

PROTOCOL AMENDMENT #7

LCCC 1813-ATL: A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects with Relapsed/Refractory B-cell Lymphoma and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

AMENDMENT INCORPORATES (check all that apply):

- ☒ Editorial, administrative changes
- ☒ Scientific changes (IRB approval)
- ☐ Therapy changes (IRB approval)
- ☐ Eligibility Changes (IRB approval)

Rationale for Amendment: The primary purpose of this amendment is to make updates and corrections throughout the protocol, including updating the supplier of rimiducid to MD Anderson Cancer Center, clarifying concomitant medication collections, updating the virus testing window and pre-lymphodepletion imaging window, and updating the management guideline links for CRS and ICANS.

Summary of Changes:

Editorial:

1. Minor administrative/mechanical changes made throughout the protocol.
2. Section [8.4.4](#): Rimiducid safety reporting email address updated.
3. Throughout: Clarified “up to” for the blood volumes indicated for sample collections
4. Throughout: Correcting the use of “enroll” vs “treatment” where appropriate since enrollment refers to procurement rather than receiving CAR-T cells
5. Sections [12.1](#) & [12.2](#): CRS and Management links updated to a QR code

Scientific:

1. Sections [3.4.2](#), [6.1.6](#), & [7.1](#): Window for imaging pre-lymphodepletion updated to 10 days.
2. Section [6.1.2](#) & [6.1.3](#): Updated medical history and concomitant medication language for additional detail.
3. Section [4.1](#), [4.2.1](#), [7.3](#): Language about the collection of PBMCs adjusted to be less protocol specific and to allow for subjects with PBMCs already collected under a different LCCC protocol to have those used for modified CAR-T production under this protocol.
4. [T&E table](#):
 - a. Footnote 2: updated for medical history
 - b. Footnote 4: updated for concomitant medications
 - c. Footnote 8: update virus testing window to 90 days
5. Added honest broker language to Section [7.3](#).

***THE ATTACHED VERSION DATED 01/14/2025 INCORPORATES THE ABOVE REVISIONS
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PROTOCOL AMENDMENT #6

LCCC 1813-ATL: A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects with Relapsed/Refractory B-cell Lymphoma and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

AMENDMENT INCORPORATES (check all that apply):

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

Rationale for Amendment: The purpose of this protocol amendment is to amend the eligibility criteria related to steroid use to allow for more lenient steroid use in participants with CNS lymphoma who may require >10mg prednisone daily or its equivalent due to their disease. In addition, lactate dehydrogenase was removed as a required assessment after treatment. The supplier of rimiducid was updated from Bellicum Pharmaceuticals to MD Anderson Cancer Center where relevant throughout the protocol.

Summary of Changes:

Editorial:

6. Minor administrative/mechanical changes made throughout the protocol.
7. Section 5.2: Bellicum Pharmaceuticals updated to MD Anderson Cancer Center
8. Section 8.4.4: Rimiducid safety reporting email address corrected.

Scientific:

5. Section 4.1, 4.2.1, 7.3: Language about the collection of PBMCs adjusted to be less protocol specific and to allow for subjects with PBMCs already collected under a different LCCC protocol to have those used for modified CAR-T production under this protocol.
6. Table 3, T&E table, 12.3: Footnotes updates to indicate that up to 20mL of blood may be drawn.
7. T&E table (and corresponding footnote) was updated to indicate that lactate dehydrogenase testing is not required post-treatment.

Eligibility

1. Sections 3.2.3, 3.4.12: Eligibility relating to corticosteroid use adjusted for participants with primary CNS lymphoma.
2. Section 3.4.6: Criterion updated to remove “murine human chimeric monoclonal antibodies”
3. In Section 3.5: Criterion 3.5.4 regarding Karnofsky score was removed.

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PROTOCOL AMENDMENT #5

LCCC 1813-ATL: A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects with Relapsed/Refractory B-cell Lymphoma and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

AMENDMENT INCORPORATES (check all that apply):

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

Rationale for Amendment: The purpose of this protocol amendment is to clarify the imaging required for subjects with Waldenström macroglobulinemia (WM) prior to lymphodepletion, and during long term follow up. Concomitant medication collection was clarified. Further, this amendment was done to fix administrative issues, clarify and/or remove certain eligibility criteria, remove restrictions for certain prohibited medications, allow for dose reduction of fludarabine in subjects with impaired renal function, make minor clarifications regarding CRS grades as it relates to receiving full dose of rimiducid after infusion, and update CRS and ICANS grading to match most recent versions. Also, revisions were made to allow for follow up for month 3 visit and beyond to be done locally and the storage of specimens was extended.

Summary of Changes:

Editorial:

9. Minor administrative/mechanical changes made throughout the protocol.
10. Section [4.2.11](#) and section [7.2](#) were revised to reference the appropriate Appendix for abbreviated follow up.
11. The last sentence in section [8.2](#) was removed.
12. “The presence of two doses of tocilizumab onsite must be confirmed prior to cell infusion” was added to footnote 1 of the [T&E table](#).
13. Redundant content was removed from section [4.2.9](#).
14. Section [7.3](#): Storage of iC9-CAR19 T cells and material from procurement were updated to indicate that this material is to be stored for up to 15 years for subject treatment and safety purposes.
15. CRS and CNS toxicity Grading Criteria were updated to the latest version in the appendix (sections [12.1](#) and [12.2](#)).
16. Reference to the Cockcroft-Gault Formula were removed from sections [3.1](#) and [3.2](#) and the formula was removed from the appendix.

Scientific:

8. [T&E table](#) (and corresponding footnote 1) was corrected to indicate that visits for month 12 to year 5 would occur annually instead of semi-annually.
 - a. Added concomitant medications row and corresponding footnote.
9. Amended the [T&E table](#) footnote 8 to clarify imaging for WM subjects.

10. [Section 6.1.3](#): Added section for concomitant medications.

Eligibility

4. Sections [3.4.2](#): Eligibility for subjects with WM to proceed to lymphodepletion clarified for circumstances where imaging is not a useful method of disease assessment.
5. “Tumor in a location where enlargement could cause airway obstruction” was removed from eligibility criteria in section [3](#) because no instances of pseudoprogression or inflammation causing enlargement of tumor have been observed.
6. “Subjects or their Legally Authorized Representative must sign a consent to undergo cell procurement” was added to section [3.1](#).
7. Creatine clearance cut offs were replaced with serum creatine levels in eligibility sections.
8. “Subject must have active disease by imaging and/or blood assessment” was added to section [3.3.5](#) and “Presence of active disease by imaging” was added to section [3.4.2](#).
9. Eligibility restriction for steroid use was added to section [3.4](#).
10. Performance status cut off was added to section [3.4](#).
11. Organ function requirements were added to all sections of the subject eligibility section.
12. “Subject has no clinical indication of rapidly progressing disease in the opinion of the treating physician” and “Subject is a good candidate for treatment with iC9-CAR19 T cells per the investigator’s discretion” criteria were added to section [3.5](#).
13. HTLV was removed from the list of infections listed in the exclusion criteria in section [3.2.4](#) and footnote 7 of the [T&E table](#).

Therapy

1. Sections [4.0](#), [5.2](#), and [7.1](#): Clarified CRS grades as it relates to receiving full dose of rimiducid after infusion.
2. Section [4.1.3](#): Clarified language describing the rimiducid sub-study.
3. Dose adjustment for fludarabine was updated to creatinine clearance <79 ml/min in sections [4.0](#), [5.3.2.8](#), and [7.1](#) based on the product package insert.
4. Section [4.1.3](#) was reorganized for clarity.
5. Ocular ultrasound assessment was removed from section [4.1.5](#).
6. PK sample collection was removed from section [4.1.5](#).
7. Section [4.2.4](#): clarified that alternative antipyretics and antihistamines may be used.
8. “Participants meeting eligibility requirements for infusion but whose samples don’t contain sufficient numbers of iC9-CART19 T cells for their specific dose level may still be infused with the maximum number of their cells available per investigator’s discretion” was added to section [4.2.6](#).
9. Footnotes of the [T&E table](#) was revised to allow local follow up.

THE ATTACHED VERSION DATED 10/17/2023 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #4

LCCC 1813-ATL: A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects with Relapsed/Refractory B-cell Lymphoma and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

AMENDMENT INCORPORATES (check all that apply):

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

Rationale for Amendment: The protocol is amended to include a wash out period prior to lymphodepletion. Due to the aggressive nature of some patients' disease as well as concern for more rapid disease progression at discontinuation of therapy without initiation of another treatment, we are concerned that a 3 week wash out may not be feasible for some patients, especially those taking therapies with short half-lives, such as a BTK inhibitor of venetoclax. In addition, this would bias the study towards patients with more indolent disease. We feel that including a wash out of 5 half-lives for patients on agents with shorter half-lives would allow for sufficient time for the drugs to wash out and not interfere with the lymphodepletion and CAR-T cells and also still not be so long that a patient may start experience rapid progression that would prevent them from being treated. Language was also updated to include dose adjustment of lymphodepletion therapy based on creatine clearance levels.

Summary of Changes:

Eligibility

14. **Sections 3.4.2, 3.4.11:** Eligibility for study participation prior to lymphodepletion therapy updated to include no prior therapy "3 weeks of 5-half-lives (whichever is short)" prior to imaging and no investigation agent or cancer-directed therapy "3 weeks or 5-half-lives (whichever is shorter)" prior to lymphodepletion therapy.
15. **Section 3.4.8:** Eligibility for study participation prior to lymphodepletion therapy for patients with prior tumor vaccine therapy updated to remove language pertaining to "investigational agents."

Therapy

10. **Sections 4.1, 4.2.2, 5.2 and 7.1:** Language included to specify that "Patient's with creatine clearance of <50 mL/min will have fludarabine dose adjusted per institutional guidelines".

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

January 14, 2025
Amendment# 7 Version 8.0

THE ATTACHED VERSION DATED 11/01/2021 INCORPORATES THE ABOVE REVISIONS

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LCCC 1813-ATL: A Phase I Study of Autologous Activated T-cells Targeting the

PROTOCOL AMENDMENT 3

CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects with Relapsed/Refractory B-cell Lymphoma and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

AMENDMENT INCORPORATES:

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

Rationale for amendment: The purpose of this amendment is to update eligibility criteria and assessments in relation to subjects with Waldenström Macroglobulinemia and bone marrow only disease. Eligibility criteria are modified to include measurable disease assessment by measurable response criteria for Waldenström Macroglobulinemia. In turn objectives and response assessment language is updated to include response criteria for Waldenström Macroglobulinemia (added as an appendix) in disease assessment. Assessments for evaluating subjects with CLL and primary central nervous system lymphoma were included. CLL was added given CD19 expression in this malignancy and prior data showing efficacy of CD19 CAR-T cells for patients with CLL. Primary CNS lymphoma was added given recent reports of safety and efficacy in treating patients with CNS involvement with CD19 CAR-T cells. Additionally, CD19 CAR-T cells are not FDA approved for CLL or primary CNS lymphoma; therefore, cell therapy options in the case of relapsed/refractory disease are limited. This amendment also updates the rimiducid sub-study adding an additional ICANS component with two dose cohorts. Patients with ICANS were excluded from the dose finding study of rimiducid initially because the understanding of best practices in management of both CRS and ICANS has evolved within the (young) field of clinical management of CAR-T toxicities. The initial intent was to use rimiducid at the 0.4 mg/kg dose expected to ablate all CAR-T cells in the setting of severe ICANS. As the field has evolved, so has the apparent area of unmet need—interventions to prevent progression of lower grade ICANS to high grade toxicity that requires ablative doses of corticosteroids, with the intention of maintaining efficacy by not completely ablating the CAR-T cells. Thus, the current amendment aims to explore that gap. Additionally, the existing CRS component was modified to change the dose of the second dose level. An additional path of rimiducid treatment is added to the rimiducid sub-study for subjects who have grade 2 CRS or ICANS after the first dose or rimiducid. With the two existing treatment pathways in the rimiducid sub-study, treatment priority rules were established to treat subjects presenting with concurrent CRS and ICANS. Rimiducid adverse events have been updated. Collection of ICE scores is updated to be collected per standard of care instead of every 12 hours when the subject is in-patient. Included updated language clarifying the pre-lymphodepletion HAMA blood draw in the study and relative to eligibility. Lymphomatoid granulomatosis was removed from the inclusion criteria. Long-

term follow-up correlative blood collections were modified to allow for ceasing collection if transgene is undetectable. Updated funding source reporting language was added in the text. Mechanical edits were made throughout and corrections to bullet and page numbering are made in the text.

Editorial, administrative changes:

1. Protocol title was updated to include subjects with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.
2. Abbreviations were updated.
3. The numbering of the subject eligibility criteria was updated to correct numbering starting at “Exclusion Criteria for the Study” and ending at “Eligibility criteria to be met prior to cell infusion after lymphodepletion.”
4. Page numbers in the appendices were added.
5. Mechanical edits throughout
6. The word “patient” changed to “subjects” where appropriate.
7. Text links were updated as needed.
8. Section 1.5 Title: Modified title for clarification.
9. Section 4.1: Added Section reference to Appendix G in “Quality of Life Assessments” Section.
10. Section 5.2.7: Rimiducid adverse events have been updated.
11. Section 4.1.5 added references to Appendices A and F
12. Section 8.4.4: Updated funding source reporting language.
13. Appendix E: Removed repeated table related to Lugano criteria.
14. Appendix F was moved to Appendix B and remaining appendices arranged as needed.
15. The Response criteria are grouped together.

Scientific changes:

1. Section 1.1: Revised language regarding the rimiducid sub-study.
2. Section 1.4: Added reference to Waldenström Macroglobulinemia.
3. Section 1.5 was added to provide an overview of CLL/SLL
4. Section 1.6.1 was updated to provide additional information relative to the clinical experiences with CD-19 CAR-T cells.
5. Objectives 2.1, 2.2.1, 2.2.3, 2.2.4, 2.2.5, 2.2.6, were updated to add CLL/SLL.
6. Exploratory Objectives 2.3.2 and 2.3.3 were up updated to indicate new dose for rimiducid.
7. Endpoints 2.5.3, 2.5.5, and 2.5.6 were updated to include response criteria for Waldenström Macroglobulinemia Primary CNS lymphoma and CLL/SLL in disease assessment.
8. Section 4.1: Schema:
 - a. Footnote 4 updated to clarify that subjects meeting the criteria in the footnote (aside of grade 4 ICANS) receiving 0.4 mg/kg rimiducid applies to those subjects in the dose finding/escalation cohort.
9. Section 4.2.6: Provided language that indicates delays in infusions over 14 days for reasons of AEs and patient safety are not considered deviations.
10. Section 4.2.11: Updated to align with new long-term follow-up sampling.

11. Section 6.1.5: Disease assessment parameters were updated for subjects with bone marrow only disease and description of additional assessments was added for Waldenström Macroglobulinemia and CLL/SLL subjects. Additionally, disease assessment was clarified for subjects with disease not measurable by imaging and for subjects that have disease that can be followed with imaging.
12. Sections 6.4.1-6.4.3 updated to include new long-term follow-up parameters. Section 6.4.2 provides updated conditions to monitor. Section 6.4.3 is renamed to Clonality and updated to describe parameters to stop collection.
13. Sections 6.4.4 and 7.1, Time and Events Table, footnote 14: Added language to clarify the timing of the pre-lymphodepletion HAMA blood draw.
14. Time and Events Table: Additional assessments (bone marrow, SPEP/IFE, and serum light chains) added for Waldenström Macroglobulinemia, bone marrow only disease. CLL was added to the bone marrow assessment row.
 - a. Footnote #1: updated to include semi-annual follow-up language and the last two sentences addressing delayed adverse events was moved to new footnote #2
 - b. Footnote #2: Targeted toward medical history in relation to specific conditions to collect.
 - c. Footnote #8: Updated to include clarification of imaging for disease assessment for Waldenström Macroglobulinemia and a modified visit window.
 - d. Two additional footnotes (new # 10 and 11) were added to add visit parameters for the additional assessments for WM, bone marrow only disease, and CLL. Footnotes were adjusted within the Time and Events Table to accommodate the revised numbering.
 - e. Rows for RCR Testing, cytokine testing and function and persistence and qPCR were combined to make one (footnote 12) "Correlative Blood Sample Collection" Row. Footnote numbering was adjusted accordingly.
 - i. Descriptions for the correlative blood sampling (now listed as sub-bullets a-d) and testing were updated for each test and provide parameters for ceasing collections. Footnote 12a decreases persistence copy number threshold from 1000 to 500 copies/ug DNA.
 - f. HAMA Testing footnote #13 was updated to clarify timing and conditions of HAMA prior to lymphodepletion.
 - g. Footnote 16: Updated to indicate that additional ICE scores will be collected per standard of care.
 - h. Footnote 19: Rimiducid has been updated relative to the new rimiducid sub-study design.
15. Section 7.2: Assessments for Waldenström Macroglobulinemia and bone marrow only disease were described in the long-term follow-up. Additionally, this section was updated to provide for stopping parameters for correlative blood sample collections.
16. Section 7.5 updated to include assessment of efficacy for CLL/SLL subjects and subjects with bone marrow only disease. In reference to assessing disease

- progression, the reference to “initial” cell infusion was removed and it was targeted toward subjects with measurable disease by imaging.
17. Section 7.5.1: Included response criteria for Waldenström Macroglobulinemia and CLL/SLL in disease assessment.
 18. Section 9.1: Added language related to the addition of subjects with ICANS into the rimiducid sub-study.
 19. Appendix A: Table 6: CRS grading is updated.
 - a. The link to management guidelines has been updated.
 20. Appendix C: Abbreviated follow-up table updated for new follow-up procedures.
 - a. RCR and Quantitative PCR rows are combined to make a single Correlative Blood Sample Collection row.
 - b. Footnote #1: Updated to include semi-annual follow-up parameters.
 - c. The last statements on delayed adverse events were moved to Footnote#2.
 - d. Footnote #2: History updated to include conditions to collect and statements on delayed adverse reactions.
 - e. New Footnote #3 combines and updates descriptions for function and persistence, RCR and clonality testing.
 21. Appendix B: : Removed last section of first paragraph.
 - a. Table 7 ICE Scores has been updated based on updated guidelines.
 - b. Table 8: ICANS Consensus Grading is updated to align with new guidelines.
 - c. New link provided to access the ICANS management guidelines.
 22. Response criteria for Waldenström Macroglobulinemia was added as Appendix L and IWCLL criteria as Appendix M.
 23. Appendix N: Response criteria for primary CNS lymphoma added.

Therapy Changes:

1. Section 4.1: Added language including ICANS into the rimiducid sub-study in the schema legend (footnote 5) and in the body of the text.
2. Section 4.1.3: Rimiducid Sub-Study: The rimiducid sub-study was modified include ICANS treatment component.
 - a. Figure 3 was designated for CRS and ICANS. For CRS, dose level 2 was modified, and ICANS dose levels were added. The schema was made editable.
3. Section 4.1.4: This new section describes the treatment priority rules if a subject presents with CRS and ICAN simultaneously.
4. Section 5.2: Updated to include new information relative to the addition of ICANS and the new dose for dose level 2 in CRS.
5. Section 7.1: Time and Events Table: Footnote #19: Updated to include ICANS and the new rimiducid treatment parameters for CRS and ICANS.

Eligibility:

1. Criterion 3.1.3: Edited sub-bullet under “Indolent Lymphomas” that includes Waldenström Macroglobulinemia for clarity. Also added CLL/SLL. Lymphomatoid granulomatosis was removed from the criterion. Primary CNS lymphoma was added to the list of Aggressive Lymphomas.

2. Criterion 3.1.4: added to include subjects with CNS involvement of their lymphoma.
3. Criterion 3.1.6: Added criterion addressing prior therapy in primary CNS lymphoma subjects.
4. Criterion 3.1.7: Added criterion for CLL directed inclusion.
5. Criterion 3.1.8: Added to align with current FDA guidance (See #5).
6. Criterion 3.1.10: The criterion was revised to include Response Criteria for Waldenström Macroglobulinemia and IWCLL criteria for CLL, and to allow for subjects with bone marrow only disease.
7. Criterion 3.2.6 was removed from exclusion criteria and an updated criterion addressing this matter aligned with current FDA guidance was added to the inclusion criteria (criterion 3.1.8).
8. Criterion 3.3.5: Criterion updated to provide clarification relative to disease in subjects that is assessed or not assessed by imaging.
9. Criterion 3.4.2: The criterion was updated to indicate that for Waldenström Macroglobulinemia, imaging does not need to be repeated prior to lymphodepletion if no evidence of disease at screening.
10. Criterion 3.4.3: Lowered the platelet threshold to $50 \times 10^9/L$ unless related to lymphoma involvement.
11. Criterion 3.4.5: Added bone marrow for subjects with CLL/SLL or lymphoma with bone marrow only involvement.
12. Criterion 3.4.6: Updated to add conditions for HAMA prior to lymphodepletion.

THE ATTACHED VERSION DATED May 25, 2021 INCORPORATES THE ABOVE REVISIONS
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PROTOCOL AMENDMENT 2

LCCC 1813-ATL: A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects with Relapsed/Refractory B-cell Lymphoma

AMENDMENT INCORPORATES:

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

Rationale for amendment: The purpose of this amendment is to add an expansion cohort at the recommended phase 2 dose. Within the expansion cohort the dosing of rimiducid will be further explored to investigate whether rimiducid can be used to address cytokine release syndrome resulting from the infusion of iC9-CAR19 cells without completely eliminating circulating iC9-CAR19 cells, which would prevent the subject from receiving possible benefits of continued expansion and persistence of the CAR T cells.

Additionally, this amendment allows subjects with bendamustine intolerance to receive lymphodepletion with cyclophosphamide. Cyclophosphamide lymphodepletion is used prior to infusion of the 2 commercially available CAR19 T cell products.

Editorial, administrative changes:

1. The Principal Investigator was updated from Anne Beaven, MD to Natalie Grover, MD.

Scientific changes:

1. Exploratory objectives 2.3.2 and 2.3.3 and exploratory endpoints 2.6.2 and 2.6.3 were added as the result of the addition of the rimiducid sub-study.
2. Exploratory endpoint 2.6.5 and Section 6.4.5 were updated to clarify that DNA analysis will be used to determine integration locations.

Therapy Changes:

1. Sections 1.1, 4.1, 9.1 and 9.2 were updated to include an expansion cohort of 18 adult subjects at the recommended phase 2 dose.
2. Sections 1.1, 4.1, 5.2, 9.1 and the Time and Events Table were updated to include a sub-study of rimiducid. Additionally, section 4.1.3 was added to describe the rimiducid sub-study.
3. The study schema, Time and Events Table and Sections 4.2.2 and 5.3 were updated to allow for patients with intolerance to bendamustine to receive cyclophosphamide

- for lymphodepletion. Additionally, Section 12.11 Appendix K was added to provide cyclophosphamide drug information.
4. Section 4.2.10 was added to clearly delineate the medications prohibited during the lymphodepletion phase of the study.

