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

July 12, 2024

SUMMARY OF CHANGES

Protocol Amendment #9

LCCC1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Pilot Study of the Rare Lymphoma Working Group

AMENDMENT INCORPORATES:

_X Editorial, administrative changes
__ Scientific changes
__ Therapy changes
__ Eligibility Changes

Rationale for amendment: This amendment clarifies a change in the funding source from Seagen to Pfizer and provides an update in safety reporting language.

Editorial, administrative changes:

1. The funding source on the title page was changed from Seagen to Pfizer.
2. Section 5: All language pertaining to Seagen as the provider of brentuximaab vedotin was replaced with Pfizer.
3. Section 7.3.3: Safety reporting information was updated to appropriate Pfizer contacts for adverse events.

THE ATTACHED VERSION DATED July 12, 2024 INCORPORATES THE ABOVE REVISIONS

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

July 12, 2024

PROTOCOL AMENDMENT #8

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Pilot Study of the Rare Lymphoma Working Group

AMENDMENT INCORPORATES (check all that apply):

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

AMENDMENT RATIONALE AND SUMMARY:

The purpose of this amendment is to remove correlative studies and associated blood specimen collections due to the departure of David Weinstock at DFCI from the study team. We have also expanded the type of scans that are acceptable for screening from just PET/CT to CT CAP in situations that would affect subject safety. This change will support accruals while allowing for staging and assessments.

Editorial, administrative Changes:

1. CT CAP added to the abbreviations list.

Scientific Changes:

1. Section 1.7 Correlative Studies was deleted.
2. Section 2.3.2 describing ATLL xenografts was deleted.
3. Section 6.1 Time and Events table,
    a. Row with Blood for correlative studies was removed from the table.
    b. Footnotes 19 and 20 were removed.
    c. Content in Footnote 4 was adjusted to include the acceptability of CT CAP in situations that would affect patient safety.
4. Content in Section 6.3 and 6.4.1 related to the collection of blood for correlative studies was deleted.
5. Content in Section 6.3 was adjusted to include the use of CT CAP for screening in situations that would affect patient safety.
6. Content in Section 6.7 describing the development of ATLL xenograft models in the Weinstock lab at DFCI was removed.
    a. Section 6.7.1 describing the handling and storage of biospecimens was deleted.

THE ATTACHED VERSION DATED March 9, 2022, INCORPORATES THE ABOVE REVISIONS

July 12, 2024

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PROTOCOL AMENDMENT #7

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Pilot Study of the Rare Lymphoma Working Group

AMENDMENT INCORPORATES (check all that apply):

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

AMENDMENT RATIONALE AND SUMMARY:

The purpose of this amendment is to allow for subjects to be evaluable as early as after the 2nd cycle of BV-CHEP if they are eligible to proceed to a stem cell transplant. This also includes a change in the End of Treatment visit occurring after treatment discontinuation. Previously, the end of treatment visit would occur 30 days (± one week), following discontinuation of study therapy. The end of treatment visit should occur 21 days (± one week) after discontinuation of study therapy. It is clarified that trial participants with CD30- disease will receive investigational brentuximab vedotin, supplied for free by Seagen. This amendment also includes a name change by the funding source.

Editorial/administrative Changes:

2. The funding source on the title page is changed from Seattle Genetics to Seagen.
3. In Section 5.1 the link to the brentixumab vedotin prescribing information is changed from http://www.seattlegenetics.com/application/files/2515/1059/6728/ADCETRIS_USPI_USP-BVP-2015-01625pdf.pdf to https://seagendocs.com/Adcetris_Full_Ltr_Master.pdf
    a. Also, it is clarified that trial participants with CD30- disease will receive investigational brentuximab vedotin, supplied for free by Seagen.
4. References to Seattle Genetics in sections 5.1.1, 5.1.2, 5.1.7, and 7.3.3 are changed to Seagen.
5. Section 6.1 Time and Events table,
    a. Footnote 5: corrected typographical error.
6. Section 6.2 Time and Events Table
    a. Footnote 8: deleted a repeated sentence.

Scientific Changes:

July 12, 2024

1. .Sections 2.1, 2.2.1, 2.2.5,2.4.1, 4.1 (Schema), 4.2.1(footnote 1), 4.7, 6.1 (Time and Events Table Note), and 6.6 have been updated to change the designation of subjects receiving 4-6 cycles of BV-CHEP to 2-6 cycles.
2. Section 6.1 Time and Events table,
    a. Footnote 1: Changed end of treatment timing from 30 days to 21 days.
3. Section 6.2
    a. Footnote 1: Changed end of maintenance treatment timing from 30 days to 21 days.

THE ATTACHED VERSION DATED February 25, 2021, INCORPORATES THE ABOVE REVISIONS

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July 12, 2024

PROTOCOL AMENDMENT #6

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Pilot Study of the Rare Lymphoma Working Group

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)

AMENDMENT RATIONALE AND SUMMARY:

The purpose of this amendment is to reflect a change in the design of the study. The study will now be a pilot study rather than a phase 2 study. Accordingly, language throughout the protocol and statistical design have been revised to reflect this new design. Additionally, the option of oral etoposide was added as an alternative to IV etoposide and an IV option for corticosteroids was added, if needed, in place of oral prednisone. Administrative changes were made to provide clarification on screening labs.

