details.

13. Data on all adverse experiences/toxicities per CTCAE v4.0 regardless of seriousness must be collected for documentation purposes only for 6 weeks after dosing of the study drug/biologic. Adverse event data collection will cease in subjects that receive any other hemopoietic cell product or receive therapy for relapse of their primary malignancy. Data on disease status will continue to be collected as appropriate.

a. If CRS signs and symptoms occur (see APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines), a serum sample (~1 mL) for IL-6 analysis and 20 mL of blood should be collected before instituting treatment for CRS. Subsequent 20 mL blood samples should be collected once a day for the first 3 days. At the discretion of the sponsor, a daily sample may be requested for an additional 4 days. See section 7.5.6 for additional details.

b. Serum (~1 mL) and 20 mL of blood should also be collected in the event of serious toxicities that develop that require hospitalization. Subsequent 20 mL blood samples should be collected once a day for the first 3 days. At the discretion of the sponsor, a daily sample may be requested for an additional 4 days. See section 7.5.6 for additional details.

c. An additional blood sample of approximately 20 mL may be collected if any subject develops an AE or event of clinical significance that is thought to be at least possibly related to the CAR T cells.

14. CoA generated at completion of required studies for production/QA of cells.

15. ATLCAR.CD30 cells infused after evidence of hematologic recovery post ASCT, see section 4.1.2 for definition of recovery. This will generally occur between 14 and 20 days following infusion of autologous stem cells following high-dose chemotherapy. All subjects will receive their ATLCAR.CD30 infusion at the lead site, the University of North Carolina, Chapel Hill.

16. Patient reported outcomes (PRO) will be measured by the PROMIS Global Health and Physical Function questionnaires and selected items from the NCI PRO-CTCAE (see section 7.6 and APPENDIX V - Patient Reported Outcomes Surveys) (optional). PRO questionnaires will only be offered to adult study participants. PRO questionnaires will first be given at time of screening consent. On the day of infusion, subjects will fill out questionnaires prior to infusion. These questionnaires are optional and may not be given to all subjects.

17. Long Term Follow Up: If a subject develops a delayed adverse event that is related to the trial drug, then more frequent (2-4 times per year) clinical observation may be indicated. Appropriate follow up will be conducted based on a particular subject's prior test results. The investigator will determine the additional testing and sample collection that is needed. New malignancies and delayed adverse events will be recorded during long term follow-up.

5.0 **STUDY POPULATION**

Unless otherwise noted, subjects must meet all of the following criteria to participate:

5.1 Inclusion Criteria for Prior to Cell Procurement

1. Informed consent explained to, understood by and signed by subject/guardian; subject/guardian given copy of the procurement/screening informed consent.

2. 3 to 17 years of age for pediatric subjects, ≥18 years of age for adults; NOTE: children will not be allowed to enroll in a dose cohort until a minimum of 2 adult subjects were enrolled and complete their DLT assessment follow-up at that dose level.

3. Diagnosis of recurrent HL with a treatment plan that will include high dose chemotherapy with/without total body irradiation and autologous cell transplantation.

4. NHL subjects with ALK negative CD30+ anaplastic large-cell lymphomas, CD30+ ALCL regardless of ALK status, with chemotherapy-sensitive relapse, CD30+ high-risk DLBCL, CD30+ cutaneous T cell lymphoma, or CD30+ mycosis fungoides who are otherwise eligible for transplant, are eligible for this study.

5. Karnofsky or Lansky score of > 60% (APPENDIX III- Lansky and Karnofsky Performance Status)

6. Evidence of adequate organ function as defined by:

   The following is required prior to procurement (NOTE: labs do not need to be redrawn if they have already been performed as part of SOC pre-transplant work-up; Subject must be eligible to receive ASCT)

   - Hgb ≥ 8.0g/dL
   - Bilirubin ≤1.5 times the upper limit of normal (ULN)
   - AST ≤ 3 times ULN
   - Serum creatinine ≤1.5 times ULN
   - Cardiac and pulmonary function that is adequate for ASCT

7. In women of child-bearing potential (WOCBP), a negative serum pregnancy test within 72 hours prior to procurement. WOCBP are those who have not been surgically sterilized or have not been free from menses for > 1 year.

8. Considered at high risk for relapse as defined by:

   The presence of ≥1 of the following: failure to achieve CR post initial treatment; relapsed disease with an initial remission duration of <12 months; **or** extranodal involvement at the start of pre-transplant salvage therapy.

9. WOCBP should be willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity for the course of the study, and for 6 months after the study is concluded. WOCBP are those who have not been surgically sterilized or have not been free from menses for > 1 year. The two birth control methods can be composed of: two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The male partner of WOCBP subjects enrolled into the trial should be instructed to use a condom by their female partner enrolled in the trial.

5.2 Inclusion Criteria Prior to Infusion of ATLCAR.CD30 Cells

1. Informed consent explained to, understood by and signed by subject/guardian; subject/guardian given copy of informed consent.

2. 3 to 17 years of age for pediatric subjects, ≥18 years of age for adults; NOTE: children will not be allowed to enroll in a dose cohort until a minimum of 2 adult subjects were enrolled and complete their DLT assessment follow-up at that dose level.

3. Diagnosis of recurrent HL with a treatment plan that will include high dose chemotherapy with/without total body irradiation and autologous cell transplantation.

4. NHL subjects with ALK negative CD30+ anaplastic large-cell lymphomas, CD30+ ALCL regardless of ALK status, with chemotherapy-sensitive relapse, CD30+ high-risk DLBCL, CD30+ cutaneous T cell lymphoma, or CD30+ mycosis fungoides who are otherwise eligible for transplant, are eligible for this study.

5. CD30+ disease (result can be pending at the time of cell procurement, but must be confirmed prior to treatment with ATLCAR.CD30 cells); NOTE: CD30+ disease requires documented CD30 expression by immunohistochemistry based on the institutional hematopathology standard.

6. Evidence of adequate organ function as defined by:

   The following is required prior to infusion of ATLCAR.CD30 cells:

   - Absolute neutrophil count (ANC) ≥500 cells/mm3 for 3 consecutive days; Note: ANC may be measured at the beginning and the end of a time frame expanding at least 3 days and does not need to be evaluated on each individual day **AND**

- Platelet count ≥25,000 cells/mm3 without transfusion over preceding 5 days; Note: Platelets may be measured at the beginning and the end of a time frame expanding at least 5 days and does not need to be evaluated on each individual day **AND**

- Hg ≥8g/dL without transfusion support over preceding 5 days; Note: Hg may be measured at the beginning and the end of a time frame expanding at least 5 days and does not need to be evaluated on each individual day

- Bilirubin ≤1.5 times the upper limit of normal (ULN)

- AST ≤ 3 times ULN

- Serum creatinine ≤1.5 times ULN

- Pulse oximetry of > 90% on room air

7. Imaging results from within 60 days prior to transplant (used as baseline measure for documentation of disease status).

8. In women of child-bearing potential (WOCBP), a negative serum pregnancy test within 72 hours prior to procurement and again 72 hours prior to infusion is required.

9. Karnofsky or Lansky score of > 60% (APPENDIX III- Lansky and Karnofsky Performance Status)

10. Considered at high risk for relapse as defined by:

    - The presence of ≥1 of the following: failure to achieve CR post initial treatment; relapsed disease with an initial remission duration of <12 months; or extranodal involvement at the start of pre-transplant salvage therapy.

11. Subjects must have autologous transduced activated T-cells that meet the Certificate of Analysis (CoA) acceptance criteria.

12. WOCBP should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study, and for 6 months after the study is concluded. WOCBP are those who have not been surgically sterilized or have not been free from menses for >1 year. The two birth control methods can be composed of: two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The male partner of WOCBP subjects enrolled into the trial should be instructed to use a condom by their female partner enrolled in the trial.

5.3 Exclusion Criteria

Subjects meeting any of the following exclusion criteria will not be able to participate in this study:

1. Received any investigational agents or received any tumor vaccines within the previous six weeks prior to cell infusion.

2. Received anti-CD30 antibody-based therapy within the previous 4 weeks prior to cell infusion

3. Pregnant or lactating

4. Tumor in a location where enlargement could cause airway obstruction.

5. Current use of systemic corticosteroids at doses >10mg/day prednisone or its equivalent; those receiving ≤10mg may be enrolled at discretion of investigator.

6. Active infection with HIV, HBV, HCV (**can be pending at the time of cell procurement; only subjects meeting the criteria as so described will be infused**). Note: To meet eligibility subjects are required to be negative for HIV antibody, negative for Hepatitis B surface antigen, and negative for HCV antibody **or** viral load.

6.0 **STUDY CONDUCT**

6.1 Duration of Therapy

Therapy in LCCC1524-ATL involves just one infusion of ATLCAR.CD30 cells. Treatment with one infusion will be administered unless:

- Subject decides to withdraw from study treatment, OR
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

6.2 Duration of Follow-Up

Subjects will be followed for up to 15 years or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Subjects who experience disease progression and start alternate therapy after receiving a cell infusion(s) will still be required to complete abbreviated follow up procedures outlined in APPENDIX IV - Abbreviated Follow Up Required After Initiating Alternative Therapy (section 18.4).

6.3 Removal of Subjects from Protocol Therapy

Subjects will be removed from protocol therapy and the PI notified when any of the criteria listed in section 6.1 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

In case a subject decides to prematurely discontinue protocol therapy ("refuses

treatment"), the subject should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

6.4 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The subject should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.

- A complete final evaluation at the time of the subject's study withdrawal should be obtained with an explanation of why the subject is withdrawing from the study.

- If the subject is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.

- If the reason for removal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

7.0 DESCRIPTION OF STUDY PROCEDURES

7.1 Clinical Assessments

Clinical assessments will be performed as outlined in the Time & Events Table.

7.1.1 Disease Assessment Guidelines for Cutaneous Lymphomas

Lymphomatoid papulosis (LP) or primary cutaneous anaplastic large cell lymphomas (ALCL):

This is by definition a skin only disease.

1. Bone marrow biopsy is not required
2. Imaging will be done:
    - **Pre-transplant** (not required at procurement) to assess that there isn't unexpected nodal or visceral disease. Imaging should be performed within 60 days prior to transplant.
        - If scans show any enlarged lymph nodes >1.5cm at baseline then that subject will be treated as systemic lymphoma and followed as outlined in the Time & Events Table in section 4.2 for other lymphomas
        - If the baseline scans performed prior to transplant are negative there will be no further imaging and response will be based on assessment of skin disease on physical exam performed as outlined in the Time & Events Table in section 4.2.
3. Dermatology consult:
    - Subjects will need to see a dermatologist **within 30 days prior to transplant**.
    - They will need to see a dermatologist at the week 6 visit.
    - Thereafter they can be followed by the oncologist or dermatologist.