Eligibility Changes:

1. Eligibility criterion 3.1.4 was updated to require that subjects must be negative to HIV antibody as opposed to either HIV antibody or HIV viral load.
2. Eligibility criterion 3.1.7 was edited to require that subjects be excluded if they have a history of intolerance to fludarabine. This eligibility criterion allows subjects with known history of intolerance to bendamustine to be lymphodepleted with cyclophosphamide in combination with fludarabine at the discretion of the clinical investigator.

THE ATTACHED VERSION DATED October 4, 2019 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT 1

LCCC 1813-ATL: A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects with Relapsed/Refractory B-cell Lymphoma

AMENDMENT INCORPORATES:

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

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.

Additionally, the purpose of this amendment is to update the treatment algorithm for neurotoxicity to reflect changes in guidance surrounding Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). Additionally, this protocol amendment adds an exploratory objective and endpoint to determine whether there are correlations between CAR T cell behavior and the integration location of CAR 19.

Editorial, administrative changes:

1. Formatting and administrative changes throughout, including the numbering and labeling of tables and figures.
2. Updated the Principal Investigator from Natalie Grover, MD to Anne Beaven, MD.
3. Updated reference to CRES to ICANS to be consistent with the new naming convention based on the new ASBMT guidelines.
4. Removed redundant listing of assessments, which are detailed in the T&E Table.
5. Updated FDA Expedited Reporting language in Section 8.4.2 to reflect LCCC current processes and to remove reference to the NIH RAC.
6. Updated Funding Source Reporting Requirements to be consistent with Bellicum reporting requirements.
7. Updated Section 8.5 to reflect current LCCC job titles.

8. Removed the reference in Appendix A to a list of providers who must approve use of rimiducid and/or steroids.
9. Added rimiducid, which is the international non-proprietary name for AP1903

Scientific changes:

1. Updated Section 1.5.2 Toxicities associated with CAR19 T cells to relay current standard of care management of CRS and ICANS and to add background for the toxicity management based on the Zuma-1 and Juliet trials.
2. Updated Section 1.6.2 Rationale for Conditioning Chemotherapy to remove references to the reduction of a patient's tumor burden enhancing persistence of CAR T cells.
3. Addition of Exploratory Objective 2.3.3 and Endpoint 2.6.3 to determine whether there are correlations between CAR T cell behavior and the integration location of CAR 19.
4. Updated the definition of Dose Limiting Toxicity (Section 4.1.2) to remove hematologic toxicity.
5. Updated the definition of Dose Limiting Toxicity (Section 4.1.2) to remove any treatment-emergent autoimmune toxicity Grade ≥ 3 and added any treatment emergent Grade 4 non-hematologic adverse event that does not resolve to Grade 2 within 7 days.
6. Updated Section 5.2.7 Adverse Events Associated with Rimiducid to include information from the most recent version of the Investigator's Brochure.
7. Added Section 6.4.5 and updated Section 9.1 to detail genomic analysis to determine whether there are correlations between CAR T cell behavior and the integration location of CAR 19.
8. Updated Section 6.4.7 to allow collected tissue to be used to assess for potential causes for loss of response to therapy, including, but not limited to, the loss of CD19 expression.

Therapy Changes:

1. Changed criteria for rimiducid administration to be only for grade 3 or higher ICANS as there is now more data about giving steroids to patients with ICANS (including grade 2 ICANS).
2. Updated Section 4.1.3 Sample Collection Plan Pre/Post Rimiducid Administration to include PK sampling and vital sign collection.
3. Added an additional blood sample that 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 iC9-CAR19 T cells (Section 6.4.6).
4. Updated the footnotes of the T&E table to allow a window of 7 days for all procurement labs unless otherwise specified.
5. Updated the footnotes of the T&E table to allow for a 30 day window for virus testing.
6. Clarified section 6.4.3 and Appendix B to reflect qPCR testing for transgene copy numbers and flow cytometry for transgene detection.
7. Updated the Section 6.4.6, the foot notes of the T&E table and Appendix B to allow for collection of 20 mL of blood in the event of CRS or other toxicities.

8. Updated Appendix F. Guidelines for Monitoring and Management of Neurotoxicity (Appendix F) based on new ASBMT guidelines.

Eligibility Changes:

1. Updated Inclusion Criterion 3.1.3 to allow subjects with Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia) and Burkitt lymphoma to enroll.
2. Clarified Inclusion Criterion 3.1.4 for aggressive lymphomas including specifying prior lines of therapy.

THE ATTACHED VERSION DATED April 11, 2019 INCORPORATES THE ABOVE REVISIONS
ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

LCCC 1813-ATL: A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing the Inducible Caspase 9 Safety Switch in Subjects with Relapsed/Refractory B-cell Lymphoma and Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Short Title: Anti-CD19 CAR-T cells with inducible caspase 9 safety switch for B-cell lymphoma and CLL/SLL.

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

Version Date: January 14, 2025
Protocol Amendment #7 Version 8.0

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
ATL	Autologous T lymphocytes
ATLCAR	Autologous T cell lymphocyte –Chimeric antigen receptor
β-HCG	Beta-human chorionic gonadotropin
BM	Bone Marrow
BSA	Body surface area
CAP	College of American Pathologists
CBC	Complete blood count
CAR-T	Chimeric antigen receptor T cell
cfDNA	Circulating free deoxyribonucleic acid
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum plasma drug concentration
CMP	Comprehensive metabolic panel
CNS	Central Nervous system
CofA	Certificate of analysis
CTO	Clinical Trials Office
CR	Complete response
CrCl	Creatinine Clearance
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computer tomography
DLBCL	Diffuse large B cell lymphoma
DLCO	Diffusing capacity for carbon monoxide
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMC	Data safety monitoring committee
EBV	Epstein–Barr virus
EC50	Concentration associated with 50% maximal effect
ECHO	Echocardiography
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ELISPOT	Enzyme-linked immunoSpot
EOI	End of infusion
FDA	Food and Drug Administration
FEV1	Forced expiratory volume during the first second
FKBP12	FK506-binding protein
GCP	Good clinical practice
GMP	Good Manufacturing Practice
GVHD	Graft-versus-host disease
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HAMA	Human anti-mouse antibodies
HIPAA	Health Insurance Portability and Accountability Act

HIV	Human immunodeficiency virus
IBC	Institutional biosafety committee
iCasp9	Inducible human caspase 9
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
ICH	International Conference on Harmonization
IDS	Investigational drug service
IFE	Immunofixation electrophoresis
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
INR	International normalized ratio
IP	Intraperitoneal
IRB	Institutional Review Board
IV	Intravenous
KPS	Karnofsky performance status
LCCC	Lineberger Comprehensive Cancer Center
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAS	Macrophage activation syndrome
MHS	Major histocompatibility complex
Mo-MuLV	Moloney murine leukemia virus-based vector
MRI	Magnetic resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NF-κB	Nuclear factor kappa light-chain enhancer of activated B cells
NGFR	Nerve growth factor receptor
NIH	National Institute of Health
NK	Natural killer
OHRE	Office of Human Research Ethics
ORR	Overall response rate
OS	Overall survival
OSP	Office of science policy
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic or Progressive disease
PET	Positron Emission Tomography
PFS	Progression free survival
PR	Partial response
PRC	Protocol review committee
PRO	Patient reported outcomes
PT	Prothrombin time
PTT	Partial thromboplastin time
QA	Quality assurance
qPCR	Quantitative polymerase chain reaction
RBC	Red blood cell
RCR	Replication competent retrovirus
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
s.c.	Subcutaneous

scFv	Single-chain Fv molecule
SCID	Severe combined immunodeficiency syndrome
sCR	Stringent complete response
SD	Stable disease
SLM	Study laboratory manual
SOC	Standard of care
SOP	Standard operating procedure
SPEP	Serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
t _{1/2}	Half-life
TCD	Tolerable cell dose
TCR	T cell receptor
TLS	Tumor lysis syndrome
ULN	Upper limit of normal
UNC	University of North Carolina
VGPR	Very good partial response
WM	Waldenström Macroglobulinemia
WOCBP	Woman of childbearing potential

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

LCCC1813-ATL is a Phase I dose finding trial to determine if chimeric antigen receptor T (CAR-T) cells targeting the CD19 antigen and containing the inducible caspase 9 safety switch can be safely administered to adult subjects with relapsed or refractory B-cell Lymphoma. The safety of iC9-CAR19 cells will be investigated using the 3+3 design. The starting dose of 1×10^6 transduced cells/kg (dose level 1) will treat at least 3 subjects in the initial cohort. If there are no dose limiting toxicities (DLTs) within 4 weeks of the cell infusion in these 3 subjects, then the next cohort will evaluate 2×10^6 transduced cells/kg. If there is toxicity in 1/3 subjects in the initial cohort, the cohort will be expanded to treat up to 6 subjects. During iC9-CAR19 T cell dose exploration, rimiducid (0.4 mg/kg), a dimerizing agent that is designed to engage and activate the caspase 9 safety switch to trigger iC9-CAR19 T cell death by apoptosis will be given to subjects who develop grade 4 cytokine release syndrome (CRS) or grade 3 CRS that is unresponsive to standard of care interventions, and to subjects who develop grade ≥ 3 ICANS that does not improve to grade ≤ 1 within 72 hours with standard of care interventions, and subjects with grade 4 ICANS of any duration that have evidence of cerebral edema and/or generalized convulsive status epilepticus. After the tolerable cell dose (TCD) of iC9-CAR19 T cells has been determined, up to 18 additional adult subjects may be treated in an expansion cohort at the TCD. Rimiducid will be given to subjects in the expansion cohort who develop grade ≥ 3 immune effector cell-associated neurotoxicity syndrome (ICANS) that does not improve to grade ≤ 1 within 72 hours with standard of care interventions, in addition to subjects with grade 4 ICANS of any duration that have evidence of cerebral edema and/or generalized convulsive status epilepticus. Subjects in the expansion cohort who experience $\geq$ grade 2 CRS or ICANS that remains $\geq$ grade 2 twenty-four hours after initial standard of care treatment (tocilizumab for CRS or steroids for ICANS) may be part of the rimiducid sub-study. These subjects will receive one of two assigned dose levels of rimiducid with their second standard of care treatment. The percent reduction in CAR T cells will be measured in these subjects. If the subjects' CRS or ICANS is unresponsive to standard treatment and the assigned dose level of rimiducid, subjects with $\geq$ grade 3 CRS or ICANS will then be given a full dose (0.4 mg/kg) of rimiducid. If the subject's CRS or ICANS is at grade 2 48 hours after the first dose of rimiducid, they will receive another dose of rimiducid at the assigned dose level.

1.2 Diffuse Large B-Cell Lymphoma (DLBCL)

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of lymphoma and accounts for about 30-40% of all cases of Non-Hodgkin lymphoma[4, 5]. Although response rates and survival are high in patients receiving standard first line therapy, the prognosis for patients with relapsed or refractory disease is poor[6]. The standard of care for subjects who are fit is salvage chemotherapy followed by autologous stem cell transplant (ASCT). Patients who do not respond to second line therapy are unlikely to respond to subsequent lines of therapy and have a median overall survival of 4 months[7]. In patients who progress after ASCT, the median overall survival is less than 10 months[8].

Effective agents are lacking in the relapsed/refractory setting and novel therapies are clearly warranted for these patients.

1.3 Current Standard of Care

There are limited treatment options for patients with relapsed or refractory DLBCL who have progressed after ASCT or ineligible for ASCT. One possible curative approach in fit patients is allogeneic stem cell transplant, although this approach has high treatment-related morbidity and mortality and moderate control[9, 10]. The goals of therapy for patients not eligible for transplant or who have progressed post-transplant are generally palliative. Enrollment in clinical trials is encouraged in these patients. Although there are some novel agents with promising activity in this population, such as lenalidomide which showed a 35% response rate in patients with relapsed aggressive lymphoma[11], more effective novel approaches are urgently needed in this population. Patients with refractory DLBCL defined as no response to last line of chemotherapy or relapse within one year of ASCT, have a complete response rate of 7% to salvage therapy and median overall survival of 6.3 months[12]. Therefore, the standard of care is inadequate in this high-risk patient group.

1.4 Indolent Lymphomas

Approximately 80,000 new cases of lymphoma were expected to be diagnosed in the US in 2017 with 21,000 deaths[13]. Almost half of these cases are indolent lymphomas (iNHL) such as follicular lymphoma (FL), Mantle Cell Lymphoma (MCL), Marginal zone lymphoma (MZL), and Waldenström macroglobulinemia (WM)[14]. Indolent non-Hodgkin lymphomas are slow growing lymphomas with median overall survivals that, in some subtypes, are over 10 years. At the time of diagnosis, many patients have a low burden of disease and do not require treatment right away; unfortunately, in most cases there is no cure for the disease. Patients are typically followed without treatment until they have signs or symptoms (weight loss, pain, bulky disease) that require treatment. Once treatment is indicated, the typical patient receives chemotherapy with a goal of obtaining a remission after which treatment is stopped. The patient is then followed until disease progression and re-occurrence of symptoms at which time they are treated again but with a different agent. This cycle can continue indefinitely as long as patients are doing well; however, the duration of each remission gets progressively shorter and eventually the lymphoma may become resistant to available treatment options. For this reason, it is important that research continue to find more effective and well-tolerated treatment for this patient population.

1.5 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Overview

CLL/SLL is a hematologic malignancy resulting in a gradual accumulation of monoclonal mature B lymphocytes. It is the most common form of leukemia in the United States, with about 21,000 new cases expected to be diagnosed in 2020 [15]. The tempo of disease progression in CLL/SLL is very heterogeneous. Most patients generally have an indolent course but certain subsets of patients can progress rapidly. In addition, CLL/SLL can occasionally undergo Richter's Transformation and transmute into an aggressive B cell lymphoma. Patients are typically followed without treatment until they have signs or

symptoms (B symptoms, symptomatic cytopenias, bulky disease) that require treatment. Initial therapy for symptomatic or advanced CLL/SLL used to be chemotherapy, but now has been increasingly replaced in the frontline setting with novel agents such as Bruton's Tyrosine Kinase Inhibitors such as ibrutinib [16] or BCL2 inhibitors such as venetoclax [17]. Usually, these novel agent treatments are given either for a fixed duration or until disease progression, depending on the agent. When disease progression is detected, their treatment is switched to a different agent or chemotherapy. This cycle continues indefinitely as long as patients are responding and tolerating treatment well. However, CLL/SLL cannot be cured with current available therapies and ultimately the disease becomes resistant to treatment options. As a result, further research is vital in exploring new, innovative approaches to treating and possibly curing this disease.

1.6 Investigational Treatment – CD19 CAR-T therapy for B-Cell Lymphomas

CD19 is a 95-kDa B lineage-specific transmembrane glycoprotein, which functions as a central response regulator in B-lymphocytes. CD19 is expressed on B-cells during all stages of their differentiation and is maintained on cells that have undergone neoplastic transformation[18]. It is expressed on the majority of cells in patients with B-cell Non-Hodgkin Lymphoma and recent studies have also shown that CD19 expression is maintained despite loss of CD20 expression following treatment with anti-CD20 antibodies. As a result, CD19 has become a promising target for therapies directed against B-cell malignancies including DLBCL. In fact, the most investigated target for chimeric antigen T cell receptor (CAR) therapy to date is CD19[19].

Since B-cell leukemias and lymphomas are sensitive to cellular immune responses and antibody treatment, there has been a great deal of interest in combining both approaches through the generation of CARs. The introduction of CARs into T cells allows the rapid generation of effector cells specific for virtually any surface molecule[20], such as CD19 and has significantly increased the applicability of adoptive transfer of tumor-specific cytotoxic T lymphocytes (CTLs). CARs are generated by joining the heavy and light chain variable regions of a monoclonal antibody with a linker to form a single-chain Fv (scFv) molecule that is then fused with co-stimulatory endodomains (such as CD28 or 4-1BB) and the cytoplasmic portion of the T cell receptor's (TCR) ζ chain[20-23]. T lymphocytes engrafted with these molecules acquire the capacity to recognize and lyse tumor cells expressing the antigen recognized by the scFv and to proliferate in response to the antigen due to the activation of either CD28 or 4-1BB signaling pathways[23, 24].

The advantages of CARs over the native antibodies or ligands from which they are derived are a consequence of their physical association with effector T cells[21, 25, 26]. Thus, CAR-modified 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 alpha, beta T cell receptors ($\alpha\beta$ TCRs) of T lymphocytes. Target cell recognition by $\alpha\beta$ TCRs is major histocompatibility complex (MHC) restricted, precluding the design of a "universal" receptor for the treatment of subjects with different

human lymphocyte antigen (HLA) polymorphisms. By contrast, CARs, like Mabs, are essentially universal as their cytotoxic activity is MHC-unrestricted[21]. Moreover, many tumors down-regulate expression of MHC molecules and/or have dysfunctional antigen processing machinery, so that the target antigenic epitopes for $\alpha\beta$ TCR 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.

1.6.1 Clinical Experience with CD-19 CAR-T cells

CD-19 was initially chosen as a target of choice for CAR-based therapy because of its common expression in most B cell leukemias and lymphomas and its absence in normal tissues other than the B cell lineage[19]. CAR19 T cell therapy has shown promise in patients with relapsed or refractory B-cell lymphomas.

In a multicenter, Phase II trial, axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 CAR-T cell product, was administered to 101 subjects with refractory DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma[27]. The objective response rate was 82% with a 54% complete response rate. At a median follow up of 15.4 months, 42% of subjects continued to have a response. The overall survival at 18 months was 52%.

In another study, CTL019, another autologous anti-CD19 CAR-T cell product, was administered to 28 adult subjects with relapsed or refractory DLBCL or follicular lymphoma [28]. The overall response rate was 64% with complete responses seen in 6 of 14 subjects with DLBCL (43%). At a median follow up of 28.6 months, 86% of responding subjects with DLBCL continued to have a response.

Twenty-four patients with CLL/SLL received an anti-CD19 CAR-T cells as part of a phase I/II open label clinical trial. The anti-CD19 CAR-T cells were infused into the patients at a defined ratio of 1:1 of CD4+ to CD8+ CD19-specific CAR-T cells. The overall response rate per by International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria was 71% , with a complete response rate of 21% [29].

FDA approved its first CAR-T cell product, tisagenlecleucel (Kymriah™) on August 30, 2017. This product was approved with the indication for patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse (Kymriah™ package insert). The FDA approval was supported by studies using tisagenlecleucel in pediatric subjects. Efficacy results demonstrated that 83% of subjects had a complete remission (defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and full recovery of peripheral blood counts) or a complete remission with incomplete blood count recovery[30]. On May 1st, 2018, FDA approved tisagenlecleucel for adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy. The overall response rate (ORR) for the 68 evaluable subjects was 50% with a complete response (CR) rate of 32%. Among subjects achieving CR, the estimated median DOR was not reached[31].

Additionally, on October 18, 2017, FDA approved Yescarta® (axicabtagene ciloleucel) to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment. 51% of subjects experienced a complete remission with a median duration of response of 9.2 months[32].

1.6.2 Toxicities associated with CAR19 T cells

Although CAR19 T cell therapy is efficacious, significant toxicities are seen in a proportion of subjects. Toxicities associated with CAR19 T cell therapy include hematologic toxicities introduced by required lymphodepleting regimens. In addition, CNS toxicities such as progressive confusion, aphasia, word finding difficulty, obtunded states with airway compromise and encephalopathy have been described[33]. Other toxicities observed with CAR19 T cell therapy include macrophage activation syndrome, CRS, sepsis, and B cell aplasia[19, 34-37]. In the axi-cel trial described above, grade 3 or higher CRS was seen in 13% of subjects with grade 3 or higher neurotoxicity seen in 28% of subjects[27]. Two CRS-related deaths occurred in this trial. In the CTL019 trial described above, severe CRS occurred in 5 subjects (18%) and serious encephalopathy occurred in 3 subjects (11%) including 1 fatal case[28].

To date, groups have not been able to predict nor control the duration of normal B-cell aplasia, and immunoglobulin infusions are required to reduce the risk of infection following CAR19 T cell therapy. Along with these noted toxicities, electrolyte disturbances and liver enzyme abnormalities have also been described.

Of the toxicities noted above, CRS is the most common toxicity experienced with CAR immunotherapy [38]. The two FDA approved CAR19 T cell products (Kymriah™ and Yescarta®) contain black box warnings in reference to severe and life-threatening cytokine release syndrome. Symptoms can vary from mild flu-like symptoms to more severe toxicities such as vascular leak, hypotension, coagulopathy, pulmonary edema and multi-organ failure. CRS-associated toxicities, when severe, require intensive medical management including vasoactive pressors, mechanical ventilation, anti-epileptics, and antipyretics [38]. Cytokine elevations are detectable in most subjects; however, the degree of elevation does not correlate with the severity of CRS or response to therapy. The most significantly elevated cytokines associated with CRS are IL-10, IL-6, and IFN- γ . IL-6 is an inflammatory cytokine involved in a large number of immune processes, including neutrophil trafficking, acute phase response, angiogenesis, B cell differentiation, and auto-antibody production. In severe CRS with T-cell engaging therapies, IL-6 levels peak during maximal T cell proliferation. High levels of IL-6, present in the context of CRS likely initiates a pro-inflammatory IL-6-mediated signaling cascade.

Neurotoxicity, or ICANS, from CAR-T therapy can occur as part of CRS or as an independent process [39]. 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 ICANS 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 patients that exhibit early sign/symptoms of neurotoxicity. Early interventions should be employed to prevent worsening, especially if therapies are already indicated such as corticosteroids.

The management of CRS and ICANS to date involves supportive care measures and targeted therapy with tocilizumab (monoclonal antibody that blocks the IL-6 receptor, approved by FDA for the treatment of severe or life-threatening CAR-T cell induced CRS in adult and pediatric subjects as part of their initial approval of Kymriah™ [40]) administered with or without corticosteroid therapy to suppress the immune response. Paradoxically, prolonged glucocorticoid administration, although effective in controlling toxicity, has led to decreased efficacy of CAR therapy as observed in the original report by Maude et al[33]. As IL-6 has been implicated in CRS, recent trials have demonstrated that tocilizumab therapy can attenuate CRS-related toxicity; however, no long-term data exist regarding the impact of CRS treatment on CAR19 persistence and efficacy, and multiple subjects have severe toxicities that still require glucocorticoid administration. The goal of management is not to extinguish all evidence of CRS but to prevent life-threatening toxicity while maximizing the potential for antitumor effects.