Editorial/Administrative Changes

1. Title and Signature Page: Changed title to reflect the new designation of a pilot study.
2. Mechanical editing throughout.
3. Added G-CSF to abbreviations table
4. Section 1.2: Clarification on number of sites
5. Section 3.1.7 and Time and Events Table: Added clarification to the specificity of the screening lab tests mentioned.
6. Section 4.1.10: updated section
7. Section 4.11: Section added to define Off-Study Criteria.
8. Section 5.3.8: Updated etoposide adverse event language.
9. Section 6.1: Time and Events Table: Updated Footnotes to adapt to the addition of new Footnotes (#3, 15 and 16) related to the addition of oral etoposide, IV corticosteroid option and corrected Footnote designations for Adverse Events Assessment, IV Brentuximab vedotin, and Follow-up.
10. Sections 6.1 Time and Events Table footnote 21 and Section 6.2 Time and events table footnote 8: Added language to clarify survival follow-up only for subjects that come off study therapy and change regimen
11. Sections 6.4.1, 6.4.3, 6.4.4, and 6.4.5: Updated footnote references.
12. Section 6.6: Clarified follow-up procedures for subjects coming off study therapy and starting a new therapy.
13. Sections 7.3.3, 9.3, 9.4, 9.5, and 9.6: Added updated multicenter language and contacts where appropriate.

14. Section 10: Citations updated

Scientific Changes:

1. Section 1.1: Revisions to the Study Synopsis to reflect the change to a pilot study
2. Section 4.1: Changed Schema to reflect new study design.
    a. Language related to the schema and study design updated.
    b. Revised language to indicate a change in regimen results in the subject being followed for survival and not coming off study.
3. Sections 8.1-8.3: Revised statistical plan and enrollment numbers to reflect the new study design.

Therapy Changes:

1. Sections 4.2, 4.2.1 and Time and Events Table Footnote #15: Added information providing the option for use of oral etoposide in place of IV etoposide at any point in which etoposide is administered to the subject. Additionally, exceptions were indicated in Section 6.4.2 and the Time and Events Table (Footnotes #3 and #16) related to the collection of vital signs and adverse events on days 2 and 3, which would only be done if the subject would be receiving IV etoposide.
2. Sections 4.2, 4.2.1 and the Time and Events Table added Footnote#16: Provided a provision to use an IV corticosteroid of equivalent dose to 100 mg prednisone, if indicated for subjects that may have problems with oral medications.
3. Section 4.2.1, Table: Added language that any G-CSF is allowed per institutional standard.

Eligibility Changes:

1. Criterion 3.2.2: Removed the contingency related to subjects being disease free from cancer for 5 years.

THE ATTACHED VERSION DATED APRIL 30, 2020, INCORPORATES THE ABOVE REVISIONS

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July 12, 2024

PROTOCOL AMENDMENT #5

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Phase II Trial of the Rare Lymphoma Working Group

AMENDMENT INCORPORATES (check all that apply):

_X Editorial, administrative changes
_X_ Scientific changes (IRB approval)
_ _Therapy changes (IRB approval)
_ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The major change in this protocol amendment is to change the lot of brentuximab vedotin to commercial supply for all subjects on this study whose disease falls within the FDA approved indication (CD30+ disease). Given that subjects will receive either commercial supply or investigational supply of brentuximab vedotin depending on whether they have CD30+ or CD30- disease, the protocol has also been amended to require that CD30 expression be determined during screening and eligibility evaluation. In addition, the protocol has been amended to remove the adverse event assessment on days 4 and 5 of cycles 1 through 6 of treatment with brentuximab vedotin combined with cyclophosphamide, doxorubicin, etoposide, and Prednisone (BV-CHEP). The adverse event assessment has been deemed unnecessary on days 4 and 5 as it is already required on days 1, 2, 3, 8, and 15 of cycles 1 through 6 of BV-CHEP treatment. Additional changes have been made to clarify that the infusion times for cyclophosphamide, doxorubicin, etoposide, and brentuximab vedotin are approximate. The term "study entry" has also been replaced with the phrase "signing the main consent form" for clarification purposes.

Changes:

- Administrative changes throughout including updating the term "UNCCN" to "multicenter" and "affiliate" to "multicenter"
- Section 1.4 – This section describing brentuximab vedotin has been updated to include the newly approved indication for the drug in previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), in combination with chemotherapy.
- Section 3.1.12 – This inclusion criterion has been revised to clarify that subjects must be previously untreated or have received a maximum of one cycle of any combination chemotherapy (e.g. CHOP, CHOEP, DA-EPOCH, CODOX-M/IVAC, HyperCVAD) within 4 weeks of signing the main consent form. The

phrase "signing the main consent form" replaces the phrase "study entry" for clarification purposes.

- Section 3.1.13 – This inclusion criterion has been added to require that CD30 expression be assessed prior to enrollment on the study.
- Section 4.1 – The key eligibility criterion listed in the schema has been revised to clarify that previously untreated ATLL or those with ATLL who have received a maximum of one cycle of combination chemotherapy (i.e. CHOP, CHOEP, DA-EPOCH, etc.) or antiretroviral therapy (i.e. AZT and/or IFN) within 4 weeks of signing the main consent form are eligible for enrollment. The phrase "signing the main consent form" replaces the phrase "study entry" for clarification purposes.
- Section 4.2.1 –
    - The Brentuximab Vedotin with Cyclophophamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) Dosing Schedule has been revised as follows:
        i. to clarify that the infusion times for cyclophophasphamide, doxorubicin, etoposide, and brentuximab vedotin are approximate.
        ii. to add a footnote stating that subjects with CD30+ disease will receive commercial brentuximab vedotin product and subjects with CD30- disease will receive investigational supply of brentuximab vedotin. The footnote also defines CD30+ disease as CD30 expression above 1 percent.
    - The BV Maintenance Dosing Schedule has also been revised as follows:
        i. to clarify that the infusion time for brentuximab vedotin is approximate.
        ii. to define CD30+ disease as CD30 expression above 1 percent.
- Section 4.5 – This section has been revised to clarify that up-to-date vaccinations are suggested, but not mandatory, prior to a patient signing the main consent form. The phrase "a patient signing the main consent form" replaces the phrase "study entry" for clarification purposes.
- Section 5.1.2 - This section has been updated to state that investigational drug supply of brentuximab veodtin will be supplied by Seattle Genetics for CD30- patients only, and CD30+ patients will receive commercial supply.
- Section 5.1.7 - This section regarding accountability, return and retention of brentuximab vedotin has been updated to clarify that these requirements apply to investigational supplies of brentuximab vedotin.
- Section 5.2 - The requirements for the return and retention of the study drug have been updated to distinguish between handling of investigational lot and commercial supply.
- Section 6.1 – The Time and Events Table for BV-CHEP has been revised:
    - to remove the adverse event assessment on days 4 and 5 of cycles 1 through 6 of BV-CHEP.
    - to include a footnote specifying that CD30+ subjects will receive commercial brentuximab vedotin while CD30- subjects will receive investigational lot and to define CD30+ disease as CD30 expression above 1 percent.