Table 5 Study Assessments for LP and ALCL

Study Assessments LP or ALCL	Screening		ATLCAR Treatment	Follow-Up				
	Pre-procure-ment	Pre-Transplant	W0D1	W1D1	W2D1	W3D1	W4D1	W6D1
Dermatology consult		X						X
Tumor imaging		X*		*if LN >1.5cm at baseline then perform scans per the Time & Events Table *If scans negative at baseline then response based on physical exam the Time & Events Table				

Mycosis fungoides or Sézary syndrome:

1. Bone marrow biopsy is not required
2. Imaging will be done:
   - *Pre-transplant* (not required at procurement). Imaging should be performed within 60 days prior to transplant.
     - If scans show any enlarged lymph nodes >1.5cm at baseline then that patient will have repeat scans performed at the 6 week assessment. Thereafter scans will only be performed if there is a partial response or better in the skin disease on physical exam performed as outlined in the Time & Events Table
     - If the baseline scans performed prior to transplant are negative there will be no further imaging and response will be based on assessment of skin disease on physical exam performed as outlined in the Time & Events Table.
3. Peripheral blood will be sent for flow cytometry/ leukemia profile.
   - Pre-transplant (within 30 days prior to transplant):
     - If this assessment shows no disease involvement in blood then it does not need to be repeated
     - If this assessment shows disease involvement in blood then it should be repeated
       - at 6 weeks post cell infusion
       - at 3 months post cell infusion

- Thereafter this assessment should be repeated only to confirm complete remission (CR) based on skin exam

4. Dermatology consult:

   - Subjects will need to see a dermatologist **within 30 days prior to transplant**.
   - They will need to see a dermatologist at the week 6 visit after the cell infusion.
   - Thereafter they can be followed by the oncologist or dermatologist.

Table 6 Study Assessment s for Mycosis Fungoides and Sézary Syndrome

Study Assessments Mycosis fungoides and Sézary syndrome	Screening		ATLCAR Treatment	Follow-Up					
	Pre-procure-ment	Pre-Transplant	W0D1	W1D1	W2D1	W3D1	W4D1	W6D1	M3D1
Blood for flow cytometry/ leukemia profile		X						X	X
Dermatology consult		X						X	
Tumor imaging		X		If scans show any enlarged LN >1.5cm at baseline, then repeat scans performed at the 6 week assessment. Thereafter scan if PR or better in skin disease If baseline scan negative: repeat imaging only if PR or better in skin disease post cell infusion					

7.2 Screening and Treatment Assessments

7.2.1 Pre-procurement

Check eligibility

Clinical evaluation: complete history, Karnofsky or Lansky performance status

Laboratory studies:

- **Pregnancy Test:** serum pregnancy testing will be done in female subjects of childbearing potential (within 72 hours prior to procurement)

- **Pulmonary function tests:** Including FEV1, FVC and DLCO
- **Ejection Fraction**
- **HIV, HBV, HCV** testing required (see footnote #6 of Time & Events Table)
- **Only labs listed below are required** (within 7 days of procurement) **NOTE:** if the following lab tests have already been performed within 7 days of procurement as part of SOC pre-transplant work-up (i.e., as part of hematology labs or CMP collected which includes BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase), they do not need to be repeated:
  - Hg
  - AST
  - Bilirubin
  - Serum creatinine

Imaging: To assess disease status, imaging will be performed at baseline (within 60 days prior to ASCT). The choice of imaging will depend on what studies have been most informative in following the subject's disease (i.e., PET, CT scans, MRI, nuclear imaging). If subject has cutaneous lymphoma see section 7.1.1 for details.

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE. Administered at time of screening consent.

Procurement: See section 4.1.1; to take place prior to ASCT. **Procurement may occur prior to or after PBSC mobilization. If procurement occurs after PBSC mobilization, it must occur at least 7 days after ending use of G-CSF.**

7.2.2 Pre-infusion

Check eligibility

Clinical evaluation: History, physical examination, Karnofsky or Lansky performance status

Laboratory studies:

- Pregnancy Test: serum pregnancy testing will be done in female subjects of childbearing potential (within 72 hours prior to infusion)
- Pulse Oximetry
- CBC with differential and platelets: (required within 24 hours prior to infusion)
- CMP: (required within 24 hours prior to infusion) BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase
- Thyroid function: obtained pre-infusion
- Dermatology consult needed for cutaneous lymphomas only
- Blood taken for leukemia profile and flow cytometry (mycosis fungiodes and Sezary syndrome patients only)
- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies: Including in vitro reactivation of PBMCs in subjects for whom the appropriate reagents are available and immunophenotyping
    - Replication competent retrovirus (RCR): Sample collected pre-infusion for PCR testing
    - Quantitative PCR
    - HAMA testing
    - Cytokine testing: obtained pre and post infusion

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0.

CoA: Generated at completion of required studies for production/QA of cell (available prior to planned infusion)

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE. This will be collected on the day of infusion prior to infusion.

7.2.3 Treatment (D1 Week 0)

ATLCAR.CD30 cells infused after evidence of hematologic recovery post ASCT, see section 4.1.2 for definition of recovery. This will generally occur between 14 and 20 days following infusion of autologous stem cells following high-dose chemotherapy. All subjects will receive their ATLCAR.CD30 infusion at the lead site, the University of North Carolina, Chapel Hill.

Laboratory studies:

- Blood Sample for Correlative Studies (see section 7.5 and LCCC1524-ATL Study Laboratory Manual)
  - Function and persistence studies: 3-4 hours post infusion
  - Quantitative PCR: 3-4 hours post infusion Genetic analysis (see Section 7.5.5)

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0, CRS Toxicity Grading Scale (See APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines).

7.3 Short-term Follow-up

7.3.1 D1 Week 1

Clinical evaluation: History, physical examination

Laboratory studies:

- CBC with differential and platelets
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase
- Blood Sample for Correlative Studies (see section 7.5)
  - Function and persistence studies
  - Quantitative PCR
  - Cytokine testing
  - Genetic analysis (see Section 7.5.5)

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0, CRS Toxicity Grading Scale (See APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines).

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

7.3.2 D1 Week 2

Clinical evaluation: history, physical examination, Karnofsky or Lansky performance status.

Laboratory studies:

- CBC with differential and platelets
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase
- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies
    - Quantitative PCR
    - Cytokine testing
    - Genetic analysis (see Section 7.5.5)

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0, CRS Toxicity Grading Scale (See APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines).

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

7.3.3 D1 Week 3 (Optional Visit)

Note: This is an optional visit that will occur if the condition of the subject is such that follow up on D1/week 3 is considered medically necessary by the investigator. Clinical labs may be performed as needed but are not required.

Clinical evaluation: History, physical examination

Laboratory studies:

- CBC with differential and platelets (performed as needed)
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase (performed as needed)
- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies: optional
    - Quantitative PCR: optional
    - Genetic analysis (optional at this time point - see Section 7.5.5)

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0, CRS Toxicity Grading Scale (See APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines).

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

7.3.4 D1 Week 4

Clinical evaluation: History, physical examination

Laboratory studies:

- CBC with differential and platelets
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase
- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies
    - Quantitative PCR
    - Genetic analysis (see Section 7.5.5)

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0, CRS Toxicity Grading Scale (See APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines).

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

7.3.5 D1 Week 6

Clinical evaluation: History, physical examination

Laboratory studies:

- CBC with differential and platelets
- Dermatology consult needed for cutaneous lymphomas only
- Blood taken for leukemia profile and flow cytometry (mycosis fungiodes and Sezary syndrome patients only).
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase
- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies
    - Quantitative PCR
    - HAMA testing
    - Genetic analysis (see Section 7.5.5)

Imaging: Imaging to assess disease status (PET, CT scans, MRI, nuclear imaging) 6-8 weeks following the infusion. The choice of imaging will depend on what studies have been most informative in following the subject's disease. If subject has cutaneous lymphoma see section 7.1.1 for details.

Toxicity: Toxicity will be assessed according to the NCI CTCAE v. 4.0, CRS Toxicity Grading Scale (See APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines).

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

7.3.6 D1 Month 3

Clinical evaluation: history, physical examination, Karnofsky or Lansky performance status.

Laboratory studies:

- CBC with differential and platelets
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase
- Blood taken for leukemia profile and flow cytometry (mycosis fundgiodes and Sezary syndrome patients only)
- Thyroid function
- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies
    - Quantitative PCR
    - Genetic analysis (see Section 7.5.5)

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

7.3.7 D1 Month 6

Clinical evaluation: history, physical examination, Karnofsky or Lansky performance status.

Laboratory studies:

- CBC with differential and platelets
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase

- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies
    - Quantitative PCR
    - Genetic analysis (see Section 7.5.5)

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

Imaging: Imaging to assess progression (PET, CT scans, MRI, nuclear imaging) at 6 months +/- 1 month following the infusion. The choice of imaging will depend on what studies have been most informative in following the subject's disease.

7.3.8 D1 Month 9

Clinical evaluation: history, physical examination, Karnofsky or Lansky performance status.

Laboratory studies:

- CBC with differential and platelets
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase
- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies
    - Quantitative PCR
    - Genetic analysis (see Section 7.5.5)

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

7.3.9 D1 Month 12

Clinical evaluation: history, physical examination, Karnofsky or Lansky performance status.

Laboratory studies:

- CBC with differential and platelets
- CMP: BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase
- Thyroid function
- Blood Sample for Correlative Studies (see section 7.5)
    - Function and persistence studies
    - Quantitative PCR
    - Genetic analysis (see Section 7.5.5)

Patient reported outcome questionnaires for adult subjects (optional): PROMIS Global Health Scale, PROMIS Physical Function, and selected questions from NCI PRO-CTCAE

Imaging: Imaging to assess progression (PET, CT scans, MRI, nuclear imaging) at 6 months +/- 1 month following the infusion. The choice of imaging will depend on what studies have been most informative in following the patient's disease.

7.4 Long Term Follow-Up

Quantitative real-time PCR to detect transgene copy numbers will be collected pre-infusion, 3-4 hours post infusion, 1, 2, 3, 4 and 6 weeks post- T cell infusion, 3, 6, 9, and 12 months post- T cell infusion and then yearly for a total of 15 years. If transgene copy number is >1000 copies/1µg DNA, then samples to determine transgene copy numbers will be collected every 6 months after the first year until transgene copy number is <1000 copies/1µg DNA at which time samples will then be collected yearly for a total of 15 years.

If at 6 months post- T cell infusion, transgene is detected at >0.5% by flow cytometry then PCR to detect retroviral integrant clonality and integrant locus will be performed and will continue every 6 months until detection is <0.5%. Samples will then be collected annually and may be archived for a total of 15 years. If the level of detection is less than 0.5%, samples will be collected annually and may be archived. Follow up will continue for 15 years.

If a subject develops a delayed adverse event that is related to the trial drug, then more frequent (2-4 times per year) clinical observation may be indicated. Appropriate follow up will be conducted based on a particular subject's prior test results. The investigator will determine the additional testing and sample collection that is needed. New malignancies and delayed adverse events will be recorded during long term follow-up.

Regarding annual genetic analysis through year 15, see Section 7.5.5.

7.5 Correlative Studies: Tests of Function, Persistence and Safety

The following investigations will be used to monitor function and persistence in peripheral blood and safety of transduced T-cells at time-points indicated in the Time and Events Table. A maximum of the lesser of 50 mL or 2 mL/kg of body weight of blood will be drawn on any one day for these assays. If a subject's hemoglobin is less than 8.0 g/dL at any of the evaluation times, the amount of blood drawn for the evaluation will be reduced and may be obtained over more than one venipuncture, if necessary. If there is insufficient blood, samples archived for RCR testing if needed, and Quantitative real-time PCR, will be the first priorities. Note: the studies are not necessarily performed at the time of blood collection. Correlative blood sample collection will cease if the samples are no longer required for persistence and function or clonality analysis.

7.5.1 Function and Persistence Studies

These will include immunophenotyping (when possible) as well as quantitative polymerase chain reaction (qPCR) to detect transgene persistence. When applicable, functional assays will be performed, such as in vitro reactivation of PBMCs in subjects for whom the appropriate reagents are available.

7.5.2 RCR Testing by PCR

Subject blood samples will be collected pre-infusion and stored. Samples will also be collected and both samples analyzed if the subject develops any of the following long-term gene therapy side effects:

- New malignancy(ies)
- Exacerbation of a pre-existing or new incidence of a neurologic disorder
- Exacerbation of a prior or new incidence of a rheumatologic or other autoimmune disorder
- New incidence of a hematologic disorder
- New incidence of infection (potentially product-related).