Trials are currently underway to determine the optimal timing for intervention with anti-cytokine therapy[41]. In the Zuma-1 and Juliet trials of CD19 directed CAR-T cells in subjects with B-cell lymphomas, the use of tocilizumab (and glucocorticoids for Zuma-1) did not appear to affect efficacy of CAR-T therapy [27, 28]. Current management guidelines allow for administration of tocilizumab in patients with signs and symptoms of severe CRS or significant comorbidities as targeting IL-6 does not appear to inhibit CAR T-cell efficacy. There is a theoretical concern that targeting IL-6 could inhibit CAR-T cell efficacy based on the hypothesis that IL-6 may represent part of a cytokine feedback loop that enhances T-cell proliferation, but this has not appeared to be seen in clinical outcomes. Another hypothesis is that targeting IL-6, which is most likely released by macrophages, can manage CRS toxicity with less impact on CAR T-cell efficacy than corticosteroids. It has been observed that patients with CRS have marked elevations in ferritin, C-reactive protein (CRP) and soluble IL-2 receptor, findings consistent with macrophage activation syndrome or hemophagocytic lymphohistiocytosis[42]. Currently, the use of tocilizumab appears to be effective in most patients with limited inherent toxicity. In some cases, concomitant administration of corticosteroids with tocilizumab may be required to alleviate symptoms related to CRS[41, 42], though the use of long-term corticosteroids has been associated with abrogation of CAR T-cell expansion and persistence[36]. For this reason, strategies to blunt severe CRS without compromising the therapeutic effect of CAR T-cells are needed.

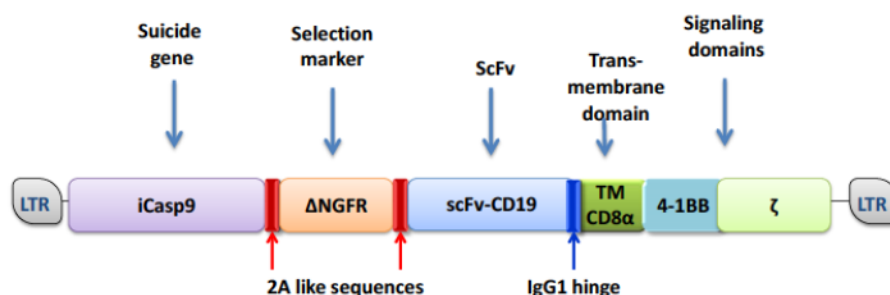
1.7 Rationale for Therapy with T Cells with an Inducible Caspase 9 Safety Switch

1.7.1 Inducible Caspase 9 Safety Switch

One alternative possibility to control the side effects due to CAR19 T cells and CAR T cells in general is based on the concept of the co-expression within CAR T cells of a safety switch gene that, when specifically activated, can rapidly eliminate the CAR T cells. We have recently clinically validated a novel safety switch that is based on the inducible human caspase 9 (iCasp9)[43, 44]. The iCasp9 construct consists of the sequence of the human FK506-binding protein (FKBP12) with an F36V mutation, connected through a Ser-Gly-Gly-Gly-Ser linker to the gene encoding human caspase 9, which is deleted of its endogenous caspase activation and recruitment domain. FKBP12-F36V binds with high affinity to an otherwise bioinert small molecule dimerizing agent, rimiducid. In the presence of the drug, the iCasp9 pro-molecule dimerizes and activates the intrinsic apoptotic pathway, leading to cell death. Recently, the iCasp9 gene was used to genetically modify donor derived T lymphocytes that were then infused into subjects receiving a haploidentical stem cell transplant to promote faster immune reconstitution[44]. The modified cells could expand and function *in vivo*; in those subjects who developed GVHD after infusion of iCasp9 T lymphocytes, a single dose of rimiducid (0.4 mg/kg) activated the safety switch and eliminated more than 90% of the injected T cells within 30 minutes of drug administration, permanently reversing GVHD.

Since the inclusion of iCasp9 in donor-derived T cells allows for their rapid elimination when these cells cause GVHD in the context of haploidentical transplant, iCasp9 seems a valuable safety switch to include in CAR19 T cells to rapidly and permanently remove them if severe CRS or ICANS develops (**Figure 1**).

Figure 1 Structure of the iC9.2A.ΔNGFR.2A.CAR.CD19 (iC9-CAR19) vector



Structure of the iC9.2A.ΔNGFR.2A.CAR.CD19 (iC9-CAR19) vector comprising the iCasp9 sequence, the truncated low-affinity nerve growth factor receptor (ΔNGFR) serving as the selectable marker and the CAR19. The sequence cassette is then incorporated into the SFG retroviral vector. In transduced cells, the selection with NGFR allows the enrichment in CAR19+ cells and the administration of rimiducid leads to dimerization of iCasp9 resulting in a caspase cascade that ends in apoptosis resulting in the rapid elimination of CAR19 T cells.

Unfortunately, like corticosteroids or other genetic safety switches, elimination of CAR19 T cells by activation of iCasp9 triggered by the infusion of rimiducid will also diminish the therapeutic effect of CAR19 T cells. However, our preclinical experiments suggest that

unlike corticosteroids and other safety switches, the function of this iCasp9 safety switch can be pharmacologically-controlled with administration of rimiducid leading to a more fine-tuned elimination of CAR19 T cells in instances of serious or life-threatening CRS-associated toxicity and grade 3 or 4 neurotoxicity that are not responsive to standard of care. Importantly, this pharmacologically-controlled safety switch allows for the persistence of CAR19 T cells in the peripheral blood and thus may preserve antitumor efficacy compared to current approaches for the treatment and management of CRS and ICANS[45].

Rimiducid which activates the iCasp9 gene has been evaluated in a Phase 1 dose escalation safety study conducted in healthy volunteers[46]. No significant adverse effects were noted when rimiducid was administered over a 0.01 mg/kg to 1.0 mg/kg dose range via intravenous (IV) infusion over 2 hours. The only drug-related adverse event observed at any of the dose levels tested was facial flushing (vasodilation) in one volunteer at the 1.0 mg/kg dose level. The drug exhibited a rapid distribution phase with mean C_{max} values ranging from 10 to 1275 ng/mL over the 0.01 to 1.0 mg/kg dose range. Following infusion, plasma levels were reduced to 18%, 7% and 1 % of the maximal concentration at 0.5, 2, and 10 hrs post dose. In our recent study, subjects who developed GVHD after infusion of iC9-CAR19 T cells were treated with 0.4 mg/kg of rimiducid, as a 2 hour IV infusion[44]. We confirmed results from previously published studies of rimiducid using an *in vitro* biological assay that showed no detectable levels of drug in the plasma within 24-48 hours of administration.

Based on this evidence, we hypothesize that T lymphocytes collected from subjects and genetically modified to co-express the iCasp9 gene will expand *in vivo* upon infusion into subjects and furthermore, exhibit anti-lymphoma activity. To test this hypothesis, we plan to infuse autologous activated T cells transduced with a gamma-retroviral vector encoding iCasp9 and CAR19 into subjects with DLBCL. We will conduct a Phase I dose escalation study to determine a tolerable dose of iC9-CAR19 T cells that can be administered. The safety of iC9-CAR19 cells will be investigated using the 3+3 design. The doses we plan on testing are cell doses that have been investigated in trials of other CD19-directed CAR-T cell constructs [27, 35, 47]. We anticipate that should CRS develop following the infusion of iC9-CAR19 cells, the *in vivo* expansion of these cells can be rapidly controlled and downregulated by the administration of rimiducid via its interaction with iCasp9.

1.7.2 Rationale for Conditioning Chemotherapy

Conditioning chemotherapy (e.g., lymphodepleting chemotherapy) has been shown to improve the persistence of modified T cells and has been associated with improved progression free survival.

Lymphodepleting chemotherapy reduces the number of the host's suppressive cells, such as regulatory T cells, allowing the genetically modified T cells to expand and eradicate tumor cells [48, 49]. The conditioning regimen may also stimulate the production of cytokines such as IL-7 or IL-15 which may also favor expansion of the infused cells [20, 50]. Grupp et al showed improved T-cell counts and proliferation in subjects who received

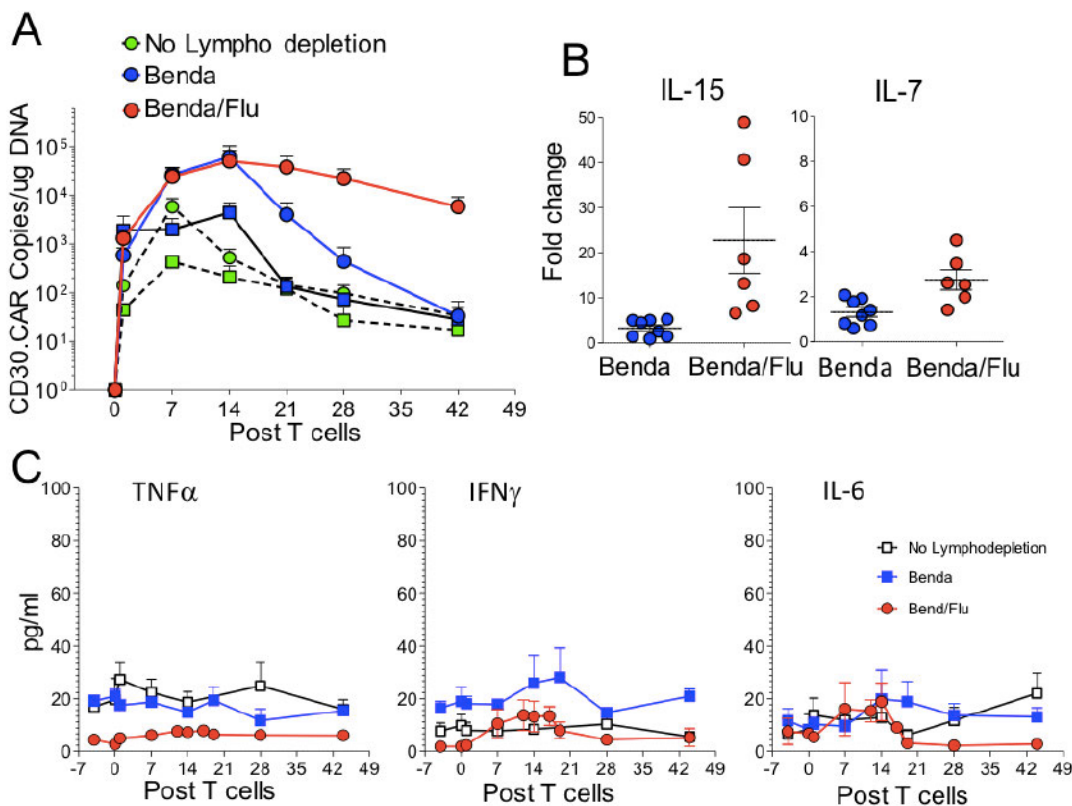
CAR-T cells on day 2 after conditioning chemotherapy compared to day 90, supporting the theory that T cell infusion should occur early after conditioning[51].

In this trial, subjects will receive lymphodepleting chemotherapy prior to infusion of iC9-CAR19 cells. Subjects will receive a lymphodepleting regimen of bendamustine 70 mg/m²/day and fludarabine 30 mg/m² for three consecutive days.

Bendamustine is an alkylating agent with properties of a purine analog, and is FDA approved in the US for treatment of chronic lymphocytic leukemia (CLL) and indolent NHL. *In vitro* studies demonstrate that bendamustine is highly active in drug resistant cells by inducing direct DNA damage and apoptosis as well as inducing cell death by mitotic catastrophe[52]. Bendamustine as a single agent is associated with an OR rate of 70 - 80% and a CR rate of approximately 30% in relapsed or refractory indolent NHL [53]. Furthermore, single agent bendamustine has shown activity in more aggressive NHL with OR and CR rates of 44% and 17%, respectively, in patients with relapsed or refractory disease[54]. Bendamustine has been used successfully for lymphodepletion in CAR-T trials targeting CD19 in CLL and NHL [28, 55].

As of April 18, 2018, eight adult subjects have been treated after lymphodepletion with 70 mg/m²/day bendamustine for three days in combination with 30 mg/m²/day fludarabine for three days, and eight adult subjects have been treated after lymphodepletion with two doses of 90 mg/m² bendamustine in a Phase I/II trial designed to determine the efficacy of T lymphocytes expressing the CD30 chimeric antigen receptor (CAR) in subjects with HL or NHL, LCCC1532-ATL (NCT02690545), that is currently being conducted at the University of North Carolina (UNC). Our data indicates that the bendamustine/fludarabine lymphodepletion regimen results in a longer sustained expansion of CAR-T cells, in agreement with the observation of significant increase in interleukin-7 (IL-7) and IL-15, and modest increase in inflammatory cytokines (TNF α , IFN γ and IL-6) in the peripheral blood of subjects that received lymphodepletion with bendamustine and fludarabine (Savoldo et al., unpublished) (**Figure 2**). Therefore, we will be using fludarabine and bendamustine as lymphodepletion as we believe it will lead to increased expansion and persistence of CAR-T cells and improved efficacy.

Figure 2 Comparison of Lymphodepletion Regimens



Panel A shows the detection of ATLCAR.CD30 molecular signals by qPCR. Data points represent critical post-infusion intervals after infusion of ATLCAR.CD30 cells. Lines denote average $\pm$ SEM for each group. Square symbols indicate DL1=1x10⁸/m² CAR⁺ T cells; circle symbols indicate DL2=2x10⁸/m² CAR⁺ T cells. Green symbols are from subjects that received ATLCAR.CD30 cells without prior lymphodepletion; blue symbols are from subjects that received ATLCAR.CD30 cells 4 days after bendamustine lymphodepletion and red symbols are from subjects that received ATLCAR.CD30 cells 4 days after bendamustine/fludarabine lymphodepletion. Data indicated that the bendamustine/fludarabine lymphodepletion results in better and sustained expansion of ATLCAR.CD30 cells. Of note, CAR T cells were also detectable in the peripheral blood by flow cytometry.

Panel B shows the fold increase in IL-15 and IL-7 cytokines between pre-lymphodepletion vs pre-infusion in the peripheral blood subjects that received bendamustine only (blue symbols) or bendamustine/fludarabine (red symbols).

Panel C shows the plasma levels of inflammatory cytokines (shown are TNFα, IFNγ and IL-6 in subjects that received CAR CD30). Lines denote average $\pm$ SEM for each group. White symbols are from subjects that received ATLCAR.CD30 cells without prior lymphodepletion; blue symbols are from subjects that received ATLCAR.CD30 cells 4 days after bendamustine lymphodepletion and red symbols are from subjects that received ATLCAR.CD30 cells 4 days after bendamustine/fludarabine lymphodepletion. Data shows only modest increase of cytokines after ATLCAR.CD30 infusion.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

To determine the safety and tolerability of autologous iC9-CAR19 T cells administered to subjects with relapsed or refractory B-cell lymphoma or chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)

2.2 Secondary Objectives

2.2.1 To identify a recommended phase 2 dose (RP2D) of iC9-CAR19 T cells in subjects with relapsed or refractory B-cell lymphoma or CLL/SLL

2.2.2 To measure the survival of iC9-CAR19 T cells *in vivo*.

2.2.3 To determine the overall response rate (ORR) mediated by autologous iC9-CAR19 T cells administered to subjects with relapsed or refractory B-cell lymphoma or CLL/SLL

2.2.4 To determine overall survival (OS) in subjects with relapsed or refractory B-cell lymphoma or CLL/SLL following infusion of iC9-CAR19 T cells.

2.2.5 To determine progression free survival (PFS) in subjects with relapsed or refractory B-cell lymphoma or CLL/SLL following infusion of iC9-CAR19 T cells.

2.2.6 To determine duration of response (DOR) in subjects with relapsed or refractory B-cell lymphoma or CLL/SLL who experience an objective response following infusion of iC9-CAR19 T cells.

2.2.7 To measure patient-reported symptoms, physical function, and health-related quality of life at baseline and over time in subjects treated with iC9-CAR19 T cells.

2.3 Exploratory Objectives

2.3.1 [REDACTED]

2.3.2 [REDACTED]

2.3.3

2.3.4

2.3.5

2.4 Primary Endpoint

Toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). ICANS symptoms will be graded per ASBMT ICANS Consensus Grading for Adults (see [Appendix B](#)) and CRS symptoms will be graded according to ASBMT CRS Consensus Grading (see [Appendix A](#))^[39].

(Note: The safety evaluation period for DLT assessment will encompass toxicities related to the cell therapy that are experienced starting on the day of iC9-CAR19 T cell infusion up through 4 weeks post infusion. See Section 4.1.2 of the protocol for definitions of DLTs and RP2D. General safety monitoring will begin at the time of procurement).

2.5 Secondary Endpoints

2.5.1 The recommended phase 2 dose of iC9-CAR19 cells will be determined based on 3+3 dose finding rules as specified in Section 4.1.1 and the tolerability of iC9-CAR19 cells assessed by NCI-CTCAE criteria, ASBMT Consensus CRS grading criteria outlined in [Appendix A](#), and ASBMT Consensus ICANS Grading outlined in [Appendix B](#).

2.5.2 Persistence of iC9-CAR19 T cells *in vivo* will be determined by quantitative polymerase chain reaction (PCR) and flow cytometry in samples of peripheral blood.

2.5.3 ORR (CR/CRi) to iC9-CAR19 T cell therapy will be determined using the revised Lugano criteria [56, 57] ([Appendix K](#)), Response Criteria for Primary CNS Lymphoma ([Appendix N](#)), Response Criteria for Waldenström Macroglobulinemia (WM) in [Appendix L](#), or International Workshop on Chronic Lymphocytic Leukemia (IWCLL) (CLL/SLL) ([Appendix M](#), Revised Criteria for Response Assessment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma).

2.5.4 OS will be measured from the date of administration of iC9-CAR19 T cells to the date of death. Subjects who have not died by the analysis data cut-off date will be censored at their last date of contact.

2.5.5 PFS is defined from day of iC9-CAR19 T cell infusion to the date of disease progression per the Lugano criteria [56, 57] ([Appendix K](#)), Response Criteria for Primary CNS Lymphoma ([Appendix N](#)), Response Criteria for WM ([Appendix L](#)).

or International Workshop on Chronic Lymphocytic Leukemia (IWCLL) (CLL/SLL) ([Appendix M](#)). Revised Criteria for Response Assessment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma), or death as a result of any cause. Subjects who do not meet criteria for progression by the analysis data cut-off date will be censored at their last evaluable disease assessment date.

2.5.6 DOR is defined for subjects who experience an objective response as the date of first objective response to disease progression per the Lugano criteria[56, 57] ([Appendix K](#)), Response Criteria for Primary CNS Lymphoma ([Appendix N](#)), response criteria for WM ([Appendix L](#)), or International Workshop on Chronic Lymphocytic Leukemia (IWCLL) (CLL/SLL) ([Appendix M](#)). Revised Criteria for Response Assessment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) or death as a result of any cause. Subjects who do not meet criteria for progression or death by the analysis cut-off date will be censored at their last evaluable disease assessment date.

2.5.7 Patient reported symptoms will be measured using selected symptoms from the NCI PRO-CTCAE (see [Appendix G](#)). Patient-reported physical function will be measured using the PROMIS Physical Function Score derived from the PROMIS Physical Function Short Form 20a v1.0. Patient-reported health-related quality of life will be measured using the PROMIS Global Health Score derived from the PROMIS Global Health Short Form v1.0-1.1 (see [Appendix F](#)).

2.6 Exploratory Endpoints

2.6.1

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.0 SUBJECT ELIGIBILITY

Note: During the period of cell procurement and iC9-CAR19 T-cell production, subjects are allowed to receive additional standard of care chemotherapy to stabilize their disease if the treating physician feels it is in the subject's best interest. *For subjects requiring bridging chemotherapy while their iC9-CAR19 T-cells are being manufactured, details regarding treatment(s) administered including dose, frequency, number of cycles, etc. will be collected.*

3.1 Inclusion Criteria for the Study

Unless otherwise noted, subjects must meet all of the following criteria to participate in all stages of this study:

3.1.1 Written informed consent and HIPAA authorization for release of personal health information. Subjects or their Legally Authorized Representative must sign a consent to undergo cell procurement.

3.1.2 Adults ≥ 18 years of age.

3.1.3 Histologically confirmed B-cell NHL, including the following types defined by WHO 2016:

Aggressive Lymphomas:

- DLBCL not otherwise specified (NOS)
- T cell/histiocyte rich large B cell lymphoma; primary cutaneous DLBCL, leg type; EBV-positive DLBCL NOS; DLBCL associated with chronic inflammation; Large B-cell lymphoma with IRF4 rearrangement; Intravascular large B-cell lymphoma; ALK-positive large B-cell lymphoma
- Primary mediastinal (thymic) large B-cell lymphoma
- High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement; high grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
- Transformation of indolent lymphoma or CLL to DLBCL will also be included
- Burkitt lymphoma
- Primary CNS lymphoma

Indolent Lymphomas:

- Follicular lymphoma
- Splenic marginal zone lymphoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
- Nodal marginal zone lymphoma
- Mantle cell lymphoma
- Waldenström's macroglobulinemia (Lymphoplasmacytic lymphoma)
- CLL/SLL by IWCLL criteria

- 3.1.4** Subjects with CNS involvement of lymphoma are eligible.
- 3.1.5** Subjects with aggressive lymphomas must have relapsed or refractory disease after having received at least 2 prior lines of systemic therapy, including, at a minimum:
- An anti-CD20 monoclonal antibody
 - An anthracycline containing chemotherapy regimen (if eligible)
 - An autologous stem cell transplant (if eligible)
- 3.1.6** Subjects with primary CNS lymphoma must have failed at least 1 prior line of therapy that included high dose methotrexate.
- 3.1.7** For indolent lymphomas, subjects must have received at least 2 prior lines of therapy for their lymphoma.
- 3.1.8** Subjects with specifically relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma must have received at least 2 prior therapy regimens which can include, but not limited to:
- A combination of an anti-CD20 monoclonal antibody and an alkylating agent, **OR**
 - A Bruton's Tyrosine Kinase Inhibitor, **OR**
 - A BCL-2 inhibitor in combination with an anti-CD20 monoclonal antibody
- 3.1.9** Subjects with prior or concurrent malignancies of the same or different tumor type whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational drug are eligible for enrollment at the discretion of clinical investigator.
- 3.1.10** Subjects relapsed after allogeneic stem cell transplant will be eligible if they meet other inclusion criteria and have no active graft vs host disease (GVHD)
- 3.1.11** Measurable or assessable disease by Lugano criteria ([Appendix K](#)), response criteria for primary CNS lymphoma provided in [Appendix N](#), or WM criteria ([Appendix L](#)) or IWCLL criteria ([Appendix M](#)). Subjects with bone marrow only involvement are eligible.
- 3.1.12** Karnofsky score of > 60% (see [Appendix E](#)).
- 3.1.13** Women of childbearing potential (WOCBP) must 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. WOCBP subjects will also be instructed to tell their male partners to use a condom.