- Section 6.2 – The note under the Time and Events Table for BV Maintenance Therapy was updated to define CD30+ disease as CD30 expression above 1 percent.
- Section 6.4.2 – This section has been revised to state that toxicity will be assessed on days 2 and 3 only of cycles 1 through 6 of BV-CHEP
- Section 6.7 Correlative Studies Procedures – A statement has been added to this section to clarify that if a participant agrees to provide the optional peripheral blood sample for correlative research, it will collected and stored even if the participant is determined not eligible for the main study.
- Section 7.3.3 Reporting was updated to remove internal processes that are dictated by SOP
- Section 7.4 – This section has been revised to remove language requiring that meetings/teleconferences for data and safety monitoring be held in consultation with the study Biostatistician and to reflect new titles of included parties
- Section 9.4 – This section has been updated in accordance with LCCC procedures for data management and monitoring and auditing.
- Section 9.5.3 – This section has been amended to clarify the reporting requirement for protocol deviations to UNC IRB.

THE ATTACHED VERSION DATED JANUARY 21, 2019, INCORPORATES THE ABOVE REVISIONS

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

July 12, 2024

PROTOCOL AMENDMENT #4

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Phase II Trial of the Rare Lymphoma Working Group

AMENDMENT INCORPORATES (check all that apply):

_X Editorial, administrative changes
_X_ Scientific changes (IRB approval)
_ _Therapy changes (IRB approval)
_ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The protocol is amended to allow for a computed tomography (CT) scan or a positron emission tomography (PET/CT) scan instead of a mandated PET/CT scan:

- on Day 1 of cycle 3 of BV-CHEP treatment,
- during BV maintenance treatment,
- at the end of treatment visit for BV maintenance, and
- during follow up.

This change is consistent with the response criteria for lymphoma for the purpose of disease monitoring. A combined PET/CT scan of diagnostic quality will continue to be required at screening for staging purposes and on Day 1 of cycle 5 and at the end of cycle 6 of BV-CHEP for the purpose of determining response and making treatment decisions (i.e. whether to take patient to alloSCT).

Scientific changes:

- Section 4.1 – The schema has been revised to clarify that a PET/CT or CT scan is required after the first two cycles of BV-CHEP
- Section 4.2 – revised to state that imaging scans will be done instead of PET/CT scans since a PET/CT or CT scan is allowed on day 1 of cycle 3 and a combined PET/CT scan is required on day 1 of cycle 5 and at the end of cycle 6; also clarified that scans will be done on day 1 of cycles 3 and 5 and at the end of cycle 6
- Section 6.1 Time and Events Table (BV+CHEP) has been updated as follows:
  - To remove "(diagnostic quality PET/CT)" after the requirement for imaging studies
  - To clarify in footnote 3 that a PET/CT scan is required at screening, day 1 of cycle 5 (-7 days), and day 21 of cycle 6 (+/-7 days) and to clarify that a PET/CT scan or CT scan is required on day 1 of cycle 3 (-7 days).

  - To clarify in footnote 17 that the imaging scans done during follow up can be either PET/CT scans or CT scans.
- Section 6.2 Time and Events Table (BV Maintenance Therapy) has been updated as follows:
  - To remove "(diagnostic quality PET/CT)" after the requirement for imaging studies
  - To change footnote 3 to state that a PET/CT or CT scan should be done every 8 cycles and at the end of study treatment visit.
  - To clarify in footnote 8 that the imaging scans done during follow up can be either PET/CT scans or CT scans.
- Section 6.3 has been revised to remove the requirement for IV contrast for the PET/CT scan at screening
- Section 6.4.1 has been revised to allow for the disease measurements at cycle 3 of BV-CHEP to be done with a PET/CT or CT scan, to clarify that a PET/CT scan be done at cycle 5 and at the end of cycle 6 of BV-CHEP, and to remove the requirement for the scans to be done with IV contrast
- Section 6.4.5 has been revised to remove the requirement that the PET/CT scan at the end of BV/CHEP treatment visit be done with contrast
- Section 6.5.1 has been revised to allow for the disease measurements every 8 cycles of BV maintenance to be done with a PET/CT or CT scan and to remove the requirement for the scans to be done with contrast.
- Section 6.5.2 has been revised to allow for the disease measurements at the end of BV maintenance treatment to be done with a PET/CT or CT scan and to remove the requirement that the scan be done with contrast
- Section 6.6 has been revised to clarify that the imaging scans required during follow up may be either PET/CT or CT scans

THE ATTACHED VERSION DATED APRIL 17, 2018, INCORPORATES THE ABOVE REVISIONS

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CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

July 12, 2024

PROTOCOL AMENDMENT #3

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Phase II Trial of the Rare Lymphoma Working Group

AMENDMENT INCORPORATES (check all that apply):

_X Editorial, administrative changes
_ Scientific changes (IRB approval)
_X_Therapy changes (IRB approval)
_X Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The protocol is amended to clarify maximum dose levels for brentuximab vedotin (BV), to add uric acid and phosphorus testing back to the protocol on days 1 and 8 of cycle 1 of BV-CHEP treatment per FDA's request, to prohibit eligibility single subject exceptions under any circumstances, and to provide additional information regarding study monitoring requirements.