7.5.3 Clonality

If the transgene is detected at > 0.5% by either flow cytometry (if feasible) or by qPCR at the 6-month sample collection timepoint, then PCR to detect retroviral integrant clonality and integrant locus will be performed. This analysis will continue every 6 months until detection is < 0.5% for up to 5 years. After this time, it will be collected

annually. If the level of detection is < 0.5% at 6-months, samples will be collected annually and may be archived. Samples will no longer be collected if detection is < 0.5% for more than 1 consecutive testing period.

7.5.4 HAMA Testing

Serum from blood drawn for functional studies at baseline and at week 6 will be stored for measurement of HAMA. These studies will be performed in the event of a suspected immunologic reaction.

7.5.5 Genetic Analysis

RNAseq, DNA and other genomic analysis may be performed on the ATLCAR.CD30 products and on blood samples collected 3-4 hours post infusion, 1, 2, 3 (optional), 4, and 6 weeks post T cell infusion, 3, 6, 9, and 12 months post infusion and yearly for a total of 15 years post infusion. These analyses will be used to determine the integration location of CAR.CD30. Differential integration locations of these samples will then be compared to CAR T cell behavior to see if integration location affects CAR T cell behavior such as expansion, persistence and trafficking. Previously, with CD19-targeted T cells, it has been observed that disruption of TET2 promotes the therapeutic efficacy of the CAR T cells [76]. The epigenetic profile of these TET2 disrupted T cells showed features consistent with altered T cell differentiation and a central memory phenotype, at the peak of expansion.

7.5.6 Sample Collection Requirements if CRS or Severe Toxicity Occurs

A serum sample (~1 mL) for IL-6 analysis and ~20 mL of blood should be collected from any subject who develops signs and symptoms of CRS. This sample should be collected before treatments are administered to alleviate CRS symptoms. Subsequent 20 mL blood samples should be collected once a day for the first 3 days. At the discretion of the sponsor, a daily sample may be requested for an additional 4 days.

In addition, a serum sample, (~1 mL) for IL-6 analysis and ~20 mL of blood should be collected in any subject who develops a SAE (i.e., requiring hospitalization) related to the cell infusion. Subsequent 20 mL blood samples should be collected once a day for the first 3 days. At the discretion of the sponsor, a daily sample may be requested for an additional 4 days.

An additional blood sample of approximately 20 mL may be collected if any subject develops an AE or event of clinical significance that is thought to be at least possibly related to the CAR T cells.

7.5.7 Other Tissue Studies

If biopsy of accessible lymph nodes or other tissue is required at any time after treatment, a sample of this will be used to assess presence of transduced peripheral blood T-cells in association with the tumor. Additionally, this tissue may be used to assess for potential causes for loss of response to therapy, including, but not limited to, the loss of CD30 expression.

If bone marrow trephine biopsy or tumor biopsy is required at any time after treatment, a sample of this will be used to assess presence of transduced peripheral blood T-cells in association with the tumor. Additionally, this tissue may be used to assess for potential causes for loss of response to therapy, including, but not limited to, the loss of CD30 expression.

If the subject dies, an autopsy may be requested. If an autopsy is granted, tissue may be requested to assess presence of transduced cells. Additionally, the autopsy tissue may be used to assess for potential causes for loss of response to therapy, including, but not limited to, the loss of CD30 expression.

7.5.8 Biobank Repository

Subjects participating in this trial will be asked to consent to allow researchers to store their biological specimens. Participants in this trial will also be required to sign a separate HIPAA authorization form to allow investigators to review their medical records.

ATLCAR.CD30 cells will be stored at the GMP facility according to standard procedures. Other specimens collected during this study as described in section 7.5.7 of this protocol will be stored at the University of North Carolina at Chapel Hill in the immunotherapy laboratory in locked liquid nitrogen tanks with controlled access. The samples will be labeled with the study ID number and date and time of sample collection.

The purpose of this repository or biobank is to store samples for immediate or future analyses to answer study-related questions, not to increase general knowledge outside the parameters of the study. These goals will be accomplished using several different kinds of specimens collected during the study as described. These specimens include:

- Tissue samples from standard of care biopsies of the bone marrow, lymph nodes and/or extramedullary tumor
- Unused ATLCAR.CD30 cells after a determination has been made that the subject is not a candidate for re-infusion or has already undergone re-infusion.

- Unused additional material collected during procurement (peripheral blood mononuclear cells)

- Leftover tissue obtained for any standard of care procedure that may provide additional information about ATLCAR.CD30 cell therapy.

For example, analyses will be performed to assist in determining if the ATLCAR.CD30 cells are associated with the tumor and if the ATLCAR.CD30 cells are present.

Tissues donated from bone marrow biopsies, lymph nodes, extramedullary tumor biopsies, or any leftover tissue obtained through standard of care procedures that may provide additional information about ATLCAR.CD30 cell therapy will be stored for 15 years in the repository. After 15 years, these samples will be destroyed. ATLCAR.CD30 cells will be kept for 5 years and destroyed thereafter.

Information about the patient's disease will be linked to the specimens stored in the repository database. Immunotherapy laboratory-associated research staff, LCCC Bioinformatics staff who support the database and the LCCC Data Warehouse, and researchers with IRB-approval for access to personal health information for each subject in this study will be able to link specimens to relevant medical information. Some results from laboratory analyses that occurred during the patient's participation in the clinical study may also be included. This information may be important for understanding how the patient's cancer developed and responded to treatment.

Storage Time:

- CAR-T cells and material from procurement are to be stored for up to 15 years for subject treatment and safety purposes. If storage of the CAR-T cells and/or extra material from procurement is no longer deemed necessary as determined by the Principal Investigator with appropriate consult, as needed (e.g., attending physician, treating physicians, etc.), the CAR-T cells and/or the extra material from procurement may be released for archiving or destruction earlier than 15 years. At the time of release determination by the Principal Investigator, if the subject did not consent for their specimens to be used for further research or quality assurance/quality control (QA/QC) activities, the specimens will be destroyed. The subject may withdraw their consent at any time to prevent the use of their specimens for further research or QA/QC activities. Withdrawing of consent will result in the destruction of the samples at 15 years or at the time consent is withdrawn if this occurs after the initial 15 years in storage.

    - Archived samples will be stored in the GMP lab (the ACT facility) and will be designated in the inventory system for use in laboratory research and/or QA/QC activities. Samples will be de-identified when they are used for

laboratory research or QA/QC activities. Total storage time (initial storage and archiving) may be up to 25 years, and then the samples will be destroyed.

- Tissue obtained from bone marrow biopsies, extramedullary tumor biopsies, or any leftover tissue obtained through standard of care procedure or as outlined as part of the protocol that may provide additional information about ATLCAR.CD30 cell therapy will be stored for up to 15 years.

Provision of Data to Correlative Scientists

Identification and Role of the Study Coordinator as the Honest Broker

The study coordinator will be in charge of collecting and maintaining all data points and data management. The study coordinator should have adequate training to enter, manage, and deidentify data. The study coordinator will provide a unique study number to each enrolled subject. All documentation and samples will be labeled with the unique study number. The correlative teams will only be provided this unique study ID number as opposed to any other patient identifiers. The clinical team will be the only people able to access identifiable data and the study coordinator will be a conduit to provide the de-identified data to the correlative team.

Requests for a data

Identifiable data will not be given out to any correlative investigators at any time. Multicenter and UNC correlative Investigators may ask the study coordinator for a specific data set, and the study coordinator will return a deidentified data set. This data may only be used for purposes of the study. Any use other than directly related to the study must be approved by the IRB of record. If there is a need for an investigator to access identifiable data during the study, then a new IRB application will need to be submitted from that investigator detailing the reasons needed to access that data. The study coordinator will also ensure that correlative results are not returned from the correlative team to the clinical team to dictate treatment or follow-up decisions unless this is specifically approved by the IRB of record and delineated in the clinical protocol.

7.6 Patient Reported Outcomes Measures

Patient reported outcome measures will be collected on adult study participants who agree to fill out questionnaires at the scheduled clinic visits. The PROMIS questionnaires corresponding to Global Health (PROMIS GHS SF v1.0-1.1) and Physical Function (PROMIS Physical Function SF20a) (www.nihpromis.org) and selected symptom questions from the NCI PRO-CTCAE will be administered (see APPENDIX V - Patient Reported Outcomes Surveys).

Adult subjects who experience disease progression following an initial or subsequent cell infusion may be asked to complete a final set of questionnaires if they are willing.

7.7 Assessment of Safety

All subjects who received a CAR.CD30 T-cell infusion will be included in the safety analysis. Each subject will be assessed periodically for the development of any toxicity according to the Time & Events Table. Toxicity will be assessed according to the NCI CTCAE v4.0 and CRS toxicity will be graded according to the toxicity scale outlined in APPENDIX V - Patient Reported Outcomes Surveys.

7.8 Assessment of Efficacy

To assess disease status, imaging will be performed at baseline (within 60 days prior to ASCT) and at 6-8 weeks, 6 months, 12 months, 18 months and 24 months (or until documented disease progression) following the infusion. The choice of imaging will depend on what studies have been most informative in following the subject's disease (i.e., PET, CT scans, MRI, nuclear imaging). If imaging studies are performed at other times after treatment on this study; that data will be collected and information gained will be used for this study.

7.8.1 Measurement of Disease

This study will use the Lugano Classification Lymphoma Response Criteria [74].

The response criteria are defined in APPENDIX II- Revised Response Criteria for Lymphoma:.

The response criteria for lymphomatoid papulosis and primary cutaneous ALCL are defined in Section 18.6 APPENDIX VI: Response Assessment for Cutaneous ALCL/Lymphomatoid Papulosis.

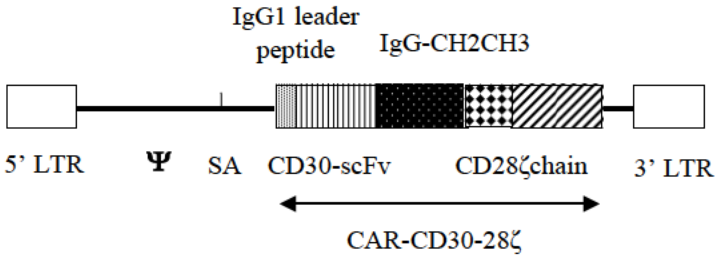
The response criteria for mycosis fungoides and Sezary syndrome are defined in Section 18.7 APPENDIX VII - Response Assessment for Mycoses Fungoides and Sézary Syndrome.

8.0 STUDY TREATMENT INFORMATION

8.1 Construction of CD30 Vector

The single chain antibody (scFv) targeting the CD30 molecule was cloned by Dr. Abken [60]. The human IgG1 immunoglobulin heavy constant region (hinge-CH2CH3 regions) was added to provide a spacer region between the scFv and the ζ and CD28ζ endodomain (CAR.CD30) [42]. This spacer region also guarantees the detectability of the CAR on transduced T cells by FACS analysis using a specific monoclonal antibody. The CAR.CD30 was then cloned into the retroviral vector SFG (provided by R.C. Mulligan, Cambridge, Massachusetts) that is a Moloney murine leukemia (Mo-MuLV) virus-based vector. A schematic representation of the retroviral construct is shown in Figure 2.