3.2 Exclusion Criteria for the Study

Subjects meeting any of the following exclusion criteria will not be able to participate in this study (procurement, lymphodepletion and cell infusion):

- 3.2.1** Subject is pregnant or lactating.
- 3.2.2** Tumor in a location where enlargement could cause airway obstruction.
- 3.2.3** Current use of systemic corticosteroids at doses ≥ 10 mg prednisone daily or its equivalent; those receiving < 10 mg daily may be enrolled at discretion of clinical investigator. Patients with primary CNS lymphoma can receive higher doses of steroids per investigator discretion.
- 3.2.4** 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) defined as not being well controlled on therapy. Subjects are required to have negative HIV antibody, negative Hepatitis B surface antigen, and negative HCV antibody or viral load. In addition, subjects with positive Hepatitis B core antibody, will have Hepatitis B viral load tested and subjects with positive Hepatitis B viral load will also be excluded.
- 3.2.5** Subject must either be core antibody negative HBV (results can be pending at the time of cell procurement) OR if a subject is hepatitis B core antibody positive they must have their hepatitis B viral load checked. These subjects will be excluded if their viral load is positive at baseline. Subjects who are core antibody positive and viral load negative at baseline will be considered eligible.
- 3.2.6** A history of intolerance to fludarabine. *Note:* subjects with history of intolerance to bendamustine may be considered for enrollment at the discretion of the clinical investigator if they are candidates for lymphodepletion with cyclophosphamide and fludarabine.

3.3 Eligibility criteria to be met prior to procurement.

- 3.3.1** Subjects must sign a consent to undergo cell procurement.
- 3.3.2** Life expectancy ≥ 12 weeks.
- 3.3.3** Evidence of adequate organ function as defined by:

The following is required within 7 days prior to procurement:

- Bilirubin ≤ 1.5 times the upper limit of normal (ULN). Subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level > 1.5 mg/dL if their conjugated bilirubin is $< 1.5 \times$ ULN)
- AST ≤ 3 times ULN
- Serum creatinine ≤ 2 times ULN
- Pulse oximetry of $> 90\%$ on room air

- 3.3.4** Left ventricular ejection fraction (LVEF) $\geq 35\%$ as measured by ECHO, with no additional evidence of decompensated heart failure.
- 3.3.5** Subject must have active disease by imaging and/or blood assessment. In patients with disease assessed by imaging, imaging results from within 90 days prior to procurement to assess presence of active disease. If disease not measurable by imaging, evidence of active disease within 90 days of procurement via bone marrow biopsy or SPEP/immunofixation.
- 3.3.6** Negative serum pregnancy test within 72 hours prior to procurement or documentation that the subject is post-menopausal. Post-menopausal status must be confirmed with documentation of absence of menses for >1 year, or documentation of surgical menopause involving bilateral oophorectomy.
- 3.4 Eligibility criteria to be met prior to lymphodepletion.**
- 3.4.1** Written informed consent to enroll in the CAR T-cell therapy trial must be obtained prior to lymphodepletion.
- 3.4.2** Presence of active disease. For patients with disease evaluated by imaging: imaging results from within 10 days prior to lymphodepletion. Imaging must occur at least 3 weeks or 5 half-lives (whichever is shorter) after most recent therapy (used as baseline measure for documentation of progression before the lymphodepletion) to document measurable or assessable disease. Imaging does not need to be repeated if it is within 10 days prior to lymphodepletion.
- For subjects with WM or bone marrow only disease, imaging does not need to be repeated prior to lymphodepletion if no evidence of disease at screening or if imaging performed between the time of screening and lymphodepletion shows no evidence of disease. WM subjects (and patients with marrow only involvement) must have active measurable disease confirmed with bone marrow biopsy and/or SPEP/immunofixation.
- 3.4.3** Evidence of adequate organ function as defined by:
- The following are required within 72 hours prior to lymphodepletion:
- Adequate bone marrow function ($ANC \geq 1.0 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$) unless related to lymphoma involvement. Subjects cannot have received platelet transfusion within 7 days of lymphodepletion.
 - Bilirubin ≤ 1.5 times the upper limit of normal (ULN). Subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >1.5 mg/dL if their conjugated bilirubin is $<1.5 \times$ ULN)
 - $AST \leq 3$ times ULN
 - Serum creatinine ≤ 2 times ULN
 - Pulse oximetry of $> 90\%$ on room air
- 3.4.4** Negative serum pregnancy test within 72 hours prior to lymphodepletion or documentation that the subject is post-menopausal. Post-menopausal status must be confirmed with

documentation of absence of menses for > 1 year, or documentation of surgical menopause involving bilateral oophorectomy.

- 3.4.5 In subjects with CLL/SLL or lymphoma with bone marrow only involvement, a bone marrow biopsy within 28 days prior to lymphodepletion.
- 3.4.6 Subjects that have received therapy with murine antibodies must have documentation of absence of human anti-mouse antibodies (HAMA) prior to lymphodepletion. Subjects who have received prior therapy with murine antibodies must have documentation of absence of HAMA within 8 weeks of lymphodepletion or after their most recent murine antibody therapy (whichever is shortest). For subjects that receive murine monoclonal antibodies between procurement and lymphodepletion, HAMA testing should be performed within 4 weeks prior to lymphodepletion and after the last monoclonal antibody dose.
- 3.4.7 Available autologous transduced activated T cells product meets the certificate of analysis.
- 3.4.8 Has not received any tumor vaccines within the previous six weeks prior to lymphodepletion.
- 3.4.9 Subject is not taking a prohibited or contraindicated medication listed in Section 12.9 prior to lymphodepletion. Contraindicated medications should be discontinued at least two weeks prior to the scheduled lymphodepletion or by at least 5 half-lives of the contraindicated medication, whichever is shorter.
- 3.4.10 Subject is not taking strong inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) as these may increase plasma concentrations of bendamustine, and decrease plasma concentrations of its metabolites. See <http://medicine.iupui.edu/clinpharm/ddis/> for an updated list of strong inhibitors of CYP1A2 (See [Appendix H](#)). (This applies to subjects who receive bendamustine for lymphodepletion (required) up through 72 hours after the last dose of bendamustine).
- 3.4.11 Subject has not received investigational agent or cancer-directed therapy within the previous 3 weeks or 5 half lives (whichever is shorter) prior to lymphodepletion.
- 3.4.12 Subjects must not be using systemic corticosteroids at doses ≥ 10 mg prednisone daily or its equivalent; those receiving <10mg daily may be enrolled at discretion of clinical

investigator. Patients with Primary CNS lymphoma may be receiving higher doses of steroids with approval of clinical investigator.

3.4.13 Karnofsky score of > 60% (see [Appendix E](#)).

3.5 Eligibility criteria to be met prior to cell infusion after lymphodepletion.

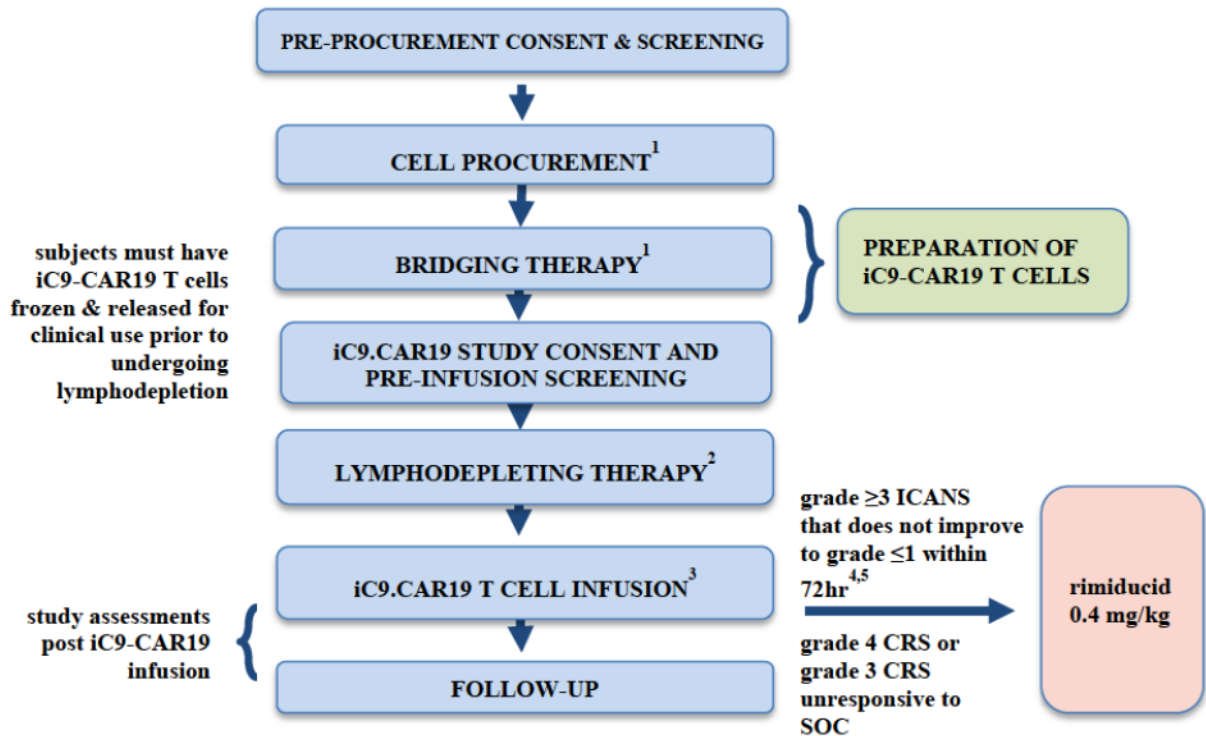
3.5.1 No evidence of uncontrolled infection or sepsis.

3.5.2 Negative serum pregnancy test within 7 days of cell infusion (does not need to be repeated if pre-lymphodepletion pregnancy test is within window).

3.5.3 Subject is a good candidate for treatment with iC9-CAR19 T cells per the investigator's discretion.

4.0 TREATMENT PLAN

4.1 Study Schema



¹If necessary to control their disease, subjects may receive standard of care treatment per physician's discretion while awaiting iC9-CAR19 T cell manufacturing (optional)

²All subjects will be given bendamustine 70 mg/m² and fludarabine 30 mg/m²x 3 days. (See Section 5.3 for details). Subjects with intolerance to bendamustine may receive cyclophosphamide 500 mg/m²/day and fludarabine 30 mg/m²/day administered over 3 consecutive days. Patients with creatinine clearance <79 ml/min will have fludarabine dose adjusted per institutional guidelines.

³iC9-CAR19 T cell infusion to occur 2-14 days after lymphodepletion. Escalating doses of iC9-CAR19 cells tested in subjects using 3+3 rules. See sections 4.1.1 and 4.2.3 for additional information.

⁴Subjects with grade 4 CRS or 3 CRS unresponsive to standard of care (SOC) interventions (i.e., does not resolve to grade 0-1 within 24 hours after 2 doses of tocilizumab, with sum of doses ≥ 12mg/kg), and subjects with grade ≥ 3 ICANS that does not improve to grade ≤ 1 within 72 hours with SOC interventions during dose finding/escalation cohort, and subjects with grade 4 ICANS of any duration that have evidence of cerebral edema and/or generalized convulsive status epilepticus.

⁵ Subjects in the expansion cohort who experience ≥ grade 2 CRS or ICANS that remains ≥ grade 2 twenty four hours after the initial administration of standard treatment (tocilizumab for CRS or steroids for ICANS) may be part of the sub-study of rimiducid. Please see **Figure 3**.

This single center, open-label Phase I dose finding trial seeks to determine if CAR-T cells targeting the CD19 antigen and containing the inducible caspase 9 safety switch can be safely administered to subjects with relapsed or refractory B-cell lymphoma. The safety of iC9-CAR19 cells will be investigated using the 3+3 design (see Section 4.1.1). The starting dose of 1×10^6 transduced cells/kg (dose level 1) will treat at least 3 subjects in the initial cohort (**Table 1**). If there are no DLTs within 4 weeks of the cell infusion in these 3 subjects, then the next cohort will evaluate 2×10^6 transduced cells/kg. If there is toxicity in 1/3 subjects in the initial cohort, the cohort will be expanded to treat 3 more subjects. If dose level 1 is determined to be above a tolerable dose, de-escalation would occur to dose level -1 where subjects would receive 1×10^5 transduced cells/kg. The first subject treated on each dose level will be evaluated for a 4-week DLT safety follow-up period prior to treating additional subjects on that dose level.

During iC9-CAR19 T cell dose exploration, rimiducid (0.4 mg/kg), a dimerizing agent that is designed to engage and activate the caspase 9 safety switch to trigger iC9-CAR19 T cell death by apoptosis will be given to subjects who develop grade 4 cytokine release syndrome (CRS) or grade 3 CRS that is unresponsive to standard of care interventions, and to subjects who develop grade ≥ 3 immune effector cell-associated neurotoxicity syndrome (ICANS) that does not improve to grade ≤ 1 within 72 hours with standard of care interventions, and subjects with grade 4 ICANS of any duration that have evidence of cerebral edema and/or generalized convulsive status epilepticus. After the TCD has been determined in adults, up to 18 additional subjects may be treated in an expansion cohort at the TCD. Subjects in the expansion cohort who experience $\geq$ grade 2 CRS or ICANS that remains $\geq$ grade 2 twenty four hours after an initial dose of standard therapy may be part of the sub-study of rimiducid, which is described below in Section 4.1.3.

Table 1 Dose levels of iC9-CAR19 cells to be tested

Dose level	Dose (#transduced cells/kg)	Maximum dose for BMI >35 (#transduced cells)
-1	1×10^5	1.25×10^7
1	1×10^6	1.25×10^8
2	2×10^6	2.5×10^8

Cell procurement, lymphodepletion, cell infusion, and safety and disease assessment procedures for all subjects:

Eligible subjects will undergo cell procurement to isolate peripheral blood mononuclear cells (PBMCs) (See Section 4.2.1). Approximately four weeks later, subjects for whom cells have been successfully generated and who meet eligibility criteria for lymphodepletion will undergo lymphodepleting chemotherapy. Subjects will receive lymphodepleting chemotherapy consisting of IV bendamustine 70 mg/m^2 and IV fludarabine $30 \text{ mg/m}^2/\text{day}$ for 3 consecutive days. Subjects with creatinine clearance $< 79 \text{ ml/min}$ will have fludarabine dose adjusted per institutional guidelines. Subjects who meet eligibility criteria for cellular therapy will receive iC9-CAR19 T cells within 2-14 days after the lymphodepleting regimen followed by close monitoring over the ensuing 4 weeks with disease assessments scheduled at 6 weeks after the cell infusion.

Quality of life assessments:

Patient reported outcomes (PRO) will be measured by PROMIS Global Health and Physical Function questionnaires ([Appendix F](#)) and selected items from the NCI PRO-CTCAE (see [Appendix G](#)). Completion of the PRO questionnaires will be optional and offered to participants as outlined in the Time and Events table in Section 7.1.

4.1.1 Dose Escalation Rules (3+3)

Table 2 Dose Escalation Rules

Number of Subjects with DLT	Action
0 out of 3 subjects	Escalate to next dose level
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level
1 out of 6 subjects	Escalate to next dose level
2 or more subjects in a dosing cohort	TCD has been exceeded. Expand a prior cohort tested at a lower dose level unless 6 subjects have been assigned to that dose already

Tolerable cell dose (TCD) = A TCD is defined as the dose at which approximately 0.20 of subjects experience DLT (0 – 1 out of 6 subjects).

- Dose escalation of iC-CAR19 cells will follow 3+3 dose escalation rules
- If 3 subjects at the higher dose do not have DLTs we might treat more subjects at that dose to get more information about toxicity at that dose
- The first subject evaluated in each dose cohort must complete the 4-week evaluation period before a second subject is dosed in that cohort. Additionally, prior to escalating or de-escalating to the next dose level, all subjects in the prior cohort must have cleared the 4-week DLT evaluation window.
- The doses of iC9-CAR19 T cells to be explored are provided in Section 4.1.
- While the RP2D of iC9 CAR19 T cells may be the TCD, the determination of RP2D will be made after taking into account TCD as well as other factors such as iC9 CAR19 T cell persistence, expansion and cell manufacturing variables.

4.1.2 Definition of Dose Limiting Toxicity

An event will be considered a DLT per NCI CTCAE criteria v5.0, and CRS grading or ICANS grading criteria outlined in Sections 12.1 and 12.2 of the protocol, if it occurs within the DLT reporting period (i.e., 4 week evaluation period following iC9-CAR19 cell infusion) as specified below:

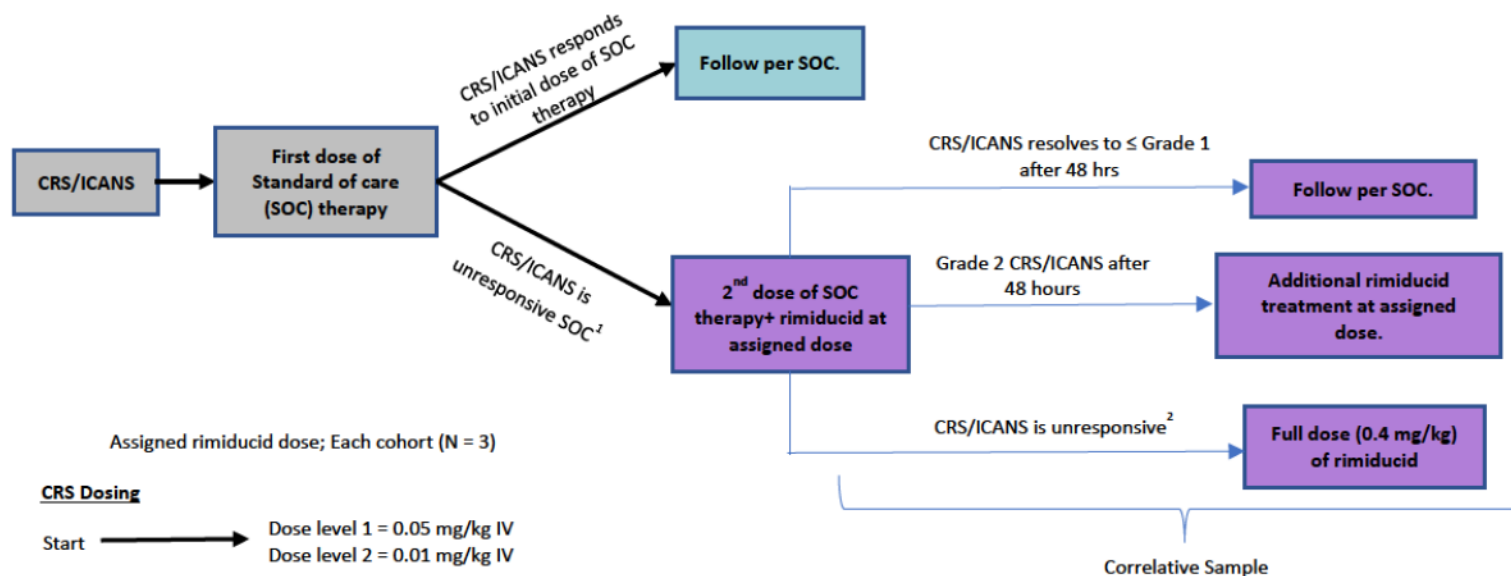
- Any treatment-emergent Grade ≥ 3 CRS event that is unresponsive to standard of care interventions and does not decrease to Grade ≤ 2 within 7 days.
- Grade ≥ 3 ICANS that is unresponsive to standard of care interventions and does not decrease to Grade ≤ 1 within 7 days or grade 4 ICANS of any duration that has evidence of cerebral edema and/or generalized convulsive status epilepticus.
- Any treatment-emergent Grade 5 event.
- Grade 3 – 5 allergic reactions related to the study cell infusion.
- Any treatment emergent Grade 4 non-hematologic adverse event that does not resolve to Grade 2 within 7 days

DLTs are defined as at least possibly related to iC9-CAR19 T cells. If an apparent DLT is clearly due to underlying lymphoma and is unrelated to the cell infusion, then the investigator will specify that the event is not a DLT. Subjects will be followed for 4 weeks for DLT assessment.

4.1.3 Rimiducid Sub-Study

Subjects in the expansion cohort who experience $\geq$ grade 2 CRS or ICANS that remains $\geq$ grade 2 twenty-four hours after an initial dose of standard of care (SOC) treatment (tocilizumab or steroids) may be part of the sub-study of rimiducid (**Figure 3**). These subjects will receive one of two assigned dose levels of rimiducid with their second SOC treatment. Subjects will first be treated on dose level 1 (N=3) and then treatment on dose level 2 (N=3) will begin. For subjects with CRS, the dose levels are 0.05 mg/kg (dose level 1) and 0.01 mg/kg (dose level 2). For subjects with ICANS, the dose levels are 0.1 mg/kg (dose level 1) or 0.01 mg/kg (dose level 2). The percent reduction in CAR T cells will be measured in these subjects. If the subject's CRS/ICANS resolves to $\leq$ grade 1 after 48 hours, then they will be followed per SOC. If after 48 hours from the first dose of rimiducid, the subject's ICANS or CRS is at grade 2, the subject will receive another dose of rimiducid at their assigned dose level. If the subject's CRS or ICANS is unresponsive to SOC treatment and the assigned dose level of rimiducid, (defined in Section 4.1), they will then be given a full dose (0.4 mg/kg) of rimiducid.

Figure 3 Rimiducid Sub-Study Schema for CRS and ICANS



*The following cases of severe CRS/ICANS will prompt administration of rimiducid 0.4 mg/kg IV, regardless of duration:

- Grade 4 ICANS with convulsive status epilepticus
- Grade 4 ICANS with evidence of cerebral edema
- Grade 4 CRS with grade 4 end-organ toxicity attributed to the CRS.

1. ≥ Grade 2 CRS/ICANS that remains ≥ Grade 2 24 hours after initial dose of tocilizumab and/or steroids.
2. ≥ Grade 3 CRS/ICANS 48 hours after the first dose of rimiducid

Possible CRS Response Outcomes After Rimiducid

Responder

- ✓ Resolution of CRS/ICANS to ≤ Grade 1 after 48 hours of 1st dose

Grade 2 CRS/ICANS

- If CRS/ICANS grade 2 at 48 hours after initial dose of rimiducid then administer another dose of rimiducid at the assigned dose level

Non-Responder

- If symptoms worsen 48 hours after 1st dose of rimiducid, subject will be treated per standard of care and will be given a full dose (0.4mg/kg) of rimiducid.
- If CRS/ICANS grade 3-4 at 48 hours after initial dose of rimiducid OR total of 72 hours of grade 3-4 CRS/ICANS then administer rimiducid 0.4 mg/kg

4.1.4 Rules for Treatment Priority

If the subject presents with both ICANS and CRS, each of the same grade, treatment for CRS should be prioritized. If one toxicity is of higher grade than the other, treatment for the higher-grade toxicity should be prioritized. If CRS is of higher grade and CRS resolves to grade 1 or less without rimiducid, then the subject may be treated for ICANS per the schema in **Figure 3**. If ICANS is of higher grade and ICANS resolves to grade 1 or less without rimiducid, then the subject may be treated for CRS per the schema in **Figure 3**.