Editorial, administrative changes:

- Section 9.4 has been revised to include additional information regarding study monitoring requirements.

Therapy changes:

- The following sections were updated: Section 4.2.1, section 4.3.1.1 and section 5.1.4. noting that for patients weighing greater than 100 kg, the dose of BV should be calculated based on a weight of 100 kg.
- Table in section 4.3.1.1 reflects max dose of BV that can be given based on allowed dose reductions in the study
- Updated link to BV package insert in section 5.1
- Section 6.1, section 6.4.1, and section 6.4.3 were revised to add uric acid and phosphorus testing back to the protocol on days 1 and 8 of cycle 1 of BV-CHEP treatment per FDA's request

Eligibility changes:

- Section 9.5.2 has been revised to prohibit eligibility single subject exceptions under any circumstances and to clarify that 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.

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

July 12, 2024

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July 12, 2024

PROTOCOL AMENDMENT #2

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Phase II Trial of the Rare Lymphoma Working Group

AMENDMENT INCORPORATES (check all that apply):

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

AMENDMENT RATIONALE AND SUMMARY:

The protocol was revised to include assessment of peripheral blood per adult T-cell leukemia/lymphoma NCCN guidelines version 2.2017 for those subjects with a leukemic component to their disease at baseline. Eligibility criteria were revised and study assessments were revised in the time and events tables. In addition, clarifications were made to the dose modification tables and the long-term follow up plans were clarified.

Editorial changes

- Editorial changes made to section 1.1
- Editorial changes made to Secondary objectives 2.2.1-2.2.4 to note that ORR, PFS, duration of response, OS will be determined in subjects that receive BV-CHEP and toxicity will be determined for subjects that receive BV-CHEP and BV maintenance therapy section 2.2.5. Added note after secondary objective 2.2.5 to clarify the possible groups of participants after completion or withdrawal from BV-CHEP.
- Enzyme-linked immunosorbent assay (ELISA) is being added to the types of confirmatory tests that may be used for positive HTLV-1 antibody testing in inclusion criterion 3.1.4.
- Reformatted inclusion/exclusion criteria to link to structure of this document (Section 3.1 and 3.2)
- Editorial changes made to Section 4.1 and in section 4.2 to tables in 4.2.1 for BV-CHEP and BV Maintenance Dosing Schedules
- Editorial change to title of section 4.3 to clearly specify that dose levels are for BV
- Moved section (4.6) up to a new position in the protocol as 4.4.1.2 and modified title for clarity to specify management guidelines for renal and hepatic AEs related to study treatments rather than just AEs.
- Clarified duration of follow up = 5 years after last cycle of study treatment (i.e. BV-CHEP or BV maintenance) in section 4.8 for all patients in this study
- Link updated in section 4.9 per template
- Revised links in section 5.1.8

- Clarified that PET/CT scans are to be of diagnostic quality in Time and Events Tables (sections 6.1 and 6.2)
- Revised Prestudy Assessments in section 6.3 to align with table 6.1
- Revised treatment assessments in section 6.4 including 6.4.1-6.4.5 to align with revisions made to table 6.1
- Revised BV Maintenance Assessments in section 6.5 including 6.5.1-6.5.2 to align with changes made to table 6.2
- Removed D8 assessments from table 6.2 and corresponding visit details related to this visit day
- Revised the amount of blood to be collected for correlative studies from 3 mLs to 10 mLs of blood in sections 6.1 (footnote #14), 6.3 and 6.7
- Revised wording in section 6.6 to clarify plans for post treatment follow up
- Clarified reporting policy for SAEs to UNC IRB in section 7.3.3
- Corrected NCI CTCAE version number in section 8.3
- Minor spelling and grammar corrections made throughout protocol

Scientific changes

- Sections 2.4 and 6.9 are updated to clarify efficacy endpoints/criteria for assessment of peripheral blood if applicable
- Updated the suggested antimicrobial prophylaxis guidelines for supportive care in section 4.2.2
    a) Removed suggested dosing of Bactrim (M, W, F)
    b) Removed "minimal" from subheading
- Revised dose modification table 4.4.1.1 for BV + CHEP regimen
- Revisions made to 4.4.1.3 Dose Modification table for BV Maintenance Therapy
- Time and Events Table in Section 6.1 of the protocol as follows:
    a) Added physical exam for end of Txt visit
    b) Clarified timing of PET/CT scan for end of cycle 6
    c) Clarified timing of pregnancy testing
    d) Added Bone Marrow biopsy to end of Txt visit to confirm CR if positive initially
    e) Clarified that G6PD/uric acid/phosphorus will be measured during screening visit
    f) Removed phosphorus and uric acid from clinical chemistry panel
    g) Changed concomitant medication review to D1 of each cycle to improve efficiency and eliminate checking each day during BV-CHEP
    h) Removed HLA Sibling typing
    i) Added Intrathecal chemotherapy and prophylaxis treatment rows with CSF to account for the two possible treatment scenarios
    j) Clarified that CT or MRI of brain will only be conducted at the screening visit unless the test if positive. If positive at screening, it will be repeated at the end of BV-CHEP treatment visit.
    k) Deleted coagulation labs and removed footnote related to this assessment (#12) and renumbered footnotes to account for deletion of this assessment

l) Added requirement for imaging scans and hematology labs during the first 2 years of follow up
m) Revised note under Time and Events table to clarify the possible groups of participants after completion or withdrawal from BV-CHEP
n) Deleted information about long term follow up from footnote#1 and described follow up in footnote #16
o) Added row for following survival
p) Clarified timing of the end of treatment visit in footnote 1
q) Clarified the timing of the PET/CT scan for cycle 6