Figure 2 Schematic Representation of SFG.CAR.CD30



8.2 Generation of Transduced Cells

All manufacturing procedures (from Section 8.2.2 onwards) will be performed in our GMP facility located at the address below:

UNC Lineberger Advanced Cellular Therapeutics Facility
6101 Quadrangle Drive, Suite 150
Chapel Hill, NC 27517

The cells will be transduced/manufactured as dictated by Standard Operating Protocols (SOP). Brief summaries are given here.

8.2.1 Source Material

See Section 4.1.1 (procurement).

8.2.2 Activated T Lymphocytes

ATL will be generated using our previously validated SOP. Briefly, PBMC will be activated with anti-CD3 and anti-CD28 antibodies, and then fed with IL-7 and IL-15[77]. Anti-CD3 and anti-CD28 are now available in GMP grade and our validation

studies show improved cell transduction when both anti-CD3 and anti-CD28 antibodies are combined.

8.2.3 Retroviral Production

A retroviral producer line has been generated for the construct at Baylor College of Medicine. A master cell-bank of producer cells has been generated and tested to exclude production of replication competent retrovirus and infection by Mycoplasma, HIV, HBV, HCV and others. Supernatant collected from the master-cell bank was filtered, aliquoted and rapidly frozen and stored at -80°C.

All batches of retroviral supernatant have been tested for sterility and to exclude RCR as issued with the Certificate of Analysis (CoA) and as directed by the SOPs and IND 14688

8.2.4 Transduction

ATL are transduced on day 3-4 after initiation as described previously using recombinant Fibronectin fragment CH-296 (RetronectinTM, Takara Bio, USA) coated plates or bags. Virus is attached to retronectin by incubating producer supernatant in coated plates or bags. Cells are then transferred to virus coated plates or bags.

8.2.5 Ex Vivo Expansion

After transduction transgenic ATL will be expanded feeding them with IL-7 and IL-15 twice a week to reach sufficient numbers as previously described [77]. After transduction a small number of cells will be removed to evaluate for transduction efficiency using flow cytometry.

8.2.6 Freezing

When sufficient number for cell infusion is achieved, cells will be collected and frozen following previously validated SOPs. Cells will be also tested for cytotoxicity against CD30+ tumor cells and CD30 negative cell lines to check receptor function. All lines will be checked for identity, phenotype and microbiological culture and cryopreserved prior to administration according to SOPs. The results will be reviewed by QA prior to issuing a CoA.

8.2.7 Testing

Products that meet study specific release criteria, as detailed on the CoA that accompany each infusion product, will be infused as per Section 4.1.2.

If a positive sterility testing result is reported after the product was infused, the FDA and other relevant parties would be notified as per our manufacturing SOP.

8.3 Potential Toxicities

Potential toxicities may be categorized as those related to: infusion of T cells; transduction; cross-reactivity with normal tissues; cytokine release syndrome; neurotoxicity; macrophage activation syndrome and tumor lysis syndrome. In addition to the information presented below, also see Sections 1.5.2., APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines.

Retroviral Transduction

There has been concern that even a single retroviral integration can contribute to oncogenesis. Insertional upregulation of cellular proto-oncogenes was the main cause of 5 serious adverse events in two different X-chromosomal linked severe combined immunodeficiency (X-SCID) gene therapy trials. The French study reported 4 cases. Fischer's group replaced the missing common gamma chain (γc) in X-SCID patients with ex vivo retroviral transduction of autologous stem cells. Four of 11 treated patients developed T-ALL associated with a single retroviral integrant[78, 79]. The integration site of the retrovirus was similar. More recently a case of leukemia has also been reported in a second study in SCID patients conducted in the UK. It is likely that correction of common-gamma chain deficiency and related immunodeficiency syndromes represent special cases. The γc is a shared component of IL-2, IL-4, IL-7, IL-9 and IL-15. Hence it is a crucial component of T- cell proliferation and thymogenesis. A proliferative advantage is expected for progeny of stem cells with functional γc. In female carriers of X-SCID there is a pattern of non-random X-inactivation in T-cells, B-cells, and NK-cells[80]. Moreover a patient with X-SCID developed substantial numbers of T-cells following reversion of the mutant allele in a single hemopoietic stem cell[81]. High efficiency retroviral transduction of human stem cells is difficult to achieve even with GALV pseudotyping. It is likely that in X-SCID, few truly pluripotent stem cells were transduced and the stem cell pool expressing the highest level of transgene (due to integration at a transcriptionally active site) then undergo numerous doublings to restore the entire T-cell compartment. Random mutations caused by this supra-physiological proliferation combined with retroviral integration in a transcriptionally active region led to leukemogenesis.

Our proposal should have a very different risk profile than that reported by Morgan and colleagues and summarized in Section 1.5.2 [45]. Large doses of transduced T-cells (in the order of 10^{10} cells) were administered to patients that received prior lymphodepletion and no leukemogenesis occurred. Although the inclusion of the CD28 endodomain in the CAR may enhance proliferation of transgenic T-cells in response to the CD30 antigen, there is no reason to believe this effect will lead to uncontrolled T-cell expansion. Ex vivo and published in vivo data using several artificial T-cell receptors shows that CD28 sustains limited and temporary expansion over approximately 3 weeks[82]. Our recent clinical trial using CD19-CAR-specific T-cells including the CD28 endodomain also indicates that these T-cells expand significantly for only 2-3 weeks and then they decline without evidence of further expansion [26]. Thereafter, the cells maintain the expression of the transgene, but proliferate further only in the presence of both antigen and exogenous cytokines.

To date, more than 200 patients have received genetically modified cells in clinical trials including patients we have treated on our protocols using retrovirally marked autologous marrow[83] or retrovirally marked EBV-CTLs[64, 84, 85]. In none of these has malignancy caused by retroviral transduction been reported. However, there is a

possibility that the vector could randomly integrate into a site that could lead to leukemogenesis.

Current intensive regimens to treat relapsed lymphoma describe subsequent secondary malignancy rates in excess of 10%[86]. In light of this, the natural history and poor prognosis of advanced lymphoma, and given the entire previous experience with retroviral gene therapy, we feel that the risks of retroviral induced leukemogenesis are small and are justified in this patient group.

Cross-reactivity

CD30 can be expressed by activated T-cells and NK cells. Direct toxicity to these cells due to targeting of their CD30 molecules by transduced cells is possible. In case of this eventuality, a number of therapeutic maneuvers are available. Corticosteroids in doses used to treat graft-versus host-disease (GvHD) will deplete the majority of circulating transduced cells.

CD30 is also expressed on first trimester decidua so there may be a risk of miscarriage in females of child-bearing potential if the cells persist long term. To evaluate this risk we will add a question about miscarriage to our annual follow up evaluation in these patients and report any such events in our annual IND report.

9.0 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

9.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility that the drug is the cause. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study investigational product is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study investigational product exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering investigational product as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with investigational product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

- One or more occurrences of an event not commonly associated with investigational product exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than one occurrence from one or multiple studies would be needed before the sponsor could determine that there is reasonable possibility that the drug caused the event.

- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the investigational product treatment group than in a concurrent or historical control group

9.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of investigational product or as anticipated from the pharmacological properties of the investigational product, but are not specifically mentioned as occurring with the particular investigational product under investigation.

9.2 Documentation of Non-Serious Adverse Events or SARs

For non-serious AEs or SARs, documentation shall begin at the time the main study consent form is signed by the subject prior to ATLCAR.CD30 infusion and continues through the 6 week follow-up period after treatment is discontinued. In addition, any AEs or SARs experienced by the subject related to the procurement procedure must also be documented.

Collected information should be recorded in the Case Report Forms (CRF) for that subject. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

10.0 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

10.2 Documentation of SAEs or Serious SARs

10.2.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout.

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 6 week follow-up period after treatment is discontinued.

10.2.2 Documentation and Notification

These events (SAEs or Serious SARs) must be recorded in the SAE console within Oncore™ for that subject within 24 hours of learning of its occurrence. For multicenter sites, the multicenter Project Manager must be notified via email of all SAEs within 24 hours of learning of its occurrence. SAEs must be recorded on the MedWatch 3500A report form.

10.3 Adverse Event Reporting

10.3.1 IRB Reporting Requirements

UNC:

The UNC IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem. Please note, these events must be reported to the sponsor within 24 hours of learning of the occurrence.

Multicenter sites:

The UNC IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem. Please note, these events must be reported to the sponsor within 24 hours of learning of the occurrence.

10.3.2 Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject at UNC or at a multicenter site, occurring while the subject is on study, or within 30 days of the subject's last dose of study product should be recorded as SAEs. The subject is to be discontinued immediately from the study.

For multicenter sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Multicenter Project Manager immediately via email (CPOMultiCenter@med.unc.edu) or facsimile to 919-966-4300. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the Multicenter Project Manager. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion),

the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

10.3.3 FDA Expedited Reporting Requirements

A sponsor must report any suspected adverse reaction (SAR) that is both serious and unexpected and related to the cellular product to the FDA. All deaths in the study should be reported expeditiously to FDA regardless of attribution if they occur within 30 days of the infusion of the study cells. Additionally, all grade 4 or greater product infusion reactions, cytokine release syndrome and/or neurologic toxicity must be reported in an expedited fashion. Please refer to section 9.1.2 for the definition of an SAR.

The sponsor must submit each IND safety report on a MedWatch Form 3500A.

Timing

FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor must be notified of the SAE by the investigator within 24 hours of the event. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-Up

The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and as such the Multicenter Project Manager should be updated within 24 hours of the information becoming available via a follow-up MedWatch Form 3500A.

Notification of Investigators

The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing cell infusion under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process

If the sponsor deems that an event is both a serious adverse reaction (SAR) AND unexpected, it must also (in addition to OnCore®) be recorded on the MedWatch Form 3500A. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch 3500A form and supporting documents defining the event and causality should be sent to the electronic mailbox (CPOMultiCenter@med.unc.edu; primary route of submission) (or facsimile (919) 966-4300 (back-up)) of the Multicenter Project Manager along with supporting documentation defining the event and causality.

The MedWatch 3500a form can be accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

Additional Reporting Requirements

The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the cell infusion.

- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the cell infusion, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.

    - *Increased rate of occurrence of serious suspected adverse reactions.*

    - *All deaths in the study regardless of attribution if they occur within 30 days of the infusion of the study cells.*

    - *Any product infusion reactions grade ≥4.*

    - *Any occurrence of cytokine release syndrome (CRS) grade ≥4.*

- *Any occurrence of neurotoxicity grade 4.*

Additional Guidance

Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

10.3.4 Institutional Biosafety Committee (IBC)

In addition to the local IRB, any qualifying serious adverse events (SAEs) must be reported to the Institutional Biosafety Committee (IBC). The IBC is responsible for reviewing recombinant DNA research conducted at or sponsored by the institution for compliance with NIH Guidelines as specified in Section III, Experiments covered by the NIH Guidelines and approving those research projects that are found to conform with the NIH Guidelines. As such, the IBC is charged with ensuring compliance with all surveillance, data reporting and adverse event reporting requirements set forth in the NIH Guidelines. The UNC study coordinator will be responsible for notifying the Regulatory Associate within 48 hours should any reportable event occur.

10.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC). Dr. Grover will discuss any DLT event as it occurs, and in consultation with the study statistician, make a decision regarding continued accrual and dose escalation as appropriate. In addition, this triad will evaluate any unexpected toxicities as they occur, and determine if any changes to toxicity monitoring are required.