4.1.5 Sample Collection Plan Pre/Post Rimiducid Administration

In the dose escalation phase, subjects who develop grade 4 CRS (See [Appendix A](#) for grading criteria) or grade 3 CRS that is unresponsive to standard of care interventions (i.e., does not resolve to grade 0 – 1 within 24 hours after 2 doses of tocilizumab, with sum of doses $\geq 12\text{mg/kg}$), and subjects who develop grade ≥ 3 ICANS that does not improve to grade ≤ 1 within 72 hours with standard of care interventions, and subjects with grade 4 ICANS of any duration that have evidence of cerebral edema and/or generalized convulsive status epilepticus will be given a single dose of rimiducid (0.4 mg/kg) via an intravenous infusion per standard of care (approximately 2 hours).

After rimiducid administration (in dose escalation cohort or as part of the rimiducid sub-study), subjects will have close monitoring until resolution of CRS or ICANS to grade ≤ 1 . Frequency of physical exams, routine hematology, metabolic panel, urinalysis, and liver function testing will be performed according to the subject's physician. NCI CTCAE version 5.0, ASBMT CRS and ICANS Consensus Grading ([Appendix A](#) and [Appendix B](#)) will be used to evaluate the subject's toxicities while on study.

Subjects will undergo additional bloodwork to assess C-reactive protein, ferritin, cytokine levels and iC9-CAR19 T cell viability *in vivo* prior to rimiducid administration, as per table below (**Table 3**).

Apart from these additional samples to be collected in subjects treated with rimiducid, all subjects should be followed as outlined in the Time and Events Table in Section 7.1.

Table 3 Monitoring after Rimiducid Administration

Study Assessments	pre-dose ¹	15 min ²	30 min ²	2 hr ²	4 hr ²	6 hr ²	8 hr ²	12 hr ²	24 hr ²	n+24 hrs post dose ^{2,3}
CRP/Ferritin	X ¹								X	
Correlative studies ⁴	X ¹				X				X ⁵	X ⁶
ICE score ⁷	X								X	X
CSF analysis ⁸	X ⁹								X ¹⁰	X ⁶
Vital Signs	X	X	X	X	X					

Footnotes

1. Collect sample within 30 minutes prior to administration of rimiducid.

2. Timing based on the start of rimiducid infusion (rimiducid is infused per standard of care (approximately 2 hours). All time points up to 2 hours will have a window of ± 5 minutes. The 2-12 hour time points will have a window of ± 15 minutes. Post 12 hour time points will have a window of ± 2 hours.
3. Until resolution of CRS or ICANS to grade ≤ 1 or subject is discharged from the hospital
4. Collect up to 2 mL of blood at the specified times points. Samples left over from cytokine and cell viability testing will be stored for future analysis of rimiducid if needed.
5. Collect up to an additional 20 mL of blood for correlative studies (see Section 6.4).
6. Per discretion of treating oncologist.
7. Only in subjects with suspected ICANS.
8. Lumbar puncture for CSF analysis (endothelial markers, cytokines, and CAR-T cells and for standard of care to rule out alternative etiologies for neurologic symptoms) will be performed if clinically indicated and feasible when ICANS is noted.
9. If feasible and safe, lumbar puncture should be performed to evaluate for other etiologies of neurotoxicity (with some CSF, if available, sent for study analysis) prior to rimiducid administration. Alternative diagnostic procedures may be considered if performing lumbar puncture delays standard of care interventions or is deemed not safe for the subject.
10. Subject may undergo second lumbar puncture based on treatment response and clinical indication, after discussion with the study PI.

4.2 Treatment Plan

4.2.1 Cell Procurement

Peripheral blood, up to 300 mL (in up to 3 collections) will be obtained from subjects during cell procurement. In subjects with inadequate lymphocyte count in the peripheral blood, a leukapheresis may be performed to isolate sufficient T cells. The parameters for apheresis will be up to 2 blood volumes. If subjects were previously collected under another LCCC CAR-T protocol and have remaining PBMCs to generate iC9.CAR19 T cells, those PBMCs may be used instead of undergoing another collection.

4.2.2 Lymphodepleting Regimen

Subjects will receive a “pre-conditioning” cytoreductive regimen of bendamustine 70 mg/m²/day administered IV followed by an IV dose of fludarabine 30 mg/m²/day administered over 3 consecutive days. These agents will be administered per institutional guidelines. Prophylaxis (e.g., hydration, antiemetics, etc.) needed prior to fludarabine and bendamustine chemotherapy will be provided per institutional guidelines. At the discretion of the clinical investigator, subjects with a known history of intolerance to bendamustine may be considered for lymphodepletion with cyclophosphamide 500 mg/m²/day administered by IV followed by an IV dose of fludarabine 30 mg/m²/day administered over 3 consecutive days. These agents will be administered per institutional guidelines. Patients with creatinine clearance < 79 ml/min will have fludarabine dose adjusted per institutional guidelines.

Note: Any subject who tests positive for Hepatitis B core antibody and negative for Hepatitis B viral load during screening must initiate an anti-Hepatitis B prophylaxis regimen prior to lymphodepletion.

4.2.3 Administration of iC9-CAR19 T Cells

Post lymphodepletion, subjects who meet eligibility criteria for cellular therapy will receive iC9-CAR19 T cells within 2 – 14 days after completing the lymphodepleting chemotherapy regimen. We will administer iC9-CAR19 post lymphodepletion at dose levels specified in the table in section 4.1. A recently published trial in refractory DLBCL established that a dose of 2×10^6 CAR19+ T cells/kg was safe and associated with significant *in vivo* expansion and we anticipate similar results with iC9-CAR19+ T cells [27].

4.2.4 Premedication

Subjects may be pre-medicated with diphenhydramine up to 50 mg and acetaminophen up to 650 mg (or equivalent alternative antipyretic and antihistamine). We will pre-medicate 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. Anti-emetics in appropriate dosage for each subject will be prescribed as necessary.

4.2.5 Cell Administration

iC9-CAR19 T cells will be given by a licensed healthcare provider via intravenous injection over 5-10 minutes through either a peripheral or a central line. The volume of infusion will depend upon the concentration of the cells when frozen and the size of the subject. The expected volume will be 1-50cc.

4.2.6 Dose Modifications

The infusion of iC9-CAR19 T cells may be delayed per clinical investigator discretion if a subject has unresolved serious adverse reactions (including pulmonary reactions, cardiac reactions, or hypotension) from preceding chemotherapies, active uncontrolled infection, active graft versus host disease, or worsening lymphoma burden following lymphodepleting chemotherapy. This may extend the time between lymphodepletion and cell infusion beyond the 14 days outlined within the protocol. If infusion of the iC9-CAR19 T cells is delayed beyond 14 days after lymphodepletion, the subject may undergo lymphodepletion again prior to iC9-CAR19 T cell infusion per investigator's discretion. Infusions delayed beyond 14 days post-lymphodepletion for the management of AEs or subject safety will not be considered protocol deviations. Participants meeting eligibility requirements for infusion but whose samples don't contain sufficient numbers of iC9-CAR19 T cells for their specific dose level may still be infused with the maximum number of their cells available per investigator's discretion.

4.2.7 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.

Fever will mandate initial hospitalization for subjects discharged after this hospitalization. Any evidence of neurotoxicity will also mandate hospitalization for all subjects. All Phase I subjects must reside in local housing (as designated by the Cellular Therapeutics Program Local Housing SOP). Subjects with medical indications for inpatient care or those whose physicians assess that outpatient care will pose an undue risk will remain inpatient for their treatment until indications for inpatient care have resolved.

Subjects will be monitored as outlined in the Time and Events Table in Section 7.1. Institutional guidelines will be followed for the monitoring and treatment of tumor lysis syndrome should the need arise.

4.2.8 Supportive Care

Subjects will receive supportive care for acute or chronic toxicity, including blood components or antibiotics, and other intervention as appropriate. Supportive care guidelines for administration of chemotherapy should be followed per UNC IDS policy.

4.2.9 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, they will come off study for adverse event reporting after the initial 6-week assessments in Section 7.1 are completed. These subjects will continue to be monitored according to the abbreviated follow-up plan presented in the Time and Events Table in [Appendix C](#).

4.2.10 Prohibited Medications

There are 33 medications known to have major interactions with fludarabine provided at this link: https://www.drugs.com/drug-interactions/fludarabine-index.html?filter=3&generic_only=. These medications are prohibited while the subject is receiving fludarabine.

Additionally, refer to Appendix I. Medications Known to Have Major Interactions with Fludarabine.

For medications known to have major interactions with bendamustine, consult Appendix H. Prohibited Medications or Those to be Used with Caution or the following link: <http://medicine.iupui.edu/clinpharm/ddis/>

Ensure that subjects are not receiving any of the prohibited medications listed at the links provided while they are undergoing lymphodepletion, and for at least 2 weeks prior to the scheduled lymphodepletion with bendamustine and fludarabine or by at least 5 half-lives of the contraindicated medication, whichever is shorter.

Please refer to Appendix J: Cyclophosphamide Drug Information for information in regard to prohibited medications for subjects receiving cyclophosphamide.

4.2.11 Duration of Follow-Up

Subjects who receive a cell infusion will be followed for up to 15 years for RCR evaluation (per Section 6.4.2 or until transgene is no longer detectable) or until death, whichever occurs first. Subjects who are removed from study and do not receive the cellular therapy product due to unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Subjects who start alternate therapy after receiving a cell infusion will still be required to complete abbreviated follow up procedures outlined in Section [Appendix C](#).

4.2.12 Duration of Therapy

Therapy in LCCC1813-ATL involves 1 infusion of iC9-CAR19 cells (see Section 4.2.3). Treatment 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.

4.2.13 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 7.6 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

In the case where 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.

4.2.14 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.

5.0 STUDY TREATMENT INFORMATION

5.1 Autologous T Lymphocytes (ATL) iC9-CAR.19 Cells

5.1.1 Construction of the iC9-CAR19 Vector

The single chain antibody (scFv) (FMC63) targeting the CD19 molecule was cloned in frame with the human IgG1hinge, the CD8a transmembrane domain, 4-1BB and ζ endodomains. The iCasp9 and Δ NGFR genes were previously described. The entire cassette (iC9-CAR19) 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 1**.

5.1.2 Generation of Transduced Cells

All manufacturing procedures 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 (SOPs). Brief summaries are provided here.

5.1.3 Source Material

See Section 4.2.1 (procurement).

5.1.4 Activated T Lymphocytes

Activated T Lymphocytes will be generated using our previously validated SOP. Briefly, PBMC will be activated with anti-CD3 and anti-CD28 antibodies, and then supplemented with IL-7 and IL-15[58]. 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.

5.1.5 Retroviral Production

A retroviral producer line will be generated for the construct at UNC. A master cell-bank of producer cells will be generated and tested to exclude production of replication competent retrovirus and infection by Mycoplasma, HIV, HBV, HCV and others. Supernatant generated from the master-cell bank will be produced by a certified vendor. All batches of retroviral supernatant will be tested for sterility and to exclude RCR as issued with the Certificate of Analysis (CofA) and as directed by the SOPs and the Vector Production master-file with the FDA for which the Lineberger Comprehensive Cancer Center is the sponsor. For this specific study we will use batches of retrovirus released for clinical use.

5.1.6 Transduction

ATL are transduced 3-4 days after initiation as described previously using recombinant Fibronectin fragment CH-296 (RetronectinTM, Takara Shuzo, Otsu, Japan) 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.

5.1.7 Ex Vivo Expansion

After transduction, transgenic ATL will be expanded by feeding them with IL-7 and IL-15 twice a week. By day 8 - 10 ATL cells will be selected using anti-NGFR antibody and CliniMACS System Miltenyi Biotech to enrich in NGFR transduced cells. Selected ATL will be further expanded to reach sufficient numbers for adoptive transfer by feeding them with IL-7 and IL-15 twice a week. After transduction and selection, a small number of cells will be removed to evaluate for transduction efficiency using flow cytometry.

5.1.8 Freezing

When a sufficient number for cells for infusion is achieved, cells will be collected and frozen following previously validated SOPs. Cells will be also tested for transduction and potency using an assay as discussed with FDA. All lines will be checked for phenotype and microbiological culture and cryopreserved prior to administration according to SOPs. The results will be reviewed by Quality Assurance (QA) prior to issuing a CofA.

5.1.9 Testing

Products that meet study specific release criteria, as detailed on the CofA that accompany each infusion product, will be infused as per Section 4.2.3.

Complete sterility test results are currently required for product release prior to infusion. However, 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 standard operating procedure (SOP) and our clinical research SOP. Subjects would be managed per established practice.

5.1.10 Potential Toxicities

Potential toxicities may be categorized as those related to infusion of T cells; transduction; cross-reactivity with normal tissues; cytokine release syndrome (CRS); neurotoxicity/ICANS; macrophage activation syndrome; and tumor lysis syndrome. In addition to the information presented below:

5.1.10.1 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 (γ_c) in X-SCID subjects with ex-vivo retroviral transduction of autologous stem cells. Four of 11 treated subjects developed T-ALL associated with a single retroviral integrant[59, 60]. The integration site of the retrovirus was similar. More recently a case of leukemia has also been reported

in a second study in SCID subjects conducted in UK. It is likely that correction of common-gamma chain deficiency and related immunodeficiency syndromes represent special cases. The γ_c 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 γ_c . In female carriers of X-SCID there is a pattern of non-random X-inactivation in T-cells, B-cells and NK-cells[61]. Moreover a subject with X-SCID developed substantial numbers of T-cells following reversion of the mutant allele in a single hematopoietic stem cell[62]. 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.

To date more than 200 subjects have received genetically modified cells in clinical trials including subjects we have treated on our protocols - using retrovirally marked autologous marrow [63] or retrovirally-marked EBV-CTLs[64-66]. 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%[67]. 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.

5.1.10.2 Cross-reactivity

CD19 is only expressed by B lymphocytes and thus the only toxic effect will be B cell aplasia which has been described in other trials using CAR.CD19-redirected T cells.

5.1.10.3 Cytokine Release Syndrome

CRS is the most common side effect of CAR-T cell therapy and is potentially life threatening [68]. Symptoms can vary from mild flu-like symptoms to more severe toxicities such as vascular leak, hypotension, coagulopathy, pulmonary edema and multi-organ failure. CRS-associated toxicities, when severe, require intensive medical management including vasoactive pressors, mechanical ventilation, anti-epileptics, and antipyretics [38]. Quite recently, tocilizumab, a monoclonal antibody specific to the IL-6 receptor, has been approved by the FDA for the treatment of subjects with CRS. Cytokine elevations are detectable in most subjects, however, the degree of elevation does not correlate with the severity of CRS or response to therapy. Similarly, the severity of CRS seems to be associated with the burden of disease at the time of therapy rather than the likelihood of remission [33]. The most significantly elevated cytokines associated with CRS are IL-10, IL-6, and IFN- γ . IL-6 is an inflammatory cytokine

involved in a large number of immune processes, including neutrophil trafficking, acute phase response, angiogenesis, B cell differentiation, and auto-antibody production. In severe CRS with T-cell engaging therapies, IL-6 levels peak during maximal T cell proliferation. High levels of IL-6, present in the context of CRS likely initiates a pro-inflammatory IL-6-mediated signaling cascade.

5.1.10.4 Neurotoxicity/ICANS

Neurotoxicity, or immune effector cell-associated neurotoxicity syndrome (ICANS), from CAR-T 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 [68]. 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 ICANS are broad and range from mild confusion/altered mental status to seizure to cerebral edema. Routine monitoring is critical in subjects receiving CAR-T therapy to identify neurologic symptoms early and neurology should be consulted for any subjects that exhibit early sign/symptoms of neurotoxicity. Early interventions should be employed to prevent worsening, especially if therapies are already indicated such as corticosteroids. Standard evaluations including imaging, evaluation of the CSF and assessments for seizure activity should be considered in any subject that develops significant neurological symptoms.

5.1.10.5 Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) has been found previously in subjects with acute lymphoblastic leukemia receiving CAR T cell therapy [69]. Macrophage activation syndrome 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 subjects 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: Pancytopenia, fever, elevated AST, ALT, triglycerides and LDH. Increased PT and 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.

5.1.11 Concomitant Therapy with IVIG

Intravenous immunoglobulin (IVIG) may be administered to prevent infection in subjects with the expected occurrence of hypogammaglobulinemia per institutional standard practice.

5.2 Rimiducid

Subjects who develop grade 4 CRS or grade 3 CRS that is unresponsive to standard of care interventions (i.e., does not resolve to grade 0 – 1 within 24 hours after 2 doses of tocilizumab, with sum of doses ≥ 12 mg/kg) (see Section 4.1.2 and [Appendix A](#)) and subjects who develop grade ≥ 3 ICANS that does not improve to grade ≤ 1 within 72 hours with standard of care interventions, and subjects with grade 4 ICANS of any duration that have evidence of cerebral edema and/or generalized convulsive status epilepticus (see [Appendix B](#)) will receive 0.4 mg/kg of rimiducid as an IV infusion over 2 hrs. After rimiducid administration subjects will have close monitoring until resolution of CRS or ICANS to grade ≤ 1 (see Section 4.1.5 for required monitoring).

Subjects in the expansion cohort who experience $\geq$ grade 2 CRS or ICANS or that remains $\geq$ grade 2 twenty four hours after an initial dose of SOC therapy, may be part of the sub-study of rimiducid (**Figure 3**). These subjects will receive one of two assigned dose levels of rimiducid with their second dose of standard treatment (for CRS: 0.05 mg/kg or 0.01 mg/kg; for ICANS: 0.1 mg/kg or 0.01 mg/kg). If the subjects' CRS or ICANS is unresponsive to the standard treatments and the assigned dose level of rimiducid or the subject has $\geq$ grade 3 CRS or ICANS, then they will be given a full dose (0.4 mg/kg) of rimiducid. If the subject's ICANS or CRS is at grade 2 48 hours after the first dose of rimiducid they will receive another dose of rimiducid at the assigned dose level.

5.2.1 Supplier/How Supplied

Rimiducid for injection is formulated as a 5 mg/mL solution of rimiducid in a 25% solution of the non-ionic solubilizer Solutol HS 15 (250 mg/mL) (**Table 4**). At room temperature the formulation is a clear, colorless solution. Upon refrigeration, this formulation undergoes a reversible phase transition, resulting in a slightly opaque white solution. This phase transition is reversed upon rewarming to room temperature.

Table 4 Rimiducid Formulation

Component	Function	Nominal amount per vial	Concentration
Rimiducid	API	10 mg	5 mg/mL
Solutol HS 15	Solubilizer	20 mg	250 mg/mL

Rimiducid for injection should be warmed to room temperature prior to dilution with normal saline.

Rimiducid for injection is incompatible with materials containing plasticizer or DEHP and materials sterilized with ethylene oxide.

MD Anderson Cancer Center is the supplier of rimiducid and will be provided to subjects at no costs by the manufacturer. Investigational supplies will be affixed with a clinical label in accordance with regulatory requirements.

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

5.2.2 Instructions for Preparation and Infusion

Rimiducid for Injection is a concentrated solution of 2.33 mL in a 3 mL vial, at a concentration of 5 mg/mL, (i.e., 10.66 mg per vial). Prior to administration, the calculated dose will be diluted to a final concentration of 0.4 mg/mL in 0.9% normal saline for infusion.

Rimiducid will be administered via IV infusion per standard of care (approximately 2 hours), using a non-DEHP, non-ethylene oxide sterilized infusion set and an infusion pump.

Rimiducid administration must be interrupted for any new grade 3 or 4 non-hematologic toxicity that is considered to be drug-related.

5.2.3 Handling and Dispensing

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

5.2.4 Recommendations for Administration

Premedication per institutional standards (acetaminophen and antihistamine) 30 minutes prior to infusion for prevention of potential hypersensitivity to the Solutol HS15 or rimiducid is recommended.

5.2.5 Stability and Storage

Rimiducid for injection is stable for at least 24 months when stored at the recommended temperature of 2-8°C.

5.2.6 Return and Retention of Study Drug

The investigator is responsible for keeping accurate records of the clinical supplies received from MD Anderson Cancer Center or designee, the amount dispensed to and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy (e.g., UNC IDS

drug destruction policy). It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.2.7 Adverse Events Associated with Rimiducid

As of 20 December 2020, 99 subjects with malignant and non-malignant hematological disorders as well as solid tumor cancers had received rimiducid administered in combination with an investigational cell therapy product.

Studies include three Phase I clinical trials that have been completed with rimiducid. The first study was a single center, randomized placebo- and saline-controlled ascending single dose study in healthy volunteers (n=28)[46]. No significant adverse effects were noted when rimiducid was administered over a 0.01 mg/kg to 1.0 mg/kg dose range via intravenous (IV) infusion over 2 hours. The only drug-related adverse event observed at any of the dose levels tested was facial flushing (vasodilation) in one volunteer at the 1.0 mg/kg dose level. There were no treatment related changes in vital signs, ECG data, clinical laboratory data, bleeding time or platelet aggregation data in this study. Plasma concentrations of rimiducid were measured as part of two Phase I/II clinical trials utilizing rimiducid. The drug formulation was the same as that employed in the preclinical toxicology and safety pharmacology programs (i.e., rimiducid, 5 mg/mL in 25% Solutol HS 15). The first trial (Covance Study Number 1711/1) was conducted in adult healthy male subjects to determine the safety, tolerability and pharmacokinetics of rimiducid. In this study, subject cohorts were administered single ascending doses of rimiducid, from 0.01 mg/kg to 1 mg/kg. The second trial (BP-PC-001) was a Phase I/II in men with progressive, metastatic castrate-resistant prostate cancer (mCRPC) evaluating BPX-101 and dimerizing agent rimiducid. BPX-101, which targets Prostate Specific Membrane Antigen (PSMA), was administered intradermally, followed 24 hours later by a 2-hour infusion of rimiducid (0.4 mg/kg). The dose of rimiducid administered in the Covance Study was 0.5 mg/kg, and the dose administered in Study BP-PC-001 was 0.4 mg/kg. A second study referred to as the CASPALLO trial evaluated a single 0.4 mg/kg dose of rimiducid administered to subjects who had received ascending doses of iCaspase T cell[44]. Four subjects between the ages of 3 and 17 years who had undergone stem-cell transplantation for relapsed acute leukemia and developed graft-versus-host disease (GVHD) were given a single intravenous dose (0.4 mg/kg) of rimiducid. This dose eliminated more than 90% of the modified T cells within 30 minutes after administration and ended the GVHD response without recurrence. No drug-related adverse events were reported in this trial.