- Time and Events Table 6.2 revised as follows:
  a) Added requirement for ECOG performance status at the end of treatment of visit
  b) Clarified timing of pregnancy testing
  c) Removed PT and INR testing from hematology assessments at baseline
  d) Removed Uric Acid from Clinical chemistry assessments at baseline
  e) Removed initiate/renew prophylactic medications
  f) Revised timing of PET/CT imaging during maintenance therapy from every 4 to 5 cycles to every 8 cycles
  g) Added row to ensure documentation of survival for up to 5 years or until death (whichever occurs first) after the subject discontinues BV maintenance.
  h) Added requirement for imaging scans and hematology labs during the first 2 years of follow up
  i) Added footnote #1 to clarify visit schedule windows and end of treatment windows during BV maintenance
  j) Revised long term follow up schedule in footnote #8 to extend survival follow up from 3 years to 5 years and to include imaging and hematology lab requirements during follow up for 2 years

Eligibility Changes:

- Revised inclusion criterion 3.1.6 to clarify requirements for inclusion of patients positive for HBV/HCV infection or exposure
- Revised inclusion criterion 3.1.7 to eliminate assessments for coagulation testing.
- Added exclusion criterion 3.2.10 to disallow enrollment of patients with parenchymal brain metastases

THE ATTACHED VERSION DATED NOVEMBER 29, 2017 INCORPORATES THE ABOVE REVISIONS

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July 12, 2024

PROTOCOL AMENDMENT #1

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Phase II Trial of the Rare Lymphoma Working Group

AMENDMENT INCORPORATES (check all that apply):

_X Editorial, administrative changes
___ Scientific changes (IRB approval)
_X_ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

- Removed continuous IV infusion (CIVI) from the abbreviations list
- Changed epirubicin to etoposide for BV-CHEP, CHEP, and CHOEP in the abbreviations list
- Section 6.1 Time and Events Table:
    - To be consistent with section 6.3 Pre-Study Assessments, clarified that testing for glucose 6 phosphate dehydrogenase (G6PD) deficiency is done only during screening
    - Added footnote 9 to echocardiogram (ECHO)/multigated acquisition_ (MUGA) scan listed for D1 to clarify that patients with baseline left ventricular ejection fraction (LVEF) of 40% to 55% should have repeat assessment performed prior to cycle 4
- Section 6.3 Pre-Study Assessments – To be consistent with the Time and Events Table, clarified that HTLV-1 Serology/ HIV/HCV/HBV testing is required during screening

Therapy Changes:

- Sections 4.2. and 4.2.2 - clarified the duration of the etoposide infusion as one hour each day for days 1-3 of each cycle of BV-CHEP therapy

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July 12, 2024

LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Pilot Study of the Rare Lymphoma Working Group

Short Title: BV-CHEP chemotherapy for Adult T cell leukemia or lymphoma

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LCCC 1637: Brentuximab Vedotin with Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (BV-CHEP) for the treatment of Adult T-Cell Leukemia/Lymphoma: A Pilot Study of the Rare Lymphoma Working Group

Short Title: BV-CHEP chemotherapy for Adult T cell leukemia or lymphoma

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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.

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PI Signature: _____

Date:_____

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LIST OF ABBREVIATIONS

The abbreviations lists can be modified/updated **WITHOUT** the need for a protocol amendment. It is provided ONLY as a helpful guide to the reader and is not a formal part of the protocol document.

ADC	Antibody drug conjugate
AE	Adverse event
alloSCT	Allogeneic stem cell transplant
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATLL	Adult T-cell leukemia/lymphoma
AZT	azidothymidine
β-HCG	Beta –human chorionic gonadotropin
BID	*Bis in die* (twice daily)
BID MC	Beth Israel Deaconess Medical Center
BMC	Boston Medical Center
BP	Blood pressure
BV	Brentuximab Vedotin
BV-CHEP	Brentuximab vedotin, cyclophosphamide, doxorubicin, etoposide, prednisone
CBC	Complete blood count
CODOX-M/IVAC	Doxorubicin, cyclophosphamide, cytarabine, vincristine, methotrexate/Etoposide, ifosfamide, cytarabine, methotrexate
CHEP	Cyclophosphamide, doxorubicin, etoposide, prednisone
CHOP	Cyclophoshamide, doxorubicin, vincristine, prednisone
CHOEP	Cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone
DA-EPOCH	Dose adjusted etoposide, vincristine, doxorubicin, bolus cyclophosphamide, prednisone
CL	Chloride
CMP	Complete metabolic panel
CNS	Central nervous system
CO2	Bicarbonate
CPO	Clinical protocol office
CR	Complete response
CRA	Clinical Research Associate
CrCl	Creatinine clearance
CRF	Case report form
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computer tomography
CT CAP	Computer tomography of the chest, abdomen, and pelvis
CYP	Cytochrome P450
D1	Day 1
DFCI	Dana-Farber Institute (DFCI)
ECHO	Echocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal

HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
Hr	Hour
HSV	Herpes simplex virus
HTLV	Human T-lymphotropic virus
Hyper-CVAD	Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone
IB	Investigator's Brochure
IDS	Investigational drug service
IDSL	Integrated Data Standards Library
IHC	Immunohistochemistry
IFN	Interferon
INR	International normalized ratio
IP	Intraperitoneal
IRB	Institutional review board
IT	Intrathecal
IV	Intravenous
K	Potassium
Kg	Kilogram
LDH	Lactate dehydrogenase
LN	Lymph node
LVEF	Left ventricular ejection fraction
µg/kg	Microgram per kilogram
Min	Minute
Mg	milligrams
MGH	Mass General Hospital
MMAE	Monomethyl auristatin E
mL	Milliliter
MRI	Magnetic resonance Imaging
MUGA	Multigated acquisition
Na	Sodium
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PE	Physical Exam
PET	Positron Emission Tomography
PFS	Progression free survival
PFT	Pulmonary function test
Pgp	P-glycoprotein
PJP	Pneumocystis jiroveci pneumonia
PML	Progressive multifocal leukoencephalopathy
PO	*Per os* (by mouth)
PR	Partial response
PT	Prothrombin time