Meetings/teleconferences will be held with the team at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as study coordinators, data coordinators, regulatory associates, clinical data management associates, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB)).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of subjects treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

11.0 STATISTICAL CONSIDERATIONS

11.1 Design, Dose Escalation and MTD

This Phase I dose-escalation trial is designed to evaluate the safety of ATLCAR.CD30 cells. Dose-limiting toxicity is defined in section 4.1.3.3. Dose escalation is guided by the continual reassessment method (CRM) [87] in order to determine the MTD of ATLCAR.CD30 cells. For this study, MTD is defined as the dose that causes DLT in 10% of eligible cases. Three dose levels are being evaluated namely, $2x10^7$ cells/m^2, $1x10^8$ cells/m^2, and $2x10^8$ cells/m^2. Based on our previous trials, we expect a shallow dose-toxicity curve for the doses proposed in this trial. In this trial, CRM is implemented based on one parameter model in O'Quigley *et al.* [87], with DLT probability at each dose modeled as a_i^b, where constants a are (0.0281, 0.0568, 0.1) and parameter b is being estimated. The prior distribution for b is exponential with mean 1 Subjects are assigned in cohorts of size 2 until the first DLT is observed or the highest dose $2x10^8$ cells/m^2 is reached without DLT in the first two subjects assigned to $2x10^8$ cells/m^2 (initial dose escalation). After that assignments are determined by the CRM and subjects are assigned one at a time. Pediatric subjects will not be allowed to enroll at a dose until 2 adult subjects are enrolled and complete their follow-up at that dose level. To reduce the probability of treating subjects at unacceptable toxic dose levels, we employ modifications to the original CRM and do not allow skipping untried doses when the dose is escalated. Subject enrollment starts at the lowest dose level.

Two subjects will initially be allocated to the lowest dose level and followed for 6 weeks post IV injection of ATLCAR.CD30 cells for evaluation of DLTs. If any of the two subjects initially enrolled develop DLTs, the trial will be suspended, and dose levels might be re-evaluated. As soon as the first DLT is observed, dose assignment will be guided by the CRM from that point on. Otherwise, we will continue assigning subjects in cohorts of 2 at escalating doses until either a DLT is observed or the highest dose is reached without a DLT in the first two subjects. After that subjects will be assigned one at a time.

The trial will be suspended, and dose levels re-evaluated as soon as, at the lowest dose, 2 DLTs are observed out of a total of 2 subjects, 3 DLTs out of a total of 3-7 subjects, or 4 DLTs out of more than 7 subjects.

DLTs that occur within 6 weeks after infusion will be factored into the CRM calculations to determine the recommended dose for the subsequent subject. During the study, real-time monitoring of subject toxicity outcome will be performed in order to implement estimation of the dose-toxicity curve and determine dose level for the next subject cohort using one of the pre-specified dose levels. If there is a need to assign a new subject when some of the current subjects are still being followed for DLT, each subject still in follow-up will be temporarily counted as x DLTs out of 1, where x is the remaining follow-out time fraction. For example, if a subject has been followed for 2 out of 6 weeks, subject will be counted as (1-2/6) = 2/3 of a DLT out of 1 subject. This is a conservative way to account for subjects

still in follow-up. The assignment for a new subject is then determined using the CRM. When the two initial subjects are being followed for DLT at a given dose, additional subjects might be enrolled at a dose prescribed by the CRM using the rule above for imputing temporary DLT for subjects still in follow-up. This applies to pediatric subjects as well as long as there are 2 adult subjects with full 6 week follow-up for DLT at that dose. At the discretion of the investigator pediatric subjects can be assigned to a dose one level lower than specified by the CRM. During the dose escalation part guided by the CRM (after the first DLT is observed), subjects with insufficient cells manufactured and therefore infused with a quantity of cells consistent with a dose lower than the one prescribed by the CRM will be included in the CRM calculations with the weight of 0.5. This will allow us to use data from these subjects and, at the same time, not to bias the dose calculated by the CRM downward. If the number of such subjects exceeds 3, we will consider increasing the sample size of the dose escalation part of the study.

11.2 Sample Size

The trial will continue until a minimum of 12 subjects is treated. Six additional subjects might be accrued to obtain more data. Assignment of these subjects will be guided by the CRM. However, a lower dose can be chosen for assignment. Depending on subject availability, a maximum of 18 subjects will be accrued into this Phase I trial. The final MTD will be the dose with estimated probability of the DLT closest to the target toxicity rate of 10%. All subjects, adult and pediatric, will be included in MTD estimation. We therefore expect to enroll between 12-18 subjects into this trial.

11.3 Data Analysis Plans

11.3.1 Safety Analysis of Adverse Event Data

All subjects who received the ATLCAR.CD30 infusion will be included in the safety analysis. Adverse event data and corresponding toxicity grades six weeks after T-cell infusion and during long-term follow-up will be summarized in the form of tables. Incidence tables will be generated to summarize incidence of subjects reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be displayed.

Listings of adverse events by subjects will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. Safety data will be summarized for the overall subject group and by dose levels.

11.3.2 Safety Analysis of Laboratory Data

Laboratory data, which includes CBC, BUN, creatinine, and liver function tests, will be examined in different ways. Descriptive statistics (means, standard deviations, medians and ranges) at pre-infusion, and at 1, 2, 4, 6 weeks post- T-cell infusion will be calculated. Laboratory data collected at 3-month intervals for the first year will also be summarized. A scatter diagram depicting laboratory values at each time point for each subject will also be generated. In order to analyze changes in laboratory values, a shift table with Stuart-Maxwell chi-square analysis of the change in the normal range from pre-infusion to post infusion time points (using high, normal, low) will be performed. When appropriate, these tables are collapsed and the McNemar's test applied in place of the Stuart-Maxwell test. These statistical tests will be primarily performed for the overall subject group.

11.3.3 Analysis of Expansion and Persistence of Transduced T Cells

The frequency of T cells transduced with the vector (T cells expressing will be summarized at pre and post-infusion time points using mean ± SD, medians and ranges to evaluate their expansion and persistence. Changes in each of these T cells from pre-infusion to each time point of post-infusion will be assessed and compared using paired t-tests, or when appropriate, the Wilcoxon signed ranks test. Paired comparisons of these T cells within a subject at each time point will also be performed. These analyses will be performed in the overall subject group.

Plots of growth curves will be generated to graphically illustrate patterns of T-cell expansion. Plots will be generated to depict patterns of survival and expansion of T cells for each of the two vectors. Longitudinal modeling techniques such as the random coefficient mixed model will be employed to model each of the repeatedly-measured T cells. These models account for variation in individual-level intercepts and slopes over the follow-up time. Thus, we will be able to model proliferation of T cells over time and estimate the magnitude of expansion or decline of T cells. We will include dose level as an independent variable in the model to account for different doses received by subjects.

Alternative strategies to analyze these outcomes include calculation of area under the curve over time for T cell frequencies or piecewise longitudinal models based on apparent trends from plots of growth curves. Despite the small subject numbers, a data-dense study will be generated due to the repeat measurements on proliferation, immune function, etc. on each subject. The modeling strategies proposed here are amenable to these types of data but will however be considered exploratory and interpreted with caution due to limited study power.

11.3.4 Analysis of Progression Free Survival

PFS is defined in section 3.2.1. We will estimate PFS using the Kaplan-Meier method.

11.3.5 Analysis of Integration Location and CAR T cell Behavior

Differential CAR-T cell behavioral analysis will be described by comparing CAR.CD30 integration location with CAR-T cell behaviors such as expansion, persistence and trafficking. Logistic regression will be used with loss of response to the experimental therapy as an outcome to assess potential causes for loss of responses. Additionally, we will assess the correlations between CAR T cell behavior and the integration locations of CAR.CD30.

12.0 STUDY MANAGEMENT

12.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

12.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial Disclosures
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

12.3 Registration Procedures

All subjects must be registered with the LCCC CPO Multicenter Office at the University of North Carolina before enrollment to study. To register a subject call the Multicenter office at 919-966-7359 Monday-Friday 8:30 am – 5:00 pm EST. Scan and email the Multicenter Project Manager (CPOMultiCenter@med.unc.edu; preferred) or fax (919-966-4300) the registration form, signed informed consents, signed eligibility form and all source documents to confirm eligibility. Eligibility may be confirmed by the UNC Study Coordinator for subjects treated at UNC. When sending registration request with eligibility documentation, please allow 24 hours for source to be reviewed.

12.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

12.4.1 Emergency Modifications

UNC and multicenter site investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

12.4.2 Single Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

12.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants

- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC or multicenter site personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems:

Multicenter Sites:

Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the Multicenter Project Manager. The Regulatory Associate will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Regulatory Associate using the IRB's web-based reporting system.

12.5 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.6 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

13.0 AUDITING AND MONITORING

The multicenter team of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based electronic data capture system, Advarra EDC. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). Multicenter personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into Advarra EDC by research coordinators from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into Advarra EDC. The UNC Clinical Data Management Associate can be reached at 919-843-2742 or 1-877-668-0683.

All data will be monitored and source data will be verified on selected subjects. Participating sites must send source documents to LCCC upon request, for remote monitoring review. Queries will be issued on an ongoing basis on all subjects. Participating sites should respond to data queries within 14 days of receipt.

As an investigator initiated study, this trial will also be audited by the Lineberger Comprehensive Cancer Center Compliance Committee every six or twelve months, depending on the participation of multicenter sites.

14.0 **AMENDMENTS**

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the subject, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

15.0 STUDY DISCONTINUATION

Both Lineberger Comprehensive Cancer Center and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Lineberger Comprehensive Cancer Center or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, Lineberger Comprehensive Cancer Center and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

16.0 **CONFIDENTIALITY**

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Lineberger Comprehensive Cancer Center. However, authorized regulatory officials, IRB/IEC personnel, Lineberger Comprehensive Cancer Center and its authorized representatives are allowed full access to the records.

Identification of subjects and eCRFs shall be by initials, screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

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18.0 APPENDICES

18.1 APPENDIX I – Names of Study Personnel

Sponsor:	Lineberger Comprehensive Cancer Center
Principal Investigator:	Natalie Grover, MD Assistant Professor Division of Hematology 170 Manning Drive 3142 Houpt Building Campus Box 7305 Chapel Hill, NC 27599 E-mail: Natalie_grover@med.unc.edu Phone: (919) 843-5968
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18.2 APPENDIX II- Revised Response Criteria for Lymphoma

(Cheson, et al. J Clin Oncol. 2014;32(27):3059-68)

Response criteria	PET-CT-based response	CT-based response
Complete remission (CR)		
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5-PS**	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 physiological uptake or with activation within spleen or marrow, e.g., with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake	No extralymphatic sites of disease
Non-measured 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 remission (PR)		
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 measureable 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 mm × 0 mm
		For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured 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 (SD)		
Target nodes/nodal masses, extranodal lesions	No response: score 4 or 5 with no significant change in FDG uptake from baseline, at interim or end of treatment	Stable disease: <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met
Non-measured 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 (PD)		
Individual target nodes/nodal masses, extranodal lesions	Score 4, 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	PPD progression: An individual node must be abnormal with: • LDi >1.5 cm • Increase by ≥50% from PPD nadir 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 (e.g., 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
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology, e.g. 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 less than 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

Measured dominant lesions: up to six of the largest dominant nodes, nodal masses and extranodal lesions selected to be clearly measurable in 2 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, e.g., liver, spleen, kidneys, lungs, etc., gastrointestinal involvement, cutaneous lesions of those noted on palpation. Non-measured 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, measurable or which 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, e.g., gastrointestinal tract, liver, and bone marrow, FDG uptake may be greater than mediastinum with CMR, but should be no higher than surrounding normal physiologic uptake, e.g., with marrow activation due to chemotherapy or myeloid growth factors. SPD, sum of the product of the perpendicular diameters for multiple lesions; LDi, longest transverse diameter of a lesion; SDi, shortest axis perpendicular to the LDi; PPD, cross product of the LDi and perpendicular diameter. *, score 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 score 3 as inadequate response (to avoid under-treatment); **, PET five point scale (5-PS): 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. Reprinted from reference (1).