A Phase I/II safety and efficacy study known as the Bellicum BPX101 trial was conducted in 18 male subjects with metastatic castration resistant prostate cancer who had received gene modified dendritic cells [70](Presented at the Annual Meeting of the American Society of Clinical Oncology in 2011; Abstract 4670). BPX-101 which targets prostate specific membrane antigen was administered intra-dermally every 2 weeks X 6 doses, followed 24 hours later by an IV infusion of rimiducid (0.4 mg/kg). One subject exhibited cytokine reaction upon infusion of rimiducid as a result of the activation of modified

dendritic cells and one subject experienced urticarial and flushing which resolved with antihistamine treatment. No other rimiducid-related events were reported. In general, rimiducid has an unremarkable safety profile with minimal risks for toxicity. Other adverse events unrelated or of improbable relationship to the administration of rimiducid reported in studies include chest pain, flu syndrome, halitosis, headache, injection site pain, vasodilatation, increased cough, rhinitis, rash, gum hemorrhage and ecchymosis.

Overall, 45 subjects have received at least 1 dose of rimiducid in combination with investigational product BPX-501 T cells containing the iCasp9 safety gene. The most frequently reported AEs regardless of causality included: pyrexia, chronic graft-versus-host disease, acute graft-versus-host disease, adenovirus infection, clostridium difficile infection, cytomegalovirus infection, gastroenteritis norovirus, sepsis, septic shock, bacteremia, disease progression, rash, febrile neutropenia, thrombocytopenia, mental status change, cough, respiratory distress, respiratory failure, acute respiratory failure, pulmonary hypertension, diarrhea, parotid gland enlargement, arthralgia, hypertension.

Pyrexia, aGVHD, and disease progression were the most frequently reported SAEs and occurred in 3 subjects (6.7%) each. A total of 12 subjects (26.7%) experienced Grade 5 events. Of the 12 subjects with a reported Grade 5 event, 3 subjects (6.7%) had disease progression, which was the most frequently reported fatal event. Two subjects (4.4%) each died of septic shock and respiratory failure. The remaining reported Grade 5 events included brain hypoxia, encephalopathy, histiocytosis hematophagic (hemophagocytic lymphohistiocytosis), gastrointestinal hemorrhage, and chronic graft-versus-host disease (cGVHD), reported in one subject each. None of these deaths were considered to be related to rimiducid.

Please refer to the Investigator's Brochure for additional information.

5.3 Conditioning Chemotherapy (Lymphodepletion) Drug Information

Subjects will receive a lymphodepletion regimen of bendamustine 70mg/m² IV and fludarabine 30 mg/m² each as a daily infusion for 3 days per institutional guidelines 2 – 14 days prior to the cell infusion. Fludarabine will be administered after the infusion of bendamustine per institutional guidelines. Subjects with known history of intolerance to bendamustine may be considered for lymphodepletion with cyclophosphamide and fludarabine at the discretion of the clinical investigator. For information regarding cyclophosphamide administration, please refer to Appendix J: Cyclophosphamide Drug Information. Subjects with creatinine clearance <79 ml/min will have fludarabine dose adjusted per institutional guidelines.

5.3.1 Bendamustine

Details on this product may be found in the Investigator's Brochure and Prescribing Information (see

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022249s0051bl.pdf ;
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208194s0001bl.pdf).

Bendamustine is a derivative of mechlorethamine with properties of a purine analog. As an alkylating agent, bendamustine forms alkyl groups which covalently bond with DNA, resulting in interstrand DNA crosslinks and ultimately leading to cell death. The exact mechanism of action of bendamustine remains unknown. Bendamustine is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL), and for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

5.3.1.1 Supplier/How Supplied

Bendamustine is supplied as a sterile, clear, and colorless to yellow ready-to-dilute solution in a multiple-dose clear glass vial. Each milliliter contains 25 mg of bendamustine hydrochloride (100 mg/4 mL). Each vial is not recommended for more than a total of 6 dose withdrawals. After first use, the partially used vial should be stored in the refrigerator in the original carton at 2° to 8° C (36° to 46° F) and then discarded after 28 days. Bendamustine should be handled and stored per institutional guidelines in accordance with the manufacturer's prescribing information. Bendamustine is commercially available and will not be supplied free of charge to the subject.

5.3.1.2 Storage Requirements/Stability

Bendamustine should be stored in a refrigerator 2° to 8° C (36° to 46° F). Retain in original package until time of use to protect from light.

5.3.1.3 Handling and Dispensing

Bendamustine must be dispensed only from official study sites by authorized personnel according to local regulations. Bendamustine should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study subjects.

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site. Please see UNC policy on hazardous drugs.

5.3.1.4 Preparation

Refer to the package insert for instructions on preparation for IV administration (see https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022249s005lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208194s000lbl.pdf).

5.3.1.5 Dosage and Administration

Fludarabine 30 mg/m² and bendamustine 70mg/m² will be administered intravenously each day for 3 consecutive days.

5.3.1.6 Adverse Events Associated with Bendamustine

Please refer to the prescribing information (PI) for bendamustine for complete information. The information below summarizes the Warnings and Precautions from the PI, focusing on safety data from the two trials conducted to support bendamustine's indication in indolent B-cell NHL. In these studies, bendamustine was administered as a

single agent at 120 mg/m² IV on days 1 and 2 every 21 days for up to eight cycles (n=176).

Myelosuppression

In the NHL studies, 98% of subjects had grade 3-4 myelosuppression. Three subjects died from myelosuppression-related adverse reactions. Hematologic nadirs were observed predominantly in the third week of therapy. Grade 3 or 4 decreases in the following variables were observed (numbers represent % of subjects): lymphocytes (94%), hemoglobin (11%), neutrophils (60%), platelets (25%).

Non-hematologic Toxicities

The most common non-hematologic adverse reactions ($\geq 30\%$) of any grade were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%) and pyrexia (34%). The most common non-hematologic Grade 3 or 4 adverse events were fatigue (11%), febrile neutropenia (6%), pneumonia (5%), hypokalemia (5%) and dehydration (5%).

Infections

Infection, including pneumonia and sepsis, has been reported in subjects in clinical trials, and in post-marketing reports. In the NHL trials, 8% of subjects experienced pneumonia. Patients receiving bendamustine are at risk for Hepatitis B reactivation. Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred. Some cases resulted in acute hepatic failure or a fatal outcome.

Infusion Reactions and Anaphylaxis

Symptoms of infusion reactions to bendamustine include fever, chills, pruritus and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Patients who experience Grade 3 or worse reactions were not typically re-challenged.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in subjects in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle, and without intervention may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of therapy, but may increase the risk of severe skin toxicity.

Skin Reactions

Rash, toxic skin reactions and bullous exanthema have been reported in clinical trials and post-marketing safety reports. One case of toxic epidermal necrolysis (TEN) occurred in a study combining bendamustine with rituximab. Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. In the NHL trials, 28 subjects (16%) experienced a rash; only 1 (<1%) was >Grade 2. When skin reactions occur, they may be progressive and increase in severity with further treatment.

Hepatotoxicity

Fatal and serious cases of liver injury have been reported with bendamustine. Combination therapy, progressive disease or reactivation of hepatitis B were confounding factors within the first 3 months of starting therapy. Monitor liver chemistry tests prior to and during bendamustine therapy.

Other Malignancies

Patients who have been treated with bendamustine have developed myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with bendamustine has not been determined.

Extravasation injury

Bendamustine extravasations have been reported in post marketing resulting in hospitalizations from erythema, marked swelling, and pain. Assure good venous access prior to starting bendamustine infusion and monitor the IV infusion site for redness, swelling, pain, infection, and necrosis during and after administration.

Embryo-fetal toxicity

Bendamustine (Pregnancy category D) can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine in mice and rats administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights. Advise woman to avoid becoming pregnant while receiving bendamustine and for 3 months after therapy is stopped. Advise men receiving bendamustine to use reliable contraception for the same time period.

Other

Grade 3 or 4 changes were seen in the following laboratory variables (numbers represent % of patients): hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).

5.3.1.7 Drug Interactions

Bendamustine's active metabolite is formed via P450 CYP1A2. Strong inhibitors (e.g., fluvoxamine and ciprofloxacin) have the potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of its active metabolites. Strong inhibitors of CYP1A2 are prohibited in this trial through 72 hours after the last dose of bendamustine. Other drugs known to induce (e.g. omeprazole, smoking) or inhibit CYP1A2 should be used with caution, or alternative treatments considered. See <http://medicine.iupui.edu/clinpharm/ddis/> for an updated list of CYP1A2 inhibitors. Please refer to [Appendix H](#), which is a patient handout on drug interactions with bendamustine.

5.3.2 Fludarabine

Subjects will receive a lymphodepletion regimen of bendamustine 70 mg/m² IV and fludarabine 30 mg/m² IV each as a daily infusion for 3 days. Fludarabine will be administered IV over 30 minutes after bendamustine based on institutional guidelines.

Details on this product may be found in the Prescribing Information:

<http://medlibrary.org/lib/rx/meds/fludarabine-phosphate-10/>

5.3.2.1 Mechanism of action

Fludarabine phosphate for injection is a fluorinated nucleotide analog of the antiviral agent vidarabine, 9-β-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase.

5.3.2.2 Indications

Fludarabine phosphate is indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia who have not responded to or whose disease has progressed during treatment with at least one standard alkylating –agent containing regimen.

5.3.2.3 Product Description

Each vial of sterile lyophilized solid cake contains 50 mg of the active ingredient fludarabine phosphate, USP, 50 mg of mannitol, USP, and sodium hydroxide to adjust to pH to 7.7. The pH range for the final product is 7.2 to 8.2. Reconstitution with 2 mL of Sterile Water for Injection, USP results in a solution containing 25 mg/mL of fludarabine phosphate, USP, intended for intravenous administration.

5.3.2.4 Storage Requirements/Stability

Fludarabine should be stored in a refrigerator 20° to 25° C (68° to 77° F). Retain in original package until time of use; excursions permitted between 15° to 30° C (59° to 86° F).

5.3.2.5 Handling and Disposal

Fludarabine should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study subjects.

Fludarabine is commercially available and will not be supplied free of charge to the subjects. Fludarabine should be handled and stored per institutional guidelines in accordance with the manufacturer's prescribing information.

Local requirements for disposal of hazardous drugs should be followed per institutional policy.

5.3.2.6 Preparation

Refer to the package insert for instructions on preparation for IV administration (see <http://medlibrary.org/lib/rx/meds/fludarabine-phosphate-10/>)

5.3.2.7 Dosage and Administration

Fludarabine 30 mg/m² and bendamustine 70mg/m² will be administered intravenously each day for 3 consecutive days.

5.3.2.8 Adverse Events Associated with Fludarabine

Please refer to the prescribing information (PI) for fludarabine for complete information. The information below summarizes the Warnings and Precautions from the PI.

Dose dependent neurologic toxicities

There are clear dose dependent toxic effects seen with fludarabine for injection, USP. Dose levels approximately 4 times greater (96 mg/m²/day for 5 to 7 days) than that recommended for CLL (25 mg/m²/day for 5 days) were associated with a syndrome characterized by delayed blindness, coma, and death.

Bone marrow suppression

Severe bone marrow suppression, notably anemia, thrombocytopenia, and neutropenia, has been reported in patients treated with fludarabine phosphate for injection. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate for injection requires careful hematologic monitoring.

Autoimmune reactions

Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune thrombocytopenic purpura, Evans syndrome, and acquired hemophilia have been reported to occur after one or more cycles of treatment with fludarabine.

Transfusion associated graft vs host disease (GVHD)

Transfusion-associated GVHD has been observed after transfusion of non-irradiated blood in fludarabine-treated patients.

Pulmonary Toxicity

A high incidence of fatal pulmonary toxicity has been observed when fludarabine is administered in combination with pentostatin for treatment of CLL.

Pregnancy category D

Fludarabine can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant if they are to receive therapy with fludarabine.

Male fertility and reproductive outcomes

Males with female partners of childbearing potential should use contraception during and after cessation of fludarabine. Possible sperm DNA damage raises concerns about loss of fertility and genetic abnormalities in fetuses.

Drug Interactions

The use of fludarabine in combination with pentostatin is contraindicated.

Renal impairment

Subjects with creatinine clearance 30 to 79 mL/min should have their fludarabine dose reduced and monitored for excessive toxicity. Fludarabine should not be administered to subjects with creatinine clearance < 30 mL/min.

6.0 CLINICAL ASSESSMENTS

Clinical assessments will be performed as outlined in the Time and Events Table in Section 7.1.

Procurement happens after pre-procurement screening and prior to lymphodepletion and/or cell infusion.

- If applicable: document therapy received after procurement and prior to lymphodepletion.
- Research personnel must keep track of any subjects who undergo procurement but do not undergo treatment with cellular products, and the reason for withholding treatment.

6.1.1 Demographics

Demographic information (date of birth, gender, race, and ethnicity) will be recorded at the procurement screening visit.

6.1.2 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history (e.g., tobacco use), and information regarding underlying diseases will be recorded at procurement and pre-lymphodepletion screening visits and a focused medical history on symptoms/toxicity will be performed thereafter.

The following information will be captured regarding prior anti-cancer therapy: 1) number of prior lines of therapy and name of each regimen (abbreviations for multi-drug regimens is acceptable) 2) number of cycles of each regimen given (if known) 3) approximate dates of therapy given (month and year, if known) 4) Best overall response (if known) and 5) date of progression (if known). If prior therapy includes radiation, dose, site, and dates will be collected, if available.

6.1.3 Concomitant Medications

Following consent to participation, the following information will be collected about bridging therapy (between procurement and lymphodepletion): 1) dose (including unit) 2) route of administration 3) frequency of administration 4) number of cycles of treatment 5) best response and 6) date of progression (if applicable). If bridging therapy is radiation, dose, site, number of fractions, and dates will be collected.

The following information will be captured for concomitant medications (also applies to hospital admissions):

- Medications taken within 30 days of initiating lymphodepleting chemotherapy related to any documented ongoing comorbidities (indication and medication name) and approximate start date (if available). Data collection on medications related to baseline comorbidities will continue through the end of the DLT period (4 weeks post-CAR-T infusion).
- Following the initiation of lymphodepleting chemotherapy, the following information will be captured for the medications administered as intervention of cell therapy-

- mediated toxicity (CRS, ICANS, HLH/MAS, etc): 1) indication 2) dose (including unit) 3) route of administration 4) frequency of administration, and 5) Start and stop dates.
- Transfusion of packed red blood cells and/ or platelet transfusions (date and number of units) during DLT period. After the DLT period, whether transfusion dependent at 3 months, 6 months, and 1 year, or until initiation of alternative therapy.
 - G-CSF administration (date and name) during DLT period. After the DLT period, whether growth factor dependent at 3 months, 6 months, and 1 year, or until initiation of alternative therapy.
 - Anti-microbial treatment, either given prophylactically in context of cytopenias, or as treatment for treatment-emergent infections during DLT period.

Data on concomitant medications given for treatment of cell therapy-mediated toxicity administered under this protocol will continue until withdrawal of consent, patient death or patient reaching end of study.

Therapy post CAR-T treatment

Following progression of underlying disease, the first next line of therapy will be collected. Data should include 1) start time of subsequent anti-cancer therapy (month and year) 2) type of therapy/ regimen names, and 3) best response to therapy (if known).

6.1.4 Physical Examination

A complete physical examination including height (at initial screening only), weight, vital signs and performance status.

Baseline information collected prior to procurement or lymphodepletion/cell infusion will be compared to changes that occur during study treatment. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

Vital signs (temperature, heart rate, respiratory rate, pulse oximetry, and blood pressure) will be performed by either the investigator or other qualified staff (MD, NP, RN, or PA).

Pulse oximetry of >90% on room air is required to meet eligibility for procurement and lymphodepletion.

Performance status

Performance status will be assessed by the Karnofsky scale provided in [Appendix E](#).

6.1.5 Adverse Events

Events should be assessed per NCI-CTCAE v5.0 criteria and ASBMT Consensus CRS and ICANS grading criteria. Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study cell infusion (drug administration if applicable) will be recorded in the case report form (CRF).

6.1.6 Disease Assessment

Baseline: To confirm presence of disease, imaging will be performed within 90 days before procurement. In subjects with disease not measurable by imaging, bone marrow biopsy or laboratory (SPEP/immunofixation) will be performed to confirm active disease within 90 days before procurement. Subjects who have disease that can be followed with imaging will be re-staged with imaging within 10 days of lymphodepletion. In subjects who receive intervening chemotherapy, the scans must be performed at least 3 weeks after the intervening chemotherapy is administered, but imaging does not need to be repeated if it is within 10 days prior to lymphodepletion. 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, or brain MRI). For CLL/SLL or subjects with bone marrow only disease, they will additionally undergo a bone marrow biopsy within a 28-day window prior to receiving lymphodepleting chemotherapy.

Post cell infusion: Imaging will be performed at 6 weeks (+/- 7-day window) following the infusion of iC9-CAR19 T cells. If imaging is consistent with progressive disease, a repeat scan will be obtained 8-12 weeks later to confirm disease progression unless subject is clinically felt to be progressing and needs to start alternative therapy more urgently by the investigator or treating physician. Imaging will be performed every 6 months ($\pm$ 14-day window) starting at month 6 until disease progression for up to two years after the (first) cell infusion. If imaging studies are performed at other times after treatment on this study, the data will be collected, and information gained will be used for this study. For subjects with bone marrow only involvement of their lymphoma, a bone marrow biopsy will be obtained at 6-10 weeks after CAR-T cell infusion. Bone marrow biopsy would be repeated at the time of imaging assessments (every 6 months starting at month 6 until disease progression for up to two years after the first cell infusion) to confirm CR if otherwise no evidence of disease.

For WM: Imaging will be performed at screening prior to procurement and repeated if there is evidence of disease. Laboratory assessments of disease consisting of serum immunoglobulins, SPEP/IFE, and serum free light chains will be obtained at baseline within 4 weeks of procurement, within 4 weeks of lymphodepletion, at 6 weeks (+/-1 week window), 6 months, 9 months, 12 months, and every 6 months for 4 years. Bone marrow biopsy will be obtained within 90 days of lymphodepletion (as long as after most recent treatment). A bone marrow biopsy will be obtained at 6-10 weeks after CAR-T cell infusion in subjects with evidence of response by peripheral blood tests (subjects in CR, VGPR, PR). Afterwards, a bone marrow biopsy would only be required to confirm a new CR (within a 1 month window of response evaluation). For CLL/SLL, subjects will additionally have a post-iC9-CAR.19 cell infusion bone marrow biopsy performed at 6 weeks ($\pm$ 14 days) to confirm with IWCLL guidelines of assessing a complete response histologically, as long as patients meet IWCLL hematologic and imaging CR criteria at that timepoint. Morphology analysis and high-resolution flow cytometry will be performed on the marrow, with conventional karyotyping and fluorescent in situ hybridization in patients with an identified cytogenetic abnormality. Minimal residual disease (MRD) assessment on the bone marrow biopsy sample will be done using immunoglobulin heavy chain (IGH) deep sequencing analysis.

6.2 Clinical Laboratory Assessments

6.2.1 Hematology

Blood will be obtained and sent to the clinical site hematology lab for a complete blood count to include: hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count.

6.2.2 Blood Chemistry Profile

Blood will be obtained and sent to the clinical site chemistry lab for determination of Comprehensive metabolic panel plus lactate dehydrogenase (LDH).

Comprehensive Metabolic Panel (CMP) [Blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, bicarbonate, glucose, calcium, albumin, total protein, total bilirubin, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), and alkaline phosphatase] + LDH. Uric acid will also be checked pre-lymphodepletion, pre-infusion, and during the first 2 weeks following therapy.

6.2.3 Pregnancy Test

A serum pregnancy test will be obtained from female subjects who are of childbearing potential as outlined in the Time and Events Table.

6.3 Patient Reported Outcomes (Quality of life assessment)

Patient reported outcomes (PRO) will be measured by the PROMIS Global Health and Physical Function questionnaires and selected items from the NCI PRO-CTCAE. These are optional and will be obtained at the time points indicated in the Time and Events Table.

6.4 Correlative Studies

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. Please consult the Laboratory Manual regarding the amount of blood to be collected at each time-point. 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, RCR testing and Quantitative real-time PCR will be the first priorities (RCR testing > T cell frequency/persistence > ELISPOT/multimer assays for cytokines > cytotoxicity assays for anti-tumor specificity and cytotoxic T lymphocyte precursor assays).

Cytokines: Our standard array for cytokine determination includes multiple cytokines (UNC immune monitoring Core) which among others include: IL-2, IFN γ , TNF α , IL-6, IL-10, IL-13, IL-1R α , IL-8, IL-12, IL-15, and GM-CSF.

6.4.1 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.

6.4.2 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)

All RCR results will also be reported to the FDA. Additionally, the FDA will be notified of how many autopsies were requested, how many were obtained, and the results of those autopsies (as they relate to RCR).

Aliquot of cells and serums will also be archived for use in future studies for RCR as required by the FDA.

6.4.3 Clonality

If the transgene is detected at $> 0.5\%$ by either flow cytometry (if feasible) or by qPCR at the 6-month sample collection time point, 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.

6.4.4 HAMA Testing

Serum from blood drawn for functional studies at baseline and at 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. Subjects who have received prior therapy with murine antibodies must have documentation of absence of HAMA within 8 weeks of lymphodepletion or after their most recent murine antibody therapy (whichever is shortest). For subjects that receive murine monoclonal antibodies between procurement and lymphodepletion, HAMA testing should be performed within 4 weeks prior to lymphodepletion and after the last monoclonal antibody dose.

6.4.5 Genomic Analysis

DNA analysis may be performed on the iC9-CAR19 cell products and on blood samples collected per the Time and Events Table. These analyses will be used to determine the integration location of CAR19. 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 [71]. 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 [71].

6.4.6 Sample Collection Requirements if CRS or Severe Toxicity Occurs

A serum sample (~1 mL) for IL-6 analysis and up to 20 mL of blood should be collected in any subject who develops signs and symptoms of CRS regardless of whether their symptoms meet severity requirements for DLT. This sample should be collected before treatments are administered to alleviate CRS symptoms. Subsequent samples may be collected at the discretion of the investigator (e.g., a single sample collection may be obtained each day until the event resolves) and will depend on the condition of the subject.