PTCL	Peripheral T cell lymphoma
PTT	Partial thromboplastin time
QD	*Quaque die* (once daily)
RBC	Red blood cell
RNA	Ribonucleic acid
RLWG	Rare Lymphoma Working Group
SAE	Serious adverse event
s.c.	subcutaneous
SD	Stable disease
SJS	Steven Johnson's syndrome
SmPc	Summary of product characteristics
SUSAR	Serious unexpected adverse reaction
TEN	Toxic epidermal necrolysis
TXT	Treatment
ULN	Upper limit of normal
UNC	University of North Carolina
VZV	Varicella virus
WOCBP	Woman of childbearing potential

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

Adult T-cell leukemia/lymphoma (ATLL) is an HTLV-1-associated malignancy that is endemic in the Caribbean islands, Western Africa, Brazil, Iran, and Japan. The majority of ATLL cases in the United States occur along the Eastern seaboard due to emigration from the Caribbean islands. Patients with the two aggressive ATLL subtypes, acute and lymphomatous, respond dismally to traditional treatment approaches. There exists no standard of care for this highly morbid disease. In this pilot study, we will collect preliminary data about the efficacy of a novel regimen, brentuximab vedotin with cyclophosphamide, doxorubicin, etoposide, and prednisone (BV-CHEP). The primary objective is to determine the proportion of subjects with complete response (CR) to BV-CHEP. We aim to enroll 14 evaluable subjects. We hypothesize that BV-CHEP administered to patients with ATLL will have a CR rate of around 45% in this population.

1.2 Adult T-Cell Leukemia/Lymphoma Background

Adult T-cell leukemia/lymphoma (ATLL) is an HTLV-1-associated malignancy that is endemic in the Caribbean islands, Western Africa, Brazil, Iran, and Japan [1, 2]. The majority of ATLL cases in the United States occur along the Eastern seaboard due to emigration from the Caribbean islands. Massachusetts has the United States' third largest population of Haitian immigrants, with the majority of this population residing in Boston [3]. This makes Boston one of the ATLL epicenters in the United States. Additionally, other Eastern seaboard regions harbor patients with ATLL, including the statewide catchment area of the University of North Carolina at Chapel Hill.

ATLL is variably CD30 positive, and, notably, CD30 positivity may be associated with a worse prognosis [4]. Patients with the two aggressive ATLL subtypes, acute and lymphomatous, respond dismally to traditional treatment approaches. There exists no standard of care for this highly morbid disease. The National Comprehensive Cancer Network (NCCN) guidelines suggest clinical trial participation as first line therapy; however, clinical trial options are limited.

The Rare Lymphoma Working Group (RLWG) arose from consensus at the Lymphoma Research Foundation (LRF) New England meetings due to the need for cooperation amongst institutions to improve ATLL treatment strategies. The RLWG originally encompassed the Boston-area hospitals: Boston Medical Center (BMC), Beth Israel Deaconess Medical Center (BIDMC), Massachusetts General Hospital (MGH), and Dana-Farber Cancer Institute (DFCI), and has now expanded to include the University of North Carolina at Chapel Hill (UNC), as well as sites in NYC and Miami. This broad participation will enable accrual of ATLL patients in clinical trials along the Eastern Seaboard. The RLWG offers an

unprecedented model for institutional collaboration that will be used to study other rare lymphomas in the future.

BMC, BIDMC, MGH, and DFCI each treat 3-5 cases per year. UNC treats approximately 1-2 cases per year. Additionally, other regional institutions have agreed to refer new ATLL cases to a participating RLWG institution. With this collaborative effort, it is estimated that a minimum of 15 eligible patients will be cared for each year. Additionally, the rate of ATLL appears to be increasing nationally. From the period between 2002 and 2011, there has been a statistically significant 6.6% percent annual increase in ATLL cases (APC) [5].

Considerable effort will be made to capture all eligible patients. Informed consent forms will be available in multiple relevant languages. Pre-treatment with bisphosphonates to control hypercalcemia will be permitted, as will one cycle of combination chemotherapy, if immediate disease control is warranted.

1.3 No Clear Standard of Care in the United States

The most compelling randomized trial for ATLL was conducted in Japan, and used the intensive chemotherapeutic regimen LSG15 (VCAP-AMP-VECP) [6]. This regimen showed an improvement in CR rate over biweekly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP-14) (40% vs. 21%), but still only had a 3-year OS of 24%. Importantly, several of the agents used in this regimen are not available in the United States. Recent research in Japan has shown a CR rate of 52% when a novel CCR-4 inhibitor, mogamulizumab, is used in combination with LSG15 [7]. Unfortunately, a recent study revealed an increased risk of severe and corticosteroid-refractory graft-versus-host disease, non-relapse mortality, and overall mortality in patients treated with mogamulizumab prior to allogeneic stem cell transplant (alloSCT) [8]. Additionally, mogamulizumab is not currently available in the United States. In other studies, the smoldering and chronic types of ATLL have been shown to respond well to antiretroviral therapy with zidovudine and interferon alpha [9-11]. For the acute type, the benefits of antiretrovirals are much less dramatic, with a median survival of 9 months. Notably, the lymphomatous type has the worst response to antiretroviral therapy with a median survival of only 7 months and limited numbers of patients surviving after five years from diagnosis [9]. Overall, there is no current standard of care regimen in the United States for ATLL, treatment options are limited, and available therapies have low response rates and sometimes severe side effects.