18.3 APPENDIX III- Lansky and Karnofsky Performance Status

Lansky		**Karnofsky**	
Score	**Description**	**Score**	**Description**
100	Fully active, normal	100	Normal, no complaints, no evidence of disease
90	Minor restrictions with strenuous physical activity	90	Able to carry on normal activity, minor signs or symptoms of disease
80	Active, but gets tired more quickly	80	Normal activity with effort; some signs or symptoms of disease
70	Both greater restriction of, and less time spent in, active play	70	Cares for self, unable to carry on normal activity or do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	60	Required occasional assistance, but is able to care for most of his/her needs
50	Lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities	50	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet activities	40	Disabled, requires special care and assistance
30	Stuck in bed; needs help even for quiet play	30	Severely disabled, hospitalization indicated. Death not imminent
20	Often sleeping; play is entirely limited to very passive activities	20	Very sick, hospitalization indicated. Death not imminent.
10	Does not play nor get out of bed	10	Moribund, fatal processes progressing rapidly.

18.4 APPENDIX IV - Abbreviated Follow Up Required After Initiating Alternative Therapy

Subjects should not receive other antineoplastic agents for at least 6 weeks post T cell infusion (for purposes of evaluation). Subjects who experience disease progression after a cell infusion may receive other therapy if needed at the discretion of their attending physician. If subjects receive other therapy they will come off study for adverse event reporting after the 6-week assessments outlined in section 4.2 are completed. Subsequent follow up assessments for subjects post progression are outlined in the table below. If subjects initiate alternative therapy after they have completed the initial 6-week follow up period for the cell infusion, they should be contacted as outlined below. The timing for each visit relates to the last cell infusion received by the subject. Follow up kits and instructions will be provided to subjects who initiate alternative therapy. Blood samples should be collected by a local health care provider as outlined in the laboratory manual.

Table 7 Abbreviated Follow-up After Initiating Alternative Therapy

Assessments[1]	**Post Disease Progression Follow Up**			
	Month 3 D1	**Month 6 D1**	**Month 12 D1**	**Yearly**
History[2]	X	X	X	X
Performance status	X	X	X	X
Correlative Samples[3]	X	X	X	X
Survival	X	X	X	X

Footnotes for the Abbreviated Follow-up After Initiating Alternative Therapy T&E Table

1. A window of +/-10 days will apply to the every 3 months study visits, and a window of +/-30 days will apply to visits separated by ≥ 6 months. Yearly follow-up visits are required during long-term follow-up for a total of 15 years or until death.

2. History and performance status information will be collected via the phone contact. Survival will also be documented. Medical history must include collecting the following information: 1. New malignancy(ies) 2. New incidence or exacerbation of pre-existing neurologic disorder 3. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder 4. New incidence of a hematologic disorder and 5. New incidence of infection (potentially product related).

3. Correlative analysis will include the following. Correlative blood sample collection will cease if the samples are no longer required for function and persistence or clonality analysis.

    a. Persistence and Function: The analyses will be used to monitor persistence and function of adoptively transferred cells in peripheral blood and will include

immunophenotyping as well as quantitative polymerase chain reaction (qPCR) to detect transgene persistence and by functional assays such as in vitro reactivation of PBMCs in subjects for whom the appropriate reagents are available. Quantitative real-time PCR to detect the transgenes will be collected at the 3-, 6-, 9-, and 12-months visits. Function and persistence will be continued for up to one-year post-CAR T cell infusion. If a transgene copy number is >500 copies/µg DNA, then samples to determine transgene copy numbers will be collected every 6 months after the first year until transgene copy number is <500 copies/µg DNA at which time samples will then be collected yearly for up to a total of 15 years. If transgene is no longer detectable by PCR after 1-year post-final CAR T infusion, then collection for function and persistence will discontinue. See Section 7.5 and the Laboratory Manual for the amount of blood collected/type of tube used for all of the correlative studies.

b. Clonality: If the transgene is detected at > 0.5% by flow cytometry at the 6-month sample collection timepoint, then PCR to detect retroviral integrant clonality and integrant locus will be performed. This analysis will continue every 6 months until detection is < 0.5% for up to 5 years. After this time, it will be collected annually. If the level of detection is < 0.5% at 6-months, samples will be collected annually and may be archived. Samples will no longer be collected if detection is < 0.5% for more than 1 consecutive testing period. See Section 7.5.3.

c. RCR: For replication competent retrovirus (RCR) testing, subject blood samples will be collected and stored pre-infusion. The pre-infusion sample will only be tested if the subject develops a long-term gene therapy side effect as described in Section 7.5.2. Additional samples for RCR testing will only be collected and subsequently analyzed in the event that the subject develops a long-term gene therapy side effect as described in Section 7.5.2.

18.5 APPENDIX V - Patient Reported Outcomes Surveys

Global Health Scale

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
Global09	How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst imaginable pain**

Physical Function – Short Form 20a

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16	Are you able to dress yourself, including tying shoelaces and doing buttons?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA34	Are you able to wash your back?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA38	Are you able to dry your back with a towel?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA51	Are you able to sit on the edge of a bed?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA56	Are you able to get in and out of a car?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB19	Are you able to squeeze a new tube of toothpaste?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB22	Are you able to hold a plate full of food?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB24	Are you able to run a short distance, such as to catch a bus?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45	Are you able to get on and off the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC46	Are you able to transfer from a bed to a chair and back?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFA1	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC12	Does your health now limit you in doing two hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36	Does your health now limit you in walking more than a mile?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

6.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

7.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

11.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

12.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

13.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

14.	In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

15.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH CONCENTRATION at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PROBLEMS WITH CONCENTRATION INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

16.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH MEMORY at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PROBLEMS WITH MEMORY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

17.	In the last 7 days, how OFTEN did you have PAIN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN INTEREFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

18.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

19.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTEREFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

20.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTEREFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

21.	In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

22.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

23.	In the last 7 days, how OFTEN did you feel ANXIETY?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

24.	In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTEFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

25.	In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)?	
	○ Yes	○ No

26.	In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

27.	In the last 7 days, how OFTEN did you have UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTIME (NOT RELATED TO HOT FLASHES)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTIME (NOT RELATED TO HOT FLASHES) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

18.6 APPENDIX VI- Response Assessment for Cutaneous ALCL/Lymphomatoid Papulosis

Table 8 CD30+ Lymphoproliferative Disorders (LPDs) – Recommended Definitions of CD30+ LPDs

Response	Definition
I. Response in skin	
A. LYP response in skin	
Complete response (CR)	100% clearance of skin lesions
Partial response (PR)	50%-99% clearance of skin disease from baseline without new larger and persistent nodule(s)† in those with papular disease only
Stable disease (SD)	< 50% increase to < 50% clearance in skin disease from baseline without new larger and persistent nodule(s) in those with papular disease only
Loss of response	Increase of skin score of greater than the sum of nadir plus 50% baseline score in patients with CR or PR
Increased disease activity (IDA)*	> 50% increase in skin disease from baseline without larger and persistent nodules†
Progressive disease (PD)	(1) Occurrence of larger and persistent nodule(s) (> 2 cm); and (2) extracutaneous spread
Relapse	Any disease recurrence in those with CR
B. PCALCL response in skin	
CR	100% clearance of skin lesions
PR	50%-99% clearance of skin disease from baseline without new tumors
SD	< 25% increase to < 50% clearance in skin disease from baseline
PD	(1) ≥ 25% increase in skin disease from baseline; or (2) loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with CR
II. Nodes: response in lymph nodes for LYP and PCALCL‡ (peripheral and central lymph nodes)	
CR	All lymph nodes are now < 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma. In addition, lymph nodes that show lymphoma involvement by biopsy and < 1.5 cm in long axis diameter at baseline must now be ≤ 1 cm in diameter of the short axis or biopsy negative for lymphoma.
PR	Cumulative reduction ≥ 50% of the SPD [sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis)] of each abnormal lymph node at baseline and no new lymph node ≥ 1.5 cm or > 1.0 cm in the short axis if long axis is 1- to 1.5-cm diameter
SD	Fails to attain the criteria for CR, PR, and PD

PD§	(1) > 50% increase in SPD from baseline of lymph nodes; or (2) any new node ≥ 1.5 cm in greatest transverse diameter or > 1 cm in short axis diameter if 1- to 1.5-cm in long axis that is proven to be lymphoma histologically; or (3) loss of response: in those with PR or CR, > 50% increase from nadir in SPD of lymph nodes
Relapse	Any new lymph node ≥ 1.5 cm in long axis diameter in those with CR
III. Visceral disease: response in viscera for LYP and PCALCL‡	
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical examination and should be considered normal by imaging. No nodules should be present on imaging of liver or spleen. Any posttreatment mass must be determined by biopsy to be negative for lymphoma.
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline. No increase in size of liver or spleen and no new sites of involvement.
SD	Fails to attain the criteria for CR, PR, or PD
PD§	(1) > 50% increase in size (SPD) of any organs involved at baseline; or (2) new organ involvement; or (3) loss of response: in those with PR or CR, > 50% increase from nadir in the size (SPD) of any previous organ involvement
Relapse	New organ involvement in those with CR

Skin tumor burden is assessed by counting the number of lesions before, during, and after therapeutic intervention regardless of morphology (macular, papular, or nodular; ulcerated or nonulcerated). Nodules or tumors > 2 cm should be captured separately. It may be particularly useful for the investigator to note the number of lesions in the body areas. Total body photographs offer additional help in tracking lesions and making assessments.

* The term increased disease activity (IDA) has been introduced for an increase of number of papulonodular lesions (< 2 cm), which does not imply impaired prognosis.

† Larger lesions are defined as > 2 cm in diameter. Persistent lesions are defined as lesions, which do not show spontaneous regression after 12 weeks.

‡ It is still unsolved and a matter of debate whether involvement of lymph nodes and viscera in LYP exists at all or whether the occurrence of CD30+ lymphoma in lymph nodes and viscera represents ALCL, even if clonally related to LYP. Use of FDG-PET scan in this instance is compatible with other NHLs.

§ Whichever criterion occurs first.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Reference: Blood 2011; 118:4024-4035.

Global Response Score for LYP and PCALCL

Table 9 Global Response Score for LYP and PCALCL

Global Score*	Definition	Skin	Node	Viscera
LYP				
CR	Complete disappearance of all clinical evidence of disease	CR	CR or NI	NI
PR	Regression of measurable disease	CR	No CR but no PD	NI
		PR	No PD	NI
SD	Failure to attain CR, PR, or PD representative of all disease	SD or IDA (Table 19, point I)	No PD	NI
PD	Progressive disease	PD in any category	PD in any category	PD in any category
Relapse	Recurrence disease in prior CR	Relapse in any category	Relapse in any category	Relapse in any category
PCALCL				
CR	Complete disappearance of all clinical evidence of disease	CR	Both categories have CR or NI	Both categories have CR or NI
PR	Regression of measurable disease	CR	Both categories do not have a CR or NI but no PD	Both categories do not have a CR or NI but no PD
		PR	No category has a PD; and if either category is involved at baseline, at least one has a CR or PR	No category has a PD; and if either category is involved at baseline, at least one has a CR or PR
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD; and if either is involved at baseline, no CR or PR in either CR/NI, PR, OR SD in any category and neither category has a PD	No category has a PD; and if either is involved at baseline, no CR or PR in either CR/NI, PR, OR SD in any category and neither category has a PD
PD	Progressive disease	PD in any category	PD in any category	PD in any category
Relapse	Recurrence disease in prior CR	Relapse in any category	Relapse in any category	Relapse in any category

NI indicates noninvolved
Reference: Blood 2011; 118:4024-4035.