In addition, a serum sample (~1 mL) for IL-6 analysis and up to 20 mL of blood should be collected in any subject who develops a SAE (i.e., requiring hospitalization) related to the cell infusion. Subsequent samples may be collected at the discretion of the investigator.

An additional blood sample of up to 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 iC9-CAR19 T cells.

6.4.7 Other Tissue Studies

If a standard of care biopsy is required at any time after treatment (while the subject is still enrolled on the clinical trial), a sample of this may 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 CD19 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 CD19 expression.

7.0 EVALUATIONS AND ASSESSMENTS

7.1 Time and Events Table

Study Assessments	Screening ¹			ALT/CAR Infusion		Study Treatment Follow-up								Long Term Follow Up ²			
	Pre-procurement	CELL PROCUREMENT BRIDGING THERAPY	Pre-lymphodepletion			W0D1 ¹	W0 D3 & D5	W1 D1 ¹	W2 D1 ¹	W3 D1 ¹	W4 D1 ¹	W6 D1 ¹	M3 ¹	M6 ¹	M9 ¹	M12 ¹	Yrly x 4 yrs ¹
History ²	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ²
Physical exam ¹	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status	X		X		X		X		X	X							
Pregnancy test ³	X		X		X ²												
Concomitant Medications ⁴	X		X	X												X	
ECHO ⁵	X																
Hematology ⁶	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry ⁷	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁷	
Virus testing ⁸	X								X ⁸	X ⁸	X ⁸		X ⁸				
Tumor imaging ⁹	X		X						X		X		X		see Reference		
IgG; IgA ¹⁰			X						X		X	X	X	X	X	X	
For WM, serum immunoglobulins, SPEP/IFE, serum free light chains ¹¹	X		X						X		X	X	X	X	X	X	
For WM subjects, BM only disease, and CLL Bone Marrow (BM) biopsy ¹²			X						X ¹²		X ¹²		X ¹²		X ¹²	X ¹²	
Correlative Blood Sample Collections ¹³			X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹³	X
HAMA testing ¹⁴			X						X								
CofA ¹⁵			X														
Clinical toxicity assessment ¹⁶	X		X	X	X	X	X	X									
ICE score ¹⁷			X	X	X	X	X	X									
PRO Questionnaires (optional) ¹⁸			X	X	X					X		X		X			
Infusion of iC9-CAR19 cells ¹⁹				X													
Rimiducid ²⁰				See Section 4.1.3 / Time points for blood sampling if rimiducid given for treatment of CRS													
Tissue studies				See Section 6.4.7													

Footnotes to Time and Events Table

1. Screening includes tests to confirm eligibility for both procurement and cellular treatment. The presence of two doses of tocilizumab onsite must be confirmed prior to cell infusion. Complete history is required at baseline only, thereafter focused history on symptoms/toxicity. Physical exam to include height (baseline only), examination of the skin, weight, and vital signs (blood pressure, pulse, oxygen saturation, respiratory rate, temperature). Neurologic examination must be performed prior to iC9-CAR19 cell infusion, and repeated daily during inpatient hospitalization following iC9-CAR19 cell infusion. A window of 7 days will apply to all procurement labs unless specified below.

A window of ± 3 days will apply to all study visits for the first 6 weeks unless otherwise noted below. 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. Annual follow-up visits during long-term follow-up for a total of 15 years or until disease progression. An annual physical exam is required for the first 5 years of follow up only. Starting at month 3 post infusion, tests and assessments may be completed at the subject's local healthcare provider clinic. The study team will 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 will collect clinical information, tests and assessments results, other clinical observations from the subject's medical record and their local health care provider. Subject history may be collected via phone contact, blood samples may be collected by a local health care provider and shipped for testing as outlined in the study Laboratory Manual.

2. 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 5. New incidence of infection (potentially product related), and 6. Prior cancer therapy. See Section 6.1.2 for additional information. If a subject develops a delayed adverse event that is related to iC9-CAR19 cell treatments described above, 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.
3. Serum pregnancy testing will be done in female subjects of childbearing potential within 72 hours prior to procurement and repeated 72 hours prior to lymphodepletion of iC9-CAR19 cells. Serum pregnancy test will be done within 7 days of cell infusion (does not need to be repeated if pre-lymphodepletion pregnancy test is within window).
4. Concomitant medications will be captured per Section 6.1.3.
5. Ejection fraction (EF) evaluated via ECHO. This test will be evaluated within 3 months prior to procurement.
6. Hematology includes complete blood count with differential.
7. Serum chemistry includes comprehensive metabolic panel (BUN, creatinine, Na, K, Cl, CO₂, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase), uric acid and lactate dehydrogenase (LDH). **NOTE:** Pre-procurement, if CMP has been performed within 7 days of procurement, they do not need to be repeated. CMP must be performed within 24 hours prior to iC9-CAR19 T cell infusion. Uric acid is only required prior to lymphodepletion, prior to infusion, and for the first 2 weeks following the infusion. LDH is only required prior to treatment.
8. HIV, HBV, HCV testing required for confirmation that no active infection exists at the time of procurement; results can be pending at the time of cell procurement; only subjects meeting these criteria will be infused. Subjects who are hepatitis B core antibody positive will have a hepatitis B viral load checked and will be excluded if viral load is positive at baseline. Subjects who are core antibody positive and viral load negative at baseline will be considered eligible. These subjects will be started on Hepatitis B prophylaxis prior to bendamustine lymphodepletion. These subjects will also be tested for Hepatitis B viral load during follow-up visits at week 6, month 3, month 6, and month 12 post-treatment. Subjects who experience disease progression or initiate other

anti-cancer therapy during this follow-up period will cease Hepatitis B testing follow-up at the time either or both occurs. Virus testing may be performed up to 90 days prior to procurement.

9. Tumor imaging for disease assessment will be performed at baseline, within 90 days of procurement and within 10 days of lymphodepletion and at 6 weeks (± 7 day window) following the infusion of iC9-CAR19 T cells and at later time points (months 6, 12, 18, 24) (± 30 day window) as denoted in the Time and Events table above. In participants who receive intervening chemotherapy between procurement and lymphodepletion, the scans must be performed at least 3 weeks after the intervening chemotherapy is administered (imaging does not need to be repeated if it is within 10 days prior to lymphodepletion). Subjects with apparent progressive disease at time of 6 week scan who do not have clinical signs of progression will be rescanned 8-12 weeks later to confirm disease progression. 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, brain MRI). If imaging studies are performed at other times after treatment on this study, the data will be collected, and information gained will be used for this study. The tests performed at baseline for assessment of disease should be performed consistently throughout the study. For WM, if disease is not measurable by imaging then imaging prior to procurement will not be required but may be performed at the Investigator's discretion (refer to Procurement Eligibility Criteria in Section 3.3).
 10. Immunoglobulin G (IgG) testing; IgA testing at pre-lymphodepletion only.
 11. The following windows apply to laboratory evaluations for WM, serum immunoglobulins, SPEP/IFE, and serum free light chains. Pre-procurement – within 4 weeks of procurement as long as it is after the most recent treatment; Pre-lymphodepletion – within 4 weeks of lymphodepletion as long as it is after the most recent treatment; Week 6 assessment – ± 1 week; Months 6, 9, 12, and yearly during the first 4 years of long-term follow-up – ± 4 -week window.
 12. The pre-lymphodepletion BM biopsy may be performed within a 90-day window before lymphodepletion as long as it is after the most recent treatment. BM biopsy is performed at 6 weeks only if the subject is in CR, VGPR, or PR for WM subjects and in CR by scan for subjects with prior marrow only disease. For future assessments, perform BM biopsy to confirm CR if the subject would otherwise meet CR criteria based on WM response criteria in [Appendix L](#). At the week 6 assessment, the BM biopsy may be performed within a 4-week window after 6 weeks (6-10 weeks after treatment) to confirm CR/PR. Ongoing biopsies for subjects with BM only disease would coincide with imaging visits and may occur until progression for every 6 months, starting at the 6-month visit, for 2 years after the first cell infusion. See also [Section 6.1.6](#).
- CLL patients will undergo a bone marrow biopsy within a 28-day window prior to receiving lymphodepleting chemotherapy. Post treatment, if they meet laboratory and imaging criteria for complete remission, they will additionally have a bone marrow biopsy performed at 6 weeks (± 14 days) to conform with IWCLL guidelines of assessing a complete response histologically, as long as patients meet IWCLL hematologic and imaging CR criteria at that timepoint. Morphology analysis and high-resolution flow cytometry will be performed on the marrow, with conventional karyotyping and fluorescent *in situ* hybridization in patients with an identified cytogenetic abnormality. Minimal residual disease (MRD) assessment on the bone marrow biopsy sample will be done using immunoglobulin heavy chain (IGH) deep sequencing analysis.
13. 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 (up to 19 mL of blood), at 3 – 4 hours post infusion (up to 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/ μ g 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 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 time point, 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 6.4.3.
 - 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 6.4.2. 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 6.4.2.
 - d. **Cytokine testing:** Serum collected before and 3-4 hours after infusion for cytokine, CRP and IL-2Rα testing.
 - e. Correlative blood sample collection will cease if the samples are no longer required for function and persistence or transgene copy number analysis.
14. 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. Subjects who have received prior therapy with murine antibodies must have documentation of absence of HAMA within 8 weeks of lymphodepletion or after their most recent murine antibody therapy (whichever is shortest). For subjects that receive murine monoclonal antibodies between procurement and lymphodepletion, HAMA testing should be performed within 4 weeks prior to lymphodepletion and after the last monoclonal antibody dose.
15. CoFA generated at completion of required studies for production/QA of cell
16. Documentation of SAEs caused by a protocol-mandated intervention (e.g. SAEs related to invasive procedures such as biopsies, medication washout) will begin after informed consent. For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin at procurement. Documentation of non-serious AEs or SARs must begin at the time of procurement. Any AEs or SARs experienced by the subject related to these procedures (procurement, lymphodepletion, and cell infusion) must be documented. Data on all adverse experiences/toxicities regardless of seriousness must be collected for documentation purposes through 4 weeks after dosing of the CAR-T per NCI-CTCAE criteria v5.0, ASBMT Consensus CRS grading criteria and ASBMT Consensus ICANS grading. Adverse event data collection will cease in subjects that receive therapy for relapse of their primary malignancy. Data on disease status will continue to be collected as appropriate and we will continue to collect data on long-term follow-up for safety of gene transfer (via RCR by PCR).
- a) During dose finding the DLT safety assessment period = 4 weeks post the cell infusion
 - b) If CRS signs and symptoms occur, a serum sample (~1 mL) for IL-6 analysis and up to 20 mL of blood should be collected before instituting treatment for CRS. See section 6.4.6 and section 12.1 for additional details. Sample collection can be repeated daily until signs and symptoms of CRS resolve.

- c) Serum (~1 mL) and up to 20 mL of blood should also be collected for serious toxicities related to cell infusion that develop that require hospitalization. See Section 6.4.6 for additional details.
17. Additional ICE score re-evaluations will be performed per standard of care while inpatient after iC9-CAR19 cell product infusion.
 18. The optional PRO Questionnaires are to be completed prior to infusion (See [Appendix F. PROMIS Global Health Scale](#) and [Appendix G. Patient-reported Outcomes Version of the Common Terminology Criteria for Adverse Events \(PRO-CTCAE\) Version 1.0](#))
 19. iC9-CAR19 T cells infused 2-14 days after completion of lymphodepletion. Research personnel will keep track of any subjects who undergo procurement but do not undergo treatment with cellular products, and the reason for withholding treatment.
 20. For subjects with grade 4 CRS or grade 3 CRS refractory to SOC and subjects with grade ≥ 3 ICANS that does not improve to grade ≤ 1 within 72 hours with SOC interventions or grade 4 ICANS of any duration that have cerebral edema and/or generalized convulsive status epilepticus: Rimiducid will be administered IV per standard of care (approximately 2 hours) at 0.4 mg/kg
 - Time points for blood sampling required prior to and after rimiducid administration depicted in section 4.1.5.
 - Refer to section 6.4.6 for information on sample collection requirements if CRS or severe toxicity occurs.

Subjects in the expansion cohort who experience $\geq$ grade 2 CRS or ICANS that remains $\geq$ grade 2 twenty-four hours after an initial dose of standard treatment may be part of the sub-study of rimiducid (**Figure 3**). These subjects will receive one of two assigned dose levels of rimiducid with their second tocilizumab infusion or steroid treatment (for CRS: 0.05 mg/kg or 0.01 mg/kg; for ICANS: 0.1 mg/kg or 0.01 mg/kg). If the subjects' CRS or ICANS is unresponsive to the second standard treatment and the assigned dose level of rimiducid after 48 hours, subjects with $\geq$ grade 3 CRS or ICANS will then be given a full dose (0.4 mg/kg) of rimiducid. Subjects with grade 2 CRS or ICANS 48 hours after the first dose of rimiducid will receive a second treatment with rimiducid at the assigned dose level.

21. Subjects will receive a lymphodepletion regimen of bendamustine 70 mg/m² IV and fludarabine 30 mg/m² each as a daily infusion for 3 days per institutional guidelines 2 – 14 days prior to the first (or single) cell infusion. Bendamustine should be administered first followed by IV administration of fludarabine. Subjects with known history of intolerance to bendamustine may be considered for lymphodepletion with cyclophosphamide and fludarabine at the discretion of the clinical investigator. For information regarding cyclophosphamide administration, please refer to Appendix J: Cyclophosphamide Drug Information. Subjects with creatinine clearance < 79 ml/min will have fludarabine adjusted per institutional guidelines.

7.2 Long Term Follow-up Assessments

Function and persistence will be continued for at least one year post-CAR T cell infusion. If transgene is no longer detectable by PCR at 1 year testing will discontinue. If the transgene is detectable by PCR at 1 year, function and persistence analysis will continue until the transgene is no longer detectable by PCR. If a transgene is detected, assays (quantitative PCR (see Section 6.4.3) and function and persistence studies) will continue every 6 months up to year 5. Otherwise, subjects will be followed yearly with function and persistence testing, RCR by PCR, and quantitative PCR for a total of 15 years or until transgene is $< 0.5\%$ for more than 1 testing period. Correlative blood sample collection will cease if the samples are no longer required for function and persistence or transgene copy number analysis. Subjects will be followed every 6 months for 2 years or until progression with imaging. Subjects will also be followed every 6 months with history, physical exam, and performance status until initiation of alternative therapy or 5 years post cell infusion. Additional visits will be obtained as clinically indicated.

Subjects who receive alternate therapy after receiving a cell infusion will still be required to complete abbreviated follow up procedures outlined in [Appendix C](#).

For subjects with WM, SPEP/IFE and serum free light chain assessments will occur at follow-up assessments as directed in the Time and Events Table. BM biopsies will occur only to confirm CR.

7.3 Biobank Repository

Subjects participating in this trial must consent to allow researchers to store their biological specimens.

CAR19 T-cells will be stored at the GMP facility according to standard procedures. Other specimens collected during this study as described in Section 6.4 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 in section 6.4. These specimens include:

- Unused iC9-CAR19 T-cells
- Unused additional material collected during procurement (peripheral blood mononuclear cells)
- Tissue samples obtained for any standard of care procedure that may provide additional information about iC9-CAR19 T-cell therapy

For example, analyses will be performed to assist in determining if the iC9-CAR19 T-cells are associated with the tumor and if the iC9-CAR19 T-cells are present.

Information about the subject'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 subject's participation in the clinical study may also be included. This information may be important for understanding how the subject's cancer developed and responded to treatment.

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 data

Identifiable data will not be given out to any correlative investigators at any time. 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.

Storage Time:

- iC9-CAR19 T cells and material from procurement are to be stored for up to 15 years for subject treatment and safety purposes. Material from procurement may be used to generate LCCC CAR-T cells under other LCCC protocols if the subject is eligible for a different CAR-T treatment. 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 any standard of care procedure that may provide additional information about CAR19 T-cell therapy will be stored for up to 15 years.

7.4 Assessment of Safety

All subjects consented for the study will be included in the safety analysis. The safety analysis will be divided into the following categories: events occurring between cell procurement and lymphodepletion, events occurring between lymphodepletion and iC9-CAR19 cell infusion, and events occurring after iC9-CAR19 cell infusion. Each subject will be assessed periodically for the development of any toxicity according to the Time and Events table (section 7.1). Toxicity will be assessed according to the NCI CTCAE v5.0, CRS criteria provided in [Appendix A](#), and ICANS criteria provided in [Appendix B. Management of Neurotoxicity/Immune Effector Cell-Associated Neurotoxicity Syndrome \(ICANS\) from CAR-T Therapy](#).

7.5 Assessment of Efficacy

To assess disease progression, imaging will be performed within 90 days prior to procurement, within 7 days prior to lymphodepletion and at least 3 weeks after most recent therapy, and at 6 weeks following cell infusion in subjects with measurable disease by imaging. If initial imaging is consistent with progressive disease, a repeat scan will be obtained 8-12 weeks after the 6 week scan to confirm disease progression if subject is otherwise doing clinically well per investigator assessment. Subsequently, subjects will receive imaging starting at 6 months after CAR-T infusion and then every 6 months until disease progression or up to 2 years post cell 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. Subjects in complete remission (CR) at the time of required disease assessment prior to lymphodepletion will be excluded from the assessment of response.

For CLL/SLL subjects or subjects with bone marrow only disease, subjects will undergo a bone marrow biopsy within 28 days prior to receiving lymphodepleting chemotherapy to establish baseline marrow infiltrate. 6 weeks post-iC9-CAR.19 cell infusion if they meet hematologic and imaging complete remission criteria, they will undergo a second bone marrow biopsy to confirm CR histologically through IHC and flow cytometry. Furthermore, MRD testing by IGH deep sequencing analysis will be done on the post- iC9-CAR.19 cell -infusion bone marrow biopsy sample if subjects have a histologic CR.

For subjects with bone marrow only involvement of their lymphoma, a bone marrow biopsy will be obtained at 6-10 weeks after CAR-T cell infusion. Bone marrow biopsy would be repeated at the time of imaging assessments (every 6 months starting at month 6 until disease progression for up to two years after the first cell infusion) to confirm CR if otherwise no evidence of disease.

In patients with WM, imaging will be performed at screening prior to procurement and repeated if there is evidence of disease. Laboratory assessments of disease consisting of serum immunoglobulins, SPEP/IFE, and serum free light chains will be obtained at baseline within 1 month of procurement, within 1 month of lymphodepletion, at 6 weeks (+/-1 week window), 6 months, 9 months, 12 months, and every 6 months for 4 years. Bone marrow biopsy will be obtained within 90 days of lymphodepletion (as long as after most recent treatment) as baseline. A bone marrow biopsy will be obtained at 6-10 weeks after CAR-T cell infusion in subjects with evidence of response by peripheral blood tests (subjects in CR, VGPR, PR). Afterwards, a bone marrow biopsy would only be required to confirm a new CR (within a 1 month window of response evaluation).

7.5.1 Measurement of Disease

This study will use the revised Lugano classification for response assessment[56, 57] ([Appendix K](#)), Response Criteria for Waldenström Macroglobulinemia ([Appendix L](#)), Primary CNS lymphoma response assessment ([Appendix N](#)), and the revised IWCLL criteria for assessment of chronic lymphocytic leukemia ([Appendix M](#))

7.6 Criteria for Removal from Protocol Therapy

7.6.1 Criteria for Removal from Protocol Therapy, but Continued Long-Term Follow Up

- 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.

7.6.2 Off Study Criteria

- Death
- Lost to follow up
- Withdrawal of consent for any further data submission

8.0 ADVERSE EVENTS

8.1 Definitions

8.1.1 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 drug or cellular therapy and drug or cellular product in a clinical investigation subject administered a pharmaceutical/cellular 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.

8.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug or cellular product is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the cell infusion 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 or cellular product.

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

- Single occurrence of an uncommon event known to be strongly associated with drug or cellular product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug or cellular 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 or cell infusion caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug or cellular product treatment group than in a concurrent or historical control group.

8.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with prior experience in CAR-T therapy trials or the applicable product information (e.g., as provided in the IND and/or 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 or IND as occurring with a class of drugs or cellular product or as anticipated from the pharmacological properties of the drug or cellular product but are not specifically mentioned as occurring with the particular drug or cellular product under investigation.

8.1.4 Serious AE or SAR

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 study treatment related experience when, based upon appropriate medical judgment, they 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.
- Grade 4 or 5 cell product infusion reactions, CRS, or neurologic toxicity

*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.

8.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin at the time of procurement through the 4-week safety follow-up period after cellular treatment. Any AEs or SARs experienced by the subject related to these procedures (procurement, lymphodepletion, and cell infusion) must be documented. Adverse event data collection will cease in subjects that receive therapy for relapse of their primary malignancy. The DLT assessment period will start at the time of the cell infusion through the 4-week DLT follow up period after the infusion. Subjects will be followed for safety and documentation of AEs for 4 weeks after the cell infusion.

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.

8.3 SAEs or Serious SARs

8.3.1 Timing

Documentation of SAEs caused by a protocol-mandated intervention (e.g. SAEs related to invasive procedures such as biopsies, medication washout) will begin after informed consent.

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin at procurement and continue through the 4-week follow-up period after treatment with the cell infusion is discontinued.

8.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within OnCore® for that subject within 24 hours of learning of its occurrence. The Regulatory Associate and Medical Monitor must be notified via email of all SAEs within 24 hours of learning of its occurrence.

8.4 Adverse Event Reporting

8.4.1 IRB Reporting Requirements:

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.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 28 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.

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 UNC Study Coordinator. 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.

8.4.2 FDA Expedited Reporting requirements for studies conducted under an IND:

A sponsor must report any suspected adverse reaction (SAR) that is both serious and unexpected and related to the cellular product to the FDA. Refer to Section 8.1.2 for the definition of 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.

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/IND 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.

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.*

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.

8.4.3 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.

8.4.4 Funding Source Reporting Requirements:

Additionally, a copy of correspondence regarding any serious adverse event, that is submitted to local and national regulatory agencies on behalf of a MD Anderson Cancer Center investigational product, must be directed to the electronic safety/pregnancy reporting mailbox mdanderson@pharsafer.com as soon as possible and no later than 1 business day of the Investigator and/or designee receiving notification of any serious adverse event experienced by a subject participating in the study..

8.5 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).

Meetings/teleconferences will be held 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 investigator 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.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

The tolerable cell dose (TCD) is defined as the dose at which approximately 0.20 of subjects experience DLT. Dose escalation is guided by the 3+3 design and it is described in Section 4.1.1. Two dose levels are being evaluated. The estimated TCD is the maximum dose with the estimated DLT rate of less than 0.33.