Despite the lack of a standard initial treatment for ATLL, most providers feel that alloSCT in first remission is a standard approach. The best evidence for this comes from studies conducted in Japan, where approximately 120 patients undergo alloSCT for ATLL yearly. One study found that patients who received an alloSCT from a HLA-matched donor had a 3-year OS of 41%, while those who received unrelated bone marrow had a 3-year OS of 39% [12]. Another study evaluated long-term outcomes after reduced-intensity conditioning and found that

10 of 29 patients survived for a median of 82 months with a 5-year OS of 34% [13]. While not curative for most patients, these findings show that certain patients can have long-term survival, which is not possible without alloSCT.

1.4 Investigational Agent: Brentuximab Vedotin (BV)

Brentuximab vedotin is a novel antibody-drug conjugate (ADC) that combines an anti-CD30 monoclonal antibody with monomethyl auristatin E (MMAE), which is a microtubule-disrupting agent. Once BV binds to CD30 on the surface of the ATLL cell, it is internalized and releases MMAE. This then disrupts the microtubule network, leading to G2/M cell cycle arrest and apoptosis [14]. Currently, BV is approved for single-agent use in relapsed/refractory classical Hodgkin lymphoma, high-risk Hodgkin lymphoma after autologous stem cell transplant, and relapsed/refractory anaplastic large cell lymphoma. In November 2018, BV was also approved for use in previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), in combination with chemotherapy.

Brentuximab vedotin has several, well-described toxicities. The most important of which is peripheral neuropathy. Because of this toxicity, the chemotherapy backbone for LCCC1637 does not include a vinca alkaloid. Other common toxicities are nausea, diarrhea, fatigue, alopecia, dyspnea, constipation, cough, and febrile neutropenia. The majority of these are grade 1 or 2 [14].

1.5 Other Agents: Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (CHEP)

The other agents that will be used in combination with BV in this trial are: cyclophosphamide, doxorubicin, etoposide, and prednisone. These agents have been studied extensively in various combinations (CHOP, CHOEP, DA-EPOCH). These regimens are the standard of care for the treatment of aggressive B-cell and T-cell lymphomas.

1.6 Rationale for BV-CHEP

BV has been studied in ATLL. A phase I multicenter trial was conducted to evaluate the safety and efficacy of BV in CD30-positive peripheral T-cell lymphomas (PTCL) [15]. This study evaluated two groups of patients: sequential (2 cycles of BV followed by 6 cycles of CHOP) and combination (BV-CHP; cyclophosphamide, doxorubicin, prednisone). The BV dose used in combination with CHP was 1.8mg/kg, which is the standard dose when used as a single agent. This dose was well-tolerated when combined with CHP. Of the 39 patients evaluated in this study, 2 had ATLL. Both of these ATLL patients were in the BV-CHP group and both experienced a complete response (CR). Specifically, one patient had stage IV ATLL with an IPI score of 3 and had a progression free survival (PFS) of 7.1 months. The other patient was stage IV with an IPI score of 5 and had a PFS of 41.4 months. Currently, a phase 3 trial is enrolling patients to compare BV-CHP with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in the initial treatment of CD30-positive mature T-cell lymphomas[14].

Both of these studies focus on peripheral T-cell lymphomas (PTCLs), the vast majority of which will not be ATLL cases. However, based on the phase I trial results, BV has promising efficacy in ATLL. As a result, we propose combining BV with an etoposide-containing regimen: cyclophosphamide, doxorubicin, etoposide, and prednisone (CHEP). The addition of etoposide to the already studied regimen, BV-CHP, is based on the improved efficacy of etoposide-containing regimens in PTCL [16, 17].

The current available literature strongly supports BV's clinical efficacy in CD30-positive lymphomas, as well as the efficacy of etoposide-containing regimens in PTCL. Moreover, BV is efficacious in cutaneous CD30-positive T-cell lymphoma regardless of baseline levels of CD30 expression. This was demonstrated in 48 patients with CD30-positive lymphoproliferative disorders or mycosis fungoides who received 1.8 mg/kg of BV every 21 days; these patients had either low (<10%), medium (10% to 50%), or high (≥ 50%) expression levels of soluble CD30 at baseline [18]. In 28 patients with mycosis fungoides/Sezary syndrome, 50% of patients (5 out of 10 patients) with low expression, 58% of patients (7 of 12 patients) with medium expression, and 50% of patients (3 of 6 patients) with high expression of CD30 responded to BV. All patients with lymphomatoid papulosis (n = 9) and primary cutaneous anaplastic T-cell lymphomas (n = 2) responded with a median duration of response of 26 weeks (range, 6 to 44 weeks); soluble baseline CD30 levels were lowest in complete responders ($P = 0.036$). Taken, together, we believe that patients with ATLL would greatly benefit from further investigation into the efficacy of BV used in combination with CHEP (BV-CHEP). In our study, patients with CD30-positive ATLL who are not candidates for BMT after completing BV-CHEP will be offered maintenance therapy with BV and CD30-negative patients will be ineligible for BV maintenance.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To define the proportion of subjects with CR after 2-6 cycles of brentuximab vedotin in combination with cyclophosphamide, doxorubicin, etoposide, and prednisone (BV-CHEP) in the treatment of adult T-cell leukemia/lymphoma.

2.2 Secondary Objectives

2.2.1 To estimate the overall response rate (ORR) associated with 2-6 cycles of BV-CHEP therapy in patients with adult T-cell leukemia/lymphoma.

2.2.2 To determine progression-free survival (PFS) for BV-CHEP in patients with adult T-cell leukemia/lymphoma who received or did not receive BV maintenance*.