18.7 APPENDIX VII - Response Assessment for Mycoses Fungoides and Sézary Syndrome

Table 10 Modified Severity Weighted Assessment Tool for Mycoses Fungoides and Sézary Syndrome

Body Region	**% BSA in Body Region**	**Assessment of Involvement in Patient's Skin**		
		Patch*	**Plaque†**	**Tumor‡**
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

NOTE. mSWAT score equals summation of each column line.
Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.
*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

(Reference: Olsen EA, et al. J Clin Oncol 2011;29(18): 2598-2607)

Table 11 Response in Lymph Nodes* for Mycoses Fungoides and Sézary Syndrome

Response	Definition
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD†	≥ 50% increase in SPD from baseline of lymph nodes or Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N3 histologically or Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N3 histologically

*Peripheral and central lymph nodes.

†Whichever criterion occurs first.

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

Table 12 Response in Blood* for Mycoses Fungoides and Sézary Syndrome

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/μL or Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

*As determined by absolute numbers of neoplastic cells/μL.

†If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.

‡There is no PR in those with B1 disease at baseline as the difference within the range of neoplastic cells that define B1 is not considered significant and should not affect determination of global objective response.

§Whichever occurs first.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

(Reference: Olsen EA, et al. J Clin Oncol 2011;29(18): 2598-2607)

Table 13 Global Response Score for Mycoses Fungoides and Sézary Syndrome

Global Score*	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

*It is recommended that not only the proportion of patients who achieve a response or an unfavorable outcome be calculated but a life table account for the length of the interval during which each patient is under observation also be generated.

Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.

(Reference: Olsen EA, et al. J Clin Oncol 2011;29(18): 2598-2607)

18.8 APPENDIX VIII- CRS Toxicity Grading Scale and Management Guidelines

Version 2.0 (November 2, 2017)

BACKGROUND

Immunotherapies in cancer care are becoming more widely available. As these therapies are being used more commonly, clinicians must be aware of their unique toxicities and the optimal strategies that are recommended for the management of these toxicities. One toxicity in particular associated with these immunotherapies is cytokine release syndrome (CRS). This life-threatening toxicity, if not managed both appropriately and in a timely manner, can lead to multi-organ failure and death.

Cytokine release syndrome has been observed with several different immunotherapies, including monoclonal antibodies, bi-specific antibodies, T-cell checkpoint inhibitors, and novel T-cell therapies. It is characterized by widespread activation and proliferation of lymphocytes leading to an abundant release of inflammatory cytokines well above physiologic levels. This cytokine storm can manifest in many ways from constitutional symptoms to cardiovascular and neurologic compromise. Management of this cytokine release storm involves both supportive care, and if clinically warranted, immunosuppression that blunts the aggressive cytokine response. However, administration of immunosuppressive therapies may also counter the desired immune response against targeted tumor cells. Thus, it is important that clinicians be prudent and reserve certain immunosuppressive strategies for the most appropriate clinical scenario. Thus, an algorithm that defines different grades of CRS and the corresponding therapy is necessary to guide clinicians in the delivery of appropriate care.

SIGNS/SYMPTOMS & CLINICAL GRADING

Severity of cytokine release syndrome is variable and may be influenced by tumor burden at the time of treatment with the immune-directed therapy or other pre-existing comorbidities. Clinical grading is important for appropriate management. Organ systems affected by CRS and their corresponding signs and symptoms are listed below in Table 14 and criteria for clinical grading are outlined below in Table 15.

Table 14 Signs and Symptoms of CRS

Organ System	Signs/Symptoms
Constitutional	Fever, rigors, malaise, fatigue, anorexia, headache, myalgias/arthralgias, nausea/ vomiting
Dermatologic	Rash
Gastrointestinal	Nausea/vomiting/diarrhea
Respiratory	Tachypnea, hypoxemia (potentially requiring supplemental oxygen/ventilation)

Organ System	Signs/Symptoms
Cardiovascular	Tachycardia, hypotension
Coagulation	Disseminated intravascular coagulation (DIC) characterized by elevated D-dimer, hypofibrinogenemia, bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Altered mental status, confusion, delirium, aphasia, hallucinations, tremor, seizures, ataxia

CRS Grading/Severity

The outlined clinical grading criteria, based on NCI CTCAE v4.0, is designed to guide clinicians in the management of CRS. Many of the signs and symptoms associated with CRS can also be attributable to other common complications of cancer therapy such as neutropenic fever, other infectious complications, and tumor lysis syndrome. Thus, in applying the criteria below, clinicians should exercise appropriate clinical judgement in each patient-specific scenario in an effort to distinguish true CRS from other cancer treatment-related toxicities. This will ensure appropriate delivery of care and avoidance of therapies that may otherwise not be indicated.

Table 15 CRS Grading

Grade 1 – Mild (Symptomatic Management)
Symptoms largely limited to constitutional symptoms listed above (Table 14) **Only requires symptomatic management**
Grade 2 – Moderate (Moderate Intervention)
Hypotension responsive to fluids or single, low dose vasopressor **Oxygen requirement <40%** **Grade 2 organ toxicity**
Grade 3 – Severe (Aggressive Intervention)
Hypotension requiring high dose or >1 vasopressor **Oxygen requirement ≥40%** **Grade 3 organ toxicity** **Grade 4 transaminitis**
Grade 4 – Life-threatening (Life-sustaining intervention)
Ventilator support required **Grade 4 organ toxicity, excluding transaminitis**
Grade 5 – Death
Death

MANAGEMENT OF CRS

MANAGEMENT OF CRS

Management of CRS involves both supportive measures and pharmacologic therapies that inhibit immune activation and amplification. Supportive measures are directed at managing constitutional symptoms and achieving and maintaining hemodynamic stability. Immune targeted therapies are directed at the cytokines released in the pathobiology of the syndrome. Cytokines identified to play a role in CRS include, but are likely not limited to, TNFα, IFNy, IL-1β, IL-2, IL-5, IL-6, IL-8, and IL-10. Therapies utilized in CRS exhibit either a non-specific inhibition of immune amplification or a more targeted inhibition of a particular cytokine. These therapies are outlined below.

Tocilizumab

Tocilizumab is a humanized monoclonal IL-6 receptor antibody that inhibits IL-6 from binding to both cell-associated and soluble IL-6 receptors. IL-6 is a cytokine that has been implicated in the pathogenesis of CRS and presents a pharmacologic target for management. Thus, treatment strategies for CRS have focused on inhibiting IL-6 signaling.

Tocilizumab can be administered in Grade 2-4 CRS, resulting in a rapid reversal of symptoms. If there is a lack of clinical improvement, a second dose can be repeated.

Dosing:

- < 30 kg: 12 mg/kg IV over 1 hour for one dose. May repeat another 12 mg/kg dose in 8 hours if there is a lack of clinical response to the initial dose. May repeat up to 3 additional doses after the initial dose (with at least an 8 hour interval between consecutive doses).

- ≥ 30 kg: 8 mg/kg IV over 1 hour for one dose (Max individual dose: 800 mg). May repeat another 8 mg/kg dose in 8 hours if there is a lack of clinical response to the initial dose (maximum of 3 additional doses after the initial dose with at least an 8 hour interval between consecutive doses).

- NOTE: Two doses of tocilizumab should be available on site for immediate use for each patient treated with CAR-T cells. These doses must be available prior to cell infusion and up to 6 weeks following cell infusion.

Corticosteroids

Steroids may be utilized in the setting of severe CRS with neurologic symptoms along with targeted cytokine therapies (i.e. tocilizumab), in severe CRS that is refractory to tocilizumab therapy, or as monotherapy for patients with isolated neurologic toxicities without systemic CRS. Steroids exhibit a non-specific immune inhibition. Intravenous dexamethasone is the preferred steroid to be initiated if steroids are warranted due to neurological symptoms given improved CNS penetration. Methylprednisolone can be used as an alternative. With appropriate response, steroids can be tapered rapidly over a few days. Dosing is as follows.

- Dexamethasone;
    - Adult: 4-10 mg (max single dose 10 mg) IV q 6 hours
    - Pediatrics: 0.1 mg/kg (max single dose 10 mg) IV q 6 hours
- Methylprednisolone
    - Adults: 1-2 mg/kg/day IV
    - Pediatrics: 1-2 mg/kg/day IV; max daily dose 125 mg

TREATMENT ALGORITHM

Important Considerations

The following adult and pediatric treatment algorithms serve as a framework for the management of patients with CRS and are not meant to replace physician discretion. Given that each patient will require thorough clinical evaluation for proper management, an attending physician should be notified at the first signs/symptoms suggestive of CRS and should be involved in each therapeutic decision made throughout the progression of care. This includes supportive and pharmacologic interventions, as well as escalation of care from the floor to ICU-level care.

Initiation of tocilizumab and/or steroids for CRS from CAR-T therapy must be approved by one of the attendings listed in the link provided:

http://intranet.unchealthcare.org/intranet/hospitaldepartments/uncsct/cell_therapy_resources

Table 16 Adult CRS Treatment Algorithm

Signs/Symptoms	Management
Grade 1 CRS	

• Fever (≥ 38.00 C)
• +/- additional constitutional symptoms (rigors, malaise, fatigue, anorexia, myalgias/arthralgias, nausea/vomiting)
• **Renal:** Scr >ULN – 1.5 x ULN and/or
  ○ Scr 1.5 – 2.0 x above baseline and/or
  ○ Scr increase > 0.3 mg/dL from baseline
• **Hepatic:** AST/ALT > ULN – 2.5 x ULN
	• Complete infectious workup (Cultures, Chest XR/CT, etc.)
	• Daily weights; accurate I/Os
	• Vital signs q30 mins. until symptom resolution
	• **Initiate empiric antibiotics**
	• **Supportive measures:** acetaminophen prn fevers; ondansetron or prochlorperazine prn nausea/vomiting; meperidine/morphine prn rigors

○ T.bili > ULN – 1.5 x ULN	
Grade 2 CRS	
• **CV:** Hypotension (SBP <90 mmHg or ≥ 20% decrease in baseline SBP or DBP) +/- asymptomatic tachycardia • **Pulmonary:** Decreased O2 saturation (≤88%) • **Renal:** Scr ≥ 1.5 – 3.0 x ULN and/or ○ Scr 2.0 – 3.0 x above baseline • **Hepatic:** AST/ALT > 2.5 – 5.0 x ULN and/or ○ T. Bili > 1.5 – 3.0 x ULN	• Continue monitoring and supportive measures outlined under Grade 1 CRS • **Supplemental O2 up to 40% to saturation ≥93%** • **Fluid bolus: 1000 mL IV over 1-2 hours;** • **Low dose vasopressor (Table 17) if unresponsive to fluid bolus** • **Tocilizumab 8 mg/kg IV over 1 hour x 1 dose (Max individual dose: 800 mg); may repeat every 8 hours for a max of 3 additional doses if no improvement from initial dose**
Grade 3 CRS	
• **CV:** Hypotension (SBP <90 mmHg or ≥ 20% decrease in baseline SBP or DBP) unresponsive to fluids and low dose vasopressors given for grade 2 CRS (Table 17) +/- symptomatic tachycardia • **Pulmonary:** Decreased O2 saturation (≤88%) requiring >40% to achieve saturation ≥93% • **Neuro:** Neurologic symptoms (confusion, AMS, seizure) • **Renal:** Scr > 3.0 – 6.0 x ULN and/or ○ Scr > 3.0 x above baseline or > 4.0	• Continue monitoring and supportive measures outlined under Grade 1 and 2 CRS • Increase supplemental O2 to achieve saturation ≥93% • High dose or multiple vasopressors (Table 17) • Tocilizumab as outlined in Grade 2 CRS • Dexamethasone 10 mg IV q6h if neurologic symptoms present or refractory to tocilizumab