After the TCD of iC9-CAR19 T cells has been determined in adults, up to 18 additional adult subjects may be enrolled in an expansion cohort at the TCD. Rimiducid will be given to subjects in the dose escalation and expansion cohorts who develop grade ≥ 3 immune effector cell-associated neurotoxicity syndrome (ICANS) that does not improve to grade ≤ 1 within 72 hours with standard of care interventions and subjects with grade 4 ICANS of any duration that have evidence of cerebral edema and/or generalized convulsive status epilepticus. Additionally, subjects in the expansion cohort who experience $\geq$ grade 2 CRS or ICANS that remains $\geq$ grade 2 twenty-four hours after an initial dose of standard treatment may be enrolled in a sub-study of rimiducid. These subjects will receive one of two assigned dose levels of rimiducid with their second standard treatment. The percent reduction in CAR T cells will be measured in these subjects. If the subject's CRS is unresponsive to tocilizumab and the assigned dose level of rimiducid, subjects with $\geq$ grade 3 CRS will then be given a full dose (0.4 mg/kg) of rimiducid. If the subject's CRS or ICANS is at grade 2 48 hours after the first dose of rimiducid they will receive another treatment of rimiducid at the assigned dose level. The dose TCD will be re-evaluated if more 33% DLTs will be observed at that dose. The "0.33%" rule is based on Bayesian calculation of probability that a dose has the DLT rate higher than 0.2 given observed data [72]. We say that the TCD has been exceeded if the probability that the DLT rate is higher than 0.2 is 80% or higher. Assuming Beta(0.5,0.5) prior on the probability of DLT at each dose yields the rule that if DLTs are observed in 1/3 or more subjects out of 4-9 subjects the TCD has been exceeded.

9.2 Sample Size, Accrual and Duration of Accrual

The total number of subjects in the trial will depend on the number of DLTs observed at each dose level. During the Phase I portion, the number of subjects will range from 6 to 12. Up to 18 additional subjects can be enrolled in an expansion cohort.

9.3 Data Analysis Plans

All subjects who receive CAR-T cell infusion will be included in the safety analysis. Adverse event data and corresponding toxicity grades through 4 weeks after CAR-T cell infusion and during long-term follow up will be summarized. In addition to the DLT evaluation, the safety analysis will be divided into the following categories: events occurring between cell procurement and lymphodepletion, events occurring between lymphodepletion and cell infusion, and events occurring after cell infusion. Tables will be generated to summarize incidence of subjects experiencing at least one episode of each adverse event, incidence of adverse events causing withdrawal, and incidence of serious

adverse events. The total number of episodes for each event reported, the severity, and attribution to study therapy of each episode reported 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, the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. Safety data will be summarized by dose level.

For laboratory data, descriptive statistics (means, standard deviations, medians and ranges) at each evaluation point through 4 weeks post- CAR-T cell infusion will be calculated. Laboratory data collected monthly intervals for the first year will also be summarized. ORR will be estimated as proportion and a 95% confidence interval will be computed. PFS, OS and DOR will be estimated using the Kaplan-Meier method.

Differential CAR T-cell behavioral analysis will be described by comparing CAR19 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 CAR19.

Descriptive statistics will be generated to assess the efficacy of rimiducid pre- to post-dose diminutions in iC9-CAR19 cell viability *in vivo* and cytokine production.

10.0 STUDY MANAGEMENT

10.1 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.

10.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trial Office (CTO) 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

10.3 Registration Procedures

All subjects must be registered by the Cellular Immunotherapy study coordinator at UNC before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Cellular Immunotherapy Study Coordinator.

10.4 Data Management and Monitoring/Auditing

The UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based electronic data captures system (EDC), Advarra. All data will be collected and entered into Advarra EDC by research coordinators from UNC LCCC.

The sponsor will provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. As an investigator initiated study, this trial will also be audited by the LCCC compliance committee every six or twelve months.

10.5 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.

10.5.1 Emergency Modifications

UNC 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.

10.5.2 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.

10.5.3 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 personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

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:

Any events that meet the criteria for “Unanticipated Problems” as defined by UNC’s IRB must be reported by the study personnel using the IRB’s web-based reporting system.

10.6 Amendments to the Protocol

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.

10.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, 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 cell infusion 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.

10.8 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.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

12.1 Appendix A. CRS Grading Criteria and Link to Management Guidelines

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.

Cytokine release syndrome (CRS) 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.

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 5 and criteria for clinical grading are outlined below in **Table 6**.

Table 5 Signs and Symptoms of CRS and Neurotoxicity

Organ system	Signs/Symptoms
Constitutional	Fever, rigors, malaise, fatigue, anorexia, headache, myalgias/artralgias, nausea/vomiting
Dermatologic	Rash
Gastrointestinal	Nausea/vomiting/diarrhea
Respiratory	Tachypnea, hypoxemia (potentially requiring supplemental oxygen/ventilation)
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 the ASBMT Consensus Grading, 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 6 CRS Grading

Grade 1 – Mild
Fever $\geq 38^{\circ}\text{C}$ No hypotension No hypoxia
Grade 2 – Moderate
Fever $\geq 38^{\circ}\text{C}$ Hypotension not requiring vasopressors Hypoxia requiring low-flow nasal cannula (≤ 6 L/minute) or blow-by
Grade 3 – Severe
Fever $\geq 38^{\circ}\text{C}$ Hypotension requiring a vasopressor with or without vasopressin Hypoxia requiring high-flow nasal cannula (>6 L/minute), facemask, nonrebreather mask, or Venturi mask
Grade 4 – Life-threatening
Fever $\geq 38^{\circ}\text{C}$ Hypotension requiring multiple vasopressors (excluding vasopressin) Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, mechanical ventilation)
Grade 5 – Death
Death

MANAGEMENT OF CRS

CRS will be managed per institutional guidelines provided via the QR code provided below:



12.2 **Appendix B. Management of Neurotoxicity/Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) from CAR-T Therapy**

Neurologic complications (referred to as immune effector cell-associated neurotoxicity syndrome, ICANS) occur in approximately 40% of patients treated with lymphodepletion chemotherapy followed by autologous chimeric antigen receptor modified T-cells (CAR-T cells) directed against the CD19 antigen [73]. While many of these patients have neurologic signs and symptoms in the context of cytokine release syndrome (CRS), occurring typically in the first 1-2 weeks following cell infusion, approximately 10% of patients experience more delayed isolated neurologic events that can range from subtle encephalopathy to focal neurologic findings, seizures and elevated intracranial pressure [27]. Risk factors for the development of ICANS appear to be high degree of leukemic bone marrow infiltration, prior neurologic events or comorbidities, and high CAR-T cell dose (Gust 2017). The pathophysiology of these events is not completely defined but CAR-T cells and elevated cytokine levels are observed in the cerebrospinal fluid of these patients and severe cases involve central nervous system endothelial activation leading to microangiopathy [73].

GENERAL BACKGROUND

Neurotoxicity from CAR-T therapy, or ICANS, 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.

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

Immune Effector Cell-Associated Encephalopathy (ICE) Score

The ICE score is a neurological assessment score that quantifies the severity of neurologic impairment. Each item in the assessment is associated with the point value indicated. The higher the score the better, with an ICE score of 10 indicating a normal neurological assessment. The score should then be considered with other assessments to accurately grade the patients ICANS as is outlined in management of neurotoxicity/ICANS below (**Table 7** and **Table 8**).

Table 7 ICE

Assessment	Score (10 = No impairment)
Orientation	
• Year	1
• Month	1
• City	1
• Hospital	1
Name 3 Objects (example: point to clock, pen, and button)	3
Ability to follow simple commands (e.g. “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	<u>1</u>
Ability to write a standard sentence	1
Ability to count backwards from 100 by 10	1
Total	10

ICANS GRADING

Table 8 ASBMT ICANS Consensus Grading for Adults

Grade 1
ICE Score: 7-9 (mild impairment) Level of consciousness: Awakens spontaneously Seizure: None Motor Findings: None Elevated ICP/Cerebral edema: None
Grade 2
ICE Score: 3-6 (moderate impairment) Level of consciousness: Awakens to voice Seizure: None Motor Findings: None Elevated ICP/Cerebral edema: None
Grade 3
ICE Score: 0-2 (severe impairment) Level of consciousness: Awakens only to tactile stimulus Seizure: Any clinical seizure (focal or generalized) that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention Motor findings: None Elevated ICP/Cerebral Edema: Elevated ICP; Focal/local edema on neuroimaging
Grade 4
ICE Score: Critical condition, and/or obtunded and cannot perform assessment of tasks Level of consciousness: Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma Seizure: Life threatening prolonged seizure (> 5 min) or repetitive clinical or electrical seizures without return to baseline in between Motor findings: Deep focal motor weakness such as hemiparesis or paraparesis Elevated ICP/Cerebral edema: Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; Cranial nerve VI palsy; Papilledema; Cushing's triad

ICANS MANAGEMENT

The Neurotoxicity treatment algorithm is available via the QR code provided below:



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12.3 Appendix C. Abbreviated Follow Up Required After Starting 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 7.1 are completed. Subsequent follow up assessments for subjects post progression are outlined in the table below. If subjects develop PD 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 experience PD. Blood samples should be collected by a local health care provider.

Assessments ¹	Post Disease Progression Follow up			
	Month 3 D1	Month 6 D1	Mth 12 D1	Yearly
History ²	X	X	X	X
Performance status	X	X	X	X
Correlative Blood Sample Collection ³	X	X	X	X
Survival	X	X	X	X

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. Semi-annual follow-up visits during long-term follow-up for a total of 5 years or until disease progression. 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). If a subject develops a delayed adverse event that is related to iC9-CAR19 cell treatment, as described above, 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.
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/ μ g 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 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 6.4.3.
- 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 6.4.2. 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 6.4.2.
- d. Collect up to 20mL of blood for RCR by PCR and/or Quantitative PCR testing. See the laboratory manual for sample collection, handling and shipping instructions.

12.4 Appendix E. Karnofsky Scale

Karnofsky Scale	
Able to carry on normal activity; no special care is needed	
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort
Unable to work, able to live at home, cares for most personal needs, a varying amount of assistance is needed	
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly	
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated, although death not imminent
20	Very sick, hospitalization necessary
10	Moribund, fatal process progressing rapidly

12.5 Appendix F. PROMIS Global Health Scale

	Please respond to each item by marking one box per row	Excellent	Very good	Good	Fair	Poor	
Global 01	In general, would you say your health is:	5 ☐	4 ☐	3 ☐	2 ☐	1 ☐	
Global 02	In general, would you say your quality of life is:	5 ☐	4 ☐	3 ☐	2 ☐	1 ☐	
Global 03	In general, how would you rate your physical health?	5 ☐	4 ☐	3 ☐	2 ☐	1 ☐	
Global 04	In general, how would you rate your mental health, including your mood and your ability to think?	5 ☐	4 ☐	3 ☐	2 ☐	1 ☐	
Global 05	In general, how would you rate your satisfaction with your social activities and relationships?	5 ☐	4 ☐	3 ☐	2 ☐	1 ☐	
Global 09	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	
Global 06	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	
Global 10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	5 ☐	4 ☐	3 ☐	2 ☐	1 ☐	
		None	Mild	Moderate	Severe	Very Severe	
Global 08	How would you rate your fatigue on average?	5 ☐	4 ☐	3 ☐	2 ☐	1 ☐	
Global 07	How would you rate your pain on average?	☐ ☐ ☐ ☐ ☐					☐ ☐ ☐
		0 1 2 3 4 5 6 7					8 9 10
		No pain					Worst pain

	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 catch a bus?	5 ☐	4 ☐	3 ☐	2 ☐	1 ☐
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?					
		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 ☐

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12.6 Appendix G. Patient-reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Version 1.0

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 NIGHTTIME (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 NIGHTTIME (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

12.7 Appendix H. Prohibited Medications or Those to be Used with Caution

Bendamustine's active metabolite is formed via P450 CYP1A2. Strong inhibitors have the potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of its active metabolites. Strong inhibitors of CYP1A2 are prohibited in this trial. Other drugs known to induce or inhibit CYP1A2 should be used with caution, or alternative treatments considered. *Note: this is not an exhaustive list and further details can be found at <http://medicine.iupui.edu/clinpharm/ddis/> and at Expert Opin. Drug Metab Toxicol (2013) 9(6) 737-751. If a drug appears on more than one list follow the conservative rule.*

CYP1A2 Inhibitors	CYP1A2 Inducers
ciprofloxacin fluvoxamine	beta-naphthoflavone Broccoli Brussel sprouts Carbamazepine Char-grilled meat Insulin Methylcholanthrene Modafinil Nafcillin Omeprazole Rifampin Rucaparib Teriflunomide tobacco

Patient Handout on Prohibited Medications or Those to be used with Caution

One of the medications you are receiving during this clinical trial is bendamustine. Bendamustine interacts with some drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement). Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. Bring this paper with you.

- Bendamustine is processed by a certain enzyme in the liver called CYP1A2. Drugs that increase the activity of this enzyme are called “inducers”, and drugs that decrease the activity of this enzyme are called “inhibitors”. Bendamustine must be used very carefully with other medicines that are inducers or inhibitors of CYP1A2.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category
- Before you start the study, your study doctor will work with your regular prescriber to switch the following medications if you are taking them:
 - Fluvoxamine
 - Ciprofloxacin
 - Enoxacin
- Your regular prescribers should look at this web site: <http://medicine.iupui.edu/clinpharm/ddis/table.asp> to see if any medicine they want to prescribe is on a list of drugs to avoid. Your study doctor may also have a list of medications for you to show your regular prescribers instead of, or in addition to, this website.
- Other medicines can be a problem with your study drugs.
 - You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
 - Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

12.8 Appendix I. Medications Known to Have Major Interactions with Fludarabine

adalimumab
BCG
certolizumab
clozapine
deferiprone
etanercept
fingolimod
golimumab
infliximab
influenza virus vaccine, H1N1, live
influenza virus vaccine, live, trivalent
leflunomide
measles virus vaccine
measles virus vaccine / mumps virus vaccine / rubella virus vaccine
measles virus vaccine / mumps virus vaccine / rubella virus vaccine / varicella virus vaccine
measles virus vaccine / rubella virus vaccine
mumps virus vaccine
mumps virus vaccine / rubella virus vaccine
natalizumab
pentostatin
poliovirus vaccine, live, trivalent
rotavirus vaccine
rubella virus vaccine
samarium SM 153 lexidronam
smallpox vaccine
talimogene laherparepvec
teriflunomide
thalidomide
tofacitinib
typhoid vaccine, live
varicella virus vaccine
yellow fever vaccine
zoster vaccine live

12.9 Appendix J: Cyclophosphamide Drug Information

Cyclophosphamide is an alkylating agent that has anticancer activity. It is converted in the liver to active alkylating metabolites such as phosphoramidate mustard by cytochrome-P450 enzymes. These alkylating metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. Alkyl radicals intercalate into DNA strands and interfere with DNA replication.

Cyclophosphamide is indicated for treatment of malignant diseases including malignant lymphomas, Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma and breast carcinoma.

Cyclophosphamide is commercially available and will not be supplied free of charge to the patient. Cyclophosphamide should be handled and stored per institutional guidelines in accordance with the manufacturer's prescribing information.

12.9.1 How Supplied

Cyclophosphamide is supplied as 500 mg, 1 gm and 2 gm vials containing white powder for IV administration.

12.9.2 Storage Requirements/Stability

Cyclophosphamide vials should be stored at or below 25°C (77°F). Cyclophosphamide does not contain any antimicrobial preservative and care must be taken to assure the sterility of prepared solutions.

12.9.3 Handling and Dispensing

Cyclophosphamide must be dispensed by authorized personnel according to local regulations. Cyclophosphamide should be stored in a secure area according to local regulations.

Please see policy on hazardous drugs:

<http://intranet.unchealthcare.org/intranet/hospitaldepartments/safetynet/policies/hazardousdrugs.pdf>

12.9.4 Preparation

Cyclophosphamide should be reconstituted in 25 mL (500 mg), 50 mL (1 gm) or 100 mL (2 gm) normal saline or sterile water for injection, USP, for IV infusion (ie, per institutional guidelines). Shake vigorously to dissolve the drug. To minimize risk of dermal exposure, always wear gloves when handling vials containing cyclophosphamide sterile powder for injection.

12.9.5 Dosage and Administration

A dose of cyclophosphamide at 500 mg/m² will be administered intravenously each day for 3 consecutive days with fludarabine 30 mg/m².

12.9.6 Adverse Events Associated with Cyclophosphamide

Please refer to the prescribing information for cyclophosphamide for complete information.

Possible side effects:

- Nausea, vomiting, diarrhea
- Urinary bladder toxicity
- Bone marrow suppression

- Gonadal suppression
- Myelodysplasia
- Alopecia
- Immunosuppression
- Hyperpigmentation of the skin

Full prescribing information on cyclophosphamide is available at:
<http://medlibrary.org/lib/rx/meds/cyclophosphamide-1/>

12.9.7 Prohibited Medications

Drugs that should not be administered concomitantly with cyclophosphamide:

- Carbamazepine
- Idarubicin
- Natalizumab
- Entanercept
- Palifermin

Consumption of alcohol should be avoided while the subject is receiving cyclophosphamide. In addition, subjects should avoid the consumption of grapefruit or grapefruit juice during treatment with cyclophosphamide. Vaccination with live vaccines are prohibited (see product insert for details). In addition, there are 46 medications known to have major interactions with cyclophosphamide provided at this link: https://www.drugs.com/drug-interactions/cyclophosphamide-index.html?filter=3&generic_only=.

12.10 Appendix K. Revised Lugano Criteria for NHL

Revised Criteria for Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (Lugano Criteria)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete Lymph nodes and extra-lymphatic sites Nonmeasured lesion Organ enlargement New lesions Bone marrow	Complete metabolic response Score 1, 2, or 3* with or without a residual mass 5 PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be interred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake Not applicable Not applicable None No evidence of FDG-avid disease in marrow	Complete radiologic response (all of the following) Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease Absent Regress to normal None Normal by morphology; if indeterminate, IHC negative
Partial Lymph nodes and extra-lymphatic sites Nonmeasured lesions Organ enlargement New lesions Bone marrow	Partial metabolic response Score of 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings indicate responding disease At end of treatment, these findings indicate residual disease Not applicable Not applicable None Residual uptake higher than uptake in normal marrow but reduced compared w/ baseline (diffuse uptake compatible w. 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 w/ MRI or biopsy or an interval scan	Partial remission (all of the following) $\geq 50\%$ decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation Absent/normal, regressed, but no increase Spleen must have regressed by > 50% in length beyond normal None Not applicable

Revised Criteria for Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (Lugano Criteria) (cont'd)

Response and Site	PET-CT-Based Response	CT-Based Response
<i>No response or stable disease</i> Target nodes/nodal masses, extranodal lesions Non measure lesions Organ enlargement New lesions Bone marrow	<i>No metabolic response</i> Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment Not applicable Not applicable None No change from baseline	<i>Stable disease</i> < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met No increase consistent with progression No increase consistent with progression None Not applicable
<i>Progressive disease</i> Individual target nodes/nodal masses Extranodal lesions Non measured lesions New lesions Bone marrow	<i>Progressive metabolic disease</i> Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment None New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered New or recurrent FDG-avid foci	<i>Progressive disease requires at least 1 of the following PPD progression:</i> An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by $\geq 50\%$ from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly New or clear progression of preexisting nonmeasured lesions Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma New or recurrent involvement

Revised Response Criteria continued from previous page (Table Key)

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

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measureable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those 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), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measure, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†*PET 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.

Reference: Cheson BD, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the lugano classification. J Clin Oncol. 2014; 32:3059-3067.

12.11 Appendix L: Response Criteria for Waldenström Macroglobulinemia

Updated response criteria adopted at the 6th International Workshop on Waldenström Macroglobulinemia.

Compete Response ¹	CR	IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy/organomegaly (if present at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixation studies.
Very Good Partial Response	VGPR	A $\geq$ 90% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. ² No new symptoms or signs of active disease.
Partial Response	PR	A $\geq$ 50% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. ² No new symptoms or signs of active disease.
Minor Response	MR	A $\geq$ 25% but < 50% reduction of serum IgM. No new symptoms or signs of active disease.
Stable Disease	SD	A < 25% reduction and < 25% increase of serum IgM without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM.
Progressive Disease ¹	PD	A $\geq$ 25% increase in serum IgM by protein confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever $\geq$ 38.4°C, drenching night sweats, $\geq$ 10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloidosis) attributable to WM

Footnotes:

1. Require two consecutive assessments made at any time before the institution of any new therapy
2. CT scan may include chest/abdomen/pelvis with contrast

12.12 Appendix M: Revised Criteria for Response Assessment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Response	Parameters
Complete Response (CR)	Meets all of the following: • Target nodes/nodal masses must regress to ≤ 1.5 cm • Normal circulating lymphocyte count • Platelets $\geq 100 \times 10^9/L$ • Hemoglobin ≥ 11.0 g/dL • ANC $\geq 1.5 \times 10^9/L$ • No evidence for typical CLL lymphocytes by morphologic criteria and immunohistochemistry and without nodular lymphoid aggregates on bone marrow biopsy • No constitutional symptoms present from CLL/SLL • No hepatosplenomegaly present
Partial Response (PR)	Has at least two of the following: • Decrease in peripheral circulating lymphocyte count by $\geq 50\%$ from baseline prior to therapy • 50% decrease in size of lymph nodes with no increase in the size of any single lymph node and no new enlarged lymph nodes • 50% decrease in size of liver and/or spleen Has at least one of the following: • Platelets $\geq 100 \times 10^9/L$ or $\geq 50\%$ increase from baseline prior to therapy • Hemoglobin ≥ 11.0 g/dL or $\geq 50\%$ increase from baseline prior to therapy
Progressive Disease (PD)	Has at least one of the following: • New appearance of enlarged lymph node ≥ 1.5 cm, new hepato- and/or splenomegaly or organ infiltration • 50% increase in size from baseline of any previously involved site (i.e. lymph node, liver, spleen, other extranodal sites) • 50% increase from baseline of circulating lymphocyte count • 50% increase from baseline of CLL cells on marrow biopsy • 50% decrease in platelet count from baseline prior to therapy • ≥ 2 gm g/dL decrease in hemoglobin from baseline secondary to CLL
Stable Disease (SD)	Having incremental or decremental changes of $\leq 49\%$ in lymph node size, hemoglobin, platelets, circulating lymphocyte count, extranodal sites, and/or no changes in marrow infiltrate

Reference: [74]

12.13 Appendix N. Response Criteria for Primary CNS Lymphoma

Response	Brain Imaging	Corticosteroid Dose	Eye Examination	CSF Cytology
CR	No contrast enhancement	None	Normal	Negative
CRu	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
PD	25% increase in lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: CNS or systemic			

Abbreviations: CR, complete response; CRu, unconfirmed complete response; RPE, retinal pigment epithelium; PR, partial response; PD, progressive disease.

Adapted from Abrey et al. 2020