2.2.3 To determine duration of response to BV-CHEP in patients with adult T-cell leukemia/lymphoma who received or did not receive BV maintenance*.

2.2.4 To determine overall survival (OS) of patients with adult T-cell leukemia/lymphoma treated with BV-CHEP who received or did not receive BV maintenance therapy*.

2.2.5 To evaluate the toxicity and tolerability of BV-CHEP and BV maintenance therapy via the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03).

***Note**: After completion or withdrawal from BV-CHEP therapy, patients will segregate into one of the following groups: 1) those who progressed on BV-CHEP; 2) those who completed 2-6 cycles of BV-CHEP and went on to allogeneic transplant; 3) those who completed 6 cycles of BV-CHEP but were CD30 negative and ineligible for maintenance therapy; and 4) those who completed 6 cycles of BV-CHEP, were CD30 positive, but continued study treatment on BV in the maintenance phase of the study.

2.3 Exploratory Objectives

2.3.1 [redacted]

2.4 Endpoints

2.4.1 Primary Endpoint

Criteria for CR after 2-6 cycles of BV-CHEP will be based on the International Workshop to standardize response criteria for malignant lymphomas (i.e., Lugano Criteria per Cheson, et al. J Clin Oncol. 2014;32(27):3059-68; See Appendix A: Revised response criteria for lymphoma*).

2.4.2 Secondary Endpoints

2.4.2.1 Criteria for overall response will be based on the International Workshop to standardize response criteria for malignant lymphomas (i.e., Lugano Criteria per Cheson, et al. J Clin Oncol. 2014;32(27):3059-68; See **Appendix A: Revised response criteria for lymphoma***).

2.4.2.2 PFS is defined as time from D1 of treatment until disease progression (based on Lugano criteria*) or death from any cause.

2.4.2.3 Duration of response is defined as the time from documentation of tumor response per Lugano criteria* to disease progression.

2.4.2.4 OS is defined as the time from D1 of treatment until death from any cause.

2.4.2.5 Toxicity and tolerability of therapy will be assessed via the NCI CTCAE v4.03.

***Note**: Subjects with a leukemic component to their disease at baseline will have peripheral blood assessed per adult T-cell leukemia/lymphoma NCCN Guidelines version 2.2017 outlined in section 6.9.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in this study:

3.1.1 Informed consent and HIPAA authorization for release of personal health information obtained.

3.1.2 Age ≥ 18 years at the time of consent.

3.1.3 ECOG Performance Status of 0-2.

3.1.4 Histological confirmation of biopsy-proven peripheral T-cell leukemia/lymphoma consistent with ATLL

- Included subtypes will be: acute, lymphomatous, and chronic unfavorable. Chronic unfavorable is defined as the chronic variant with at least one of the following: LDH>ULN, BUN>ULN, Albumin<LLN
- Positive HTLV-1 antibody testing with confirmatory testing via Western blot, enzyme-linked immunosorbent assay (ELISA), or molecular testing (PCR).

3.1.5 Documented negative serologic testing for human immunodeficiency virus (HIV).

3.1.6 If positive for HBV exposure or prior infection, can continue to participate in trial with prophylactic entecavir (for HBV). If positive for HCV exposure or active infection, can participate in trial with monitoring for liver function abnormalities.

3.1.7 Demonstrate adequate organ function as defined in the table below; the screening labs in the table below to be obtained within three days prior to study treatment.

System	Laboratory Value
Renal	
Calculated creatinine clearance	≥ 30 mL/min using the Cockcroft-Gault formula for subjects with creatinine levels > 2.0 x institutional ULN
Hepatic	
Bilirubin	≤ 3.0 mg/dL
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN

3.1.8 Females of childbearing potential must have a negative serum pregnancy test within three days (72 hours) prior to initiating study treatment. NOTE: Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

3.1.9 Females of childbearing potential must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 24 weeks (6 months) after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method or an intrauterine device that meets <1% failure rate for protection from pregnancy in the product label.

3.1.10 Male patients with female partners must have had a prior vasectomy or agree to use an adequate method of contraception (i.e., double barrier method: condom plus spermicidal agent) starting with the first dose of study therapy through 24 weeks (6 months) after the last dose of study therapy.

3.1.11 As determined by the enrolling physician or protocol designee, willingness and ability of the subject to understand and comply with study procedures

3.1.12 Prior Treatment: Previously untreated or has received a maximum of one cycle of any combination chemotherapy (e.g. CHOP, CHOEP, DA-EPOCH, CODOX-M/IVAC, HyperCVAD) within 4 weeks of signing the main consent form.

Additionally, a patient may have taken antiretroviral therapy (e.g. AZT and/or IFN) at any time prior to study enrollment.

3.1.13 CD30 expression determined by flow cytometry or IHC. NOTE: If CD30 testing was previously done on the biopsy sample from diagnosis, this information will be collected. If CD30 testing was not done, an archival sample from the biopsy used for diagnosis will be requested and tested for CD30. CD30 testing will also be done on the bone marrow tissue collected from the bone marrow exam. If we are unable to obtain an archival sample or if the bone marrow exam is negative, a new biopsy will be performed to confirm the diagnosis and test for CD30.

3.2 Exclusion Criteria

Subjects who meet any of the following criteria should be excluded from study participation:

3.2.1 Pregnant or breastfeeding (NOTE: breast milk cannot be stored for future use while the mother is being treated on study).

3.2.2 Has a known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, or other cancer for which the subject has been disease-free.

3.2.3 Previous exposure to brentuximab vedotin (BV).

3.2.4 History of allergic response to BV-CHEP or its components or to any of the required prophylactic medications or reasonable alternatives.

3.2.5 Symptomatic cardiac disease including ventricular dysfunction, left ventricular ejection fraction