• **Hepatic:** AST/ALT > 5.0 – 20.0 x ULN and/or o T. Bili > 3.0 -10.0 x ULN	
Grade 4 CRS	
• **CV:** Persistent hemodynamic instability (hypotension and tachycardia refractory to aggressive fluids and pressor support) • **Pulmonary:** Hypoxic respiratory failure: O2 saturation ≥93% not able to be achieved with supplemental O2 (nasal cannula, non-rebreather) • **Neuro:** Neurologic symptoms (confusion, AMS, seizures) • **Renal:** Scr > 6.0 x ULN • **Hepatic:** AST/ALT > 20.0 x ULN and/or o T. Bili > 10.0 x ULN	• Continue monitoring and supportive measures outlined in Grade 1, 2, and 3 CRS • Continue/initiate vasopressors, tocilizumab, and dexamethasone as outlined in Grade 3 CRS • **Ventilatory support** • **Dialysis if indicated (CVVHD or HD)**

Table 17. High dose vasopressors in adult patients

Vasopressor	Dose (high dose)*
Norepinephrine	≥ 20 mcg/min monotherapy
Dopamine	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200 mcg/min
Epinephrine	≥ 10 mcg/min
Vasopressin + additional vasopressor	Vasopressin + norepinephrine equivalent of ≥ 10 mcg/min

*Vasopressors at doses lower than those outlined are considered low dose vasopressors

Table 18. Pediatric CRS Treatment Algorithm

Signs/Symptoms	Management
Grade 1 CRS	

• Fever (≥ 38.00 C)
• +/- additional constitutional symptoms (rigors, malaise, fatigue, anorexia, myalgias/arthralgias, nausea/vomiting)
• **Renal:** Scr >ULN – 1.5 x ULN and/or
  ○ Scr 1.5 – 2.0 x above baseline and/or
  ○ Scr increase > 0.3 mg/dL from baseline
• **Hepatic:** AST/ALT > ULN – 2.5 x ULN and/or
  ○ T.bili > ULN – 1.5 x ULN
	• Complete infectious workup (Cultures, Chest XR/CT, etc.)
	• Daily weights; accurate I/Os
	• Vital signs q30 mins. until symptom resolution
	• **Initiate empiric antibiotics**
	• **Supportive measures:** acetaminophen prn fevers; ondansetron or prochlorperazine prn nausea/vomiting; meperidine/morphine prn rigors

Grade 2 CRS	

• **CV:** Hypotension +/- asymptomatic tachycardia (Table 19 & Table 20)
• **Pulmonary:** Decreased O2 saturation (≤88%)
• **Renal:** Scr ≥ 1.5 – 3.0 x ULN and/or
  ○ Scr 2.0 – 3.0 x above baseline
• **Hepatic:** AST/ALT > 2.5 – 5.0 x ULN and/or
  ○ T. Bili > 1.5 – 3.0 x ULN
	• Continue monitoring and supportive measures outlined under Grade 1 CRS
	• **Supplemental O2 up to 40% to saturation ≥93%**
	• **Fluid bolus: 20 mL/kg (Max: 1000 mL) IV over 1-2 hours;**
	• **Low dose vasopressor (Table 21) if unresponsive to fluid bolus**
	• **Tocilizumab**

	○ **- <30 kg: 12 mg/kg IV over 1 hour x 1 dose; May repeat every 8 hours for a max of 3 additional doses if no improvement from initial dose** ○ **- ≥30 kg: 8 mg/kg IV over 1 hour x 1 dose (Max individual dose: 800 mg); may repeat every 8 hours for a max of 3 additional doses if no improvement from initial dose**
Grade 3 CRS	
• **CV:** Hypotension unresponsive to fluids and low dose vasopressors given for grade 2 CRS +/- symptomatic tachycardia (Table 19 & Table 20)) • **Pulmonary:** Decreased O2 saturation (≤88%) requiring >40% to achieve saturation ≥93% • **Neuro:** Neurologic symptoms (confusion, AMS, seizure) • **Renal:** Scr > 3.0 – 6.0 x ULN and/or ○ Scr > 3.0 x above baseline or > 4.0 • **Hepatic:** AST/ALT > 5.0 – 20.0 x ULN and/or ○ T. Bili > 3.0 -10.0 x ULN	• Continue monitoring and supportive measures outlined under Grade 1 and 2 CRS • **Increase supplemental O2 to achieve saturation ≥93%** • **High dose or multiple vasopressors (Table 21)** • Tocilizumab as outlined in Grade 2 CRS • **Dexamethasone 0.1 mg/kg (Max 10 mg) IV q6h if neurologic symptoms present or refractory to tocilizumab**
Grade 4 CRS	
• **CV:** Persistent hemodynamic instability (hypotension and tachycardia refractory to aggressive fluids and pressor support)	• Continue monitoring and supportive measures outlined in Grade 1, 2, and 3 CRS

• **Pulmonary:** Hypoxic respiratory failure: O2 saturation ≥93% not able to be achieved with supplemental O2 (nasal cannula, non-rebreather) • **Neuro:** Neurologic symptoms (confusion, AMS, seizures) • **Renal:** Scr > 6.0 x ULN • **Hepatic:** AST/ALT > 20.0 x ULN and/or o T. Bili > 10.0 x ULN	• Continue/initiate vasopressors, tocilizumab, and dexamethasone as outlined in Grade 3 CRS • **Ventilatory support** • **Dialysis if indicated (CVVHD or HD)**

Table 19. Definition of hypotension in pediatric patients

Age	Hypotension (SBP)
0 – 28 days	< 60 mmHg
1 – 12 months	< 70 mmHg
1 – 10 years	< 70 mmHg + (age x 2)
>10 years	< 90 mmHg

Table 20. Definition of tachycardia in pediatric patients

Age	Tachycardia (HR at Rest)	Tachycardia (HR while Awake)
0 – 3 months	> 160 BPM	> 205 BPM
3 months – 2 years	> 160 BPM	> 190 BPM
2 – 10 years	> 90 BPM	> 140 BPM
>10 years	> 90 BPM	> 100 BPM

Table 21. High dose vasopressors in pediatric patients

Vasopressor	Dose (high dose)*
Norepinephrine	≥ 2 mcg/kg/min
Dopamine	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 5 mcg/kg/min
Epinephrine	≥ 1 mcg/kg/min
Vasopressin	> 100 milliunits/kg/hr

*vasopressors at doses lower than those outlined are considered low dose vasopressors

References

1. Maude SL, Barrett D, Teachey DT, Grupp S. Managing cytokine release syndrome associated with novel T cell-engaging therapies. J Cancer 2014;20(2):119-122.

2. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195.

3. Frey NV, Levine BL, Lacey SF, et al. Refractory cytokine release syndrome in recipients of chimeric antigen receptor (CAR) T cells. Blood 2014;124(21):2296.

4. National Cancer Institute Common Terminology Criteria for Adverse Events v4.03; 2010. Available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (accessed 11/28/2015).

18.9 APPENDIX IX - Neurotoxicity Treatment Algorithm

Version 1.0, November 2, 2017

BACKGROUND

Neurotoxicity from CAR-T therapy can occur as part of cytokine release syndrome (CRS) or as an independent process. The underlying pathophysiology for neurologic toxicity from CAR-T therapy is not fully understood. CAR-T cells in the CNS may play a role. However, the heightened systemic inflammatory and cytokine state resulting from CAR-T therapy may also be a factor, as other therapies associated with increased cytokine levels have also been associated with neurologic toxicities, such as high-dose interleukin-2 (IL-2) and blinatumomab.

The symptoms and manifestations of neurotoxicity are broad and range from confusion/altered mental status to seizures. Routine monitoring is critical in patients receiving CAR-T therapy to identify neurologic symptoms early and neurology should be consulted for any patients that exhibit early signs/symptoms of neurotoxicity. Early interventions should be employed to prevent worsening, especially if therapies are already indicated such as corticosteroids.

Neurotoxicity grading should follow CTCAE v4.03.

Note that tocilizumab has no clear role in managing CAR-T-induced neurotoxicity, largely because tocilizumab is not thought to penetrate the central nervous system (CNS). If neurotoxicity occurs with concomitant CRS then tocilizumab should be employed per CRS management algorithm to treat CRS, but for neurotoxicity in the absence of CRS, tocilizumab should generally not be used.

Table 22. Neurotoxicity Treatment Algorithm

Signs/Symptoms	**Management**
Grade 1-2 neurotoxicity, excluding seizures	
• Non-life threatening symptoms which may include: moderate headaches not responding to oral medications, confusion, dizziness, hallucinations, tremor, or psychiatric changes.	• Notify covering providers, including oncology (CAR-T) attending physician. • Ensure other etiologies have been excluded as much as possible, such as

• Grade 1: Symptoms are mild and do not substantially impair function. • Grade 2: Symptoms are moderate and may impair function such as conducting instrumental activities of daily living (IADL's) like self-administering medications or using a telephone, but NOT activities of daily living (ADL's) such as dressing, walking or bathing. • **Any generalized seizures should be managed as grade 3 or greater events (see below).**	infection or toxicity from other medications. • If not already admitted, admit to inpatient for grade 2 or rapidly worsening grade 1. • Daily neurological exam including mini-mental status exam. • Consider urgent MRI brain with and without contrast. • Consider lumbar puncture to evaluate for infection. If sufficient material is available these samples may also be used for CAR T cell and cytokine analysis.
Grade 3 neurotoxicity or any non-sustained / non-recurrent generalized seizures	
• Symptoms may be severe and impair ADL's (listed above). Symptoms may include confusion/altered mental status, disorientation, aphasia, tremor, stupor, loss of consciousness, hallucinations, unstable balance, cranial nerve deficits, or psychiatric changes. • Any non-sustained / non-recurrent generalized seizures should be managed as a grade 3 neurological event. • Likely or definite strokes should be managed as a grade 4 neurological event.	• Notify covering providers, including oncology fellow and oncology (CAR-T) attending • If not already admitted, admit to inpatient floor bed with seizure precautions. Consider stepdown / ICU, particularly if event is a seizure. • **Neurological exam at least every 8 hours plus daily mini-mental status exam.** • **Consult neurology service.** • **Obtain urgent MRI brain with and without contrast if feasible.** • **Obtain lumbar puncture to evaluate for infection if feasible. If sufficient material is available these samples may also be used for CAR T cell and cytokine analysis.**

	• **Give corticosteroids as indicated below for any grade 3 neurotoxicity or for generalized seizures of any duration.** • **Dexamethasone:** o **Adults: 10 mg IV q6h** o **Pediatrics: 0.1 mg/kg (Max 10 mg) IV q6h** • **Continue corticosteroids until symptoms have improved to Grade 1 or resolved completely.** • **If seizure activity, add levetiracetam 500 mg PO BID and/or other antiepileptics as appropriate**.
Grade 4 neurotoxicity, any recurrent / sustained generalized seizures, or any stroke	
• Life threatening symptoms including recurrent or sustained generalized seizures, or obtundation. • Likely strokes should be managed as grade 4 neurological events until if and when stroke is excluded as a probable diagnosis.	• Notify covering providers, including oncology fellow and oncology (CAR-T) attending. • Manage as grade 3 event as above, but admit to ICU. • If stroke is felt to be possible, call CODE STROKE and notify Brain Attack Team (BAT).

References:

1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195.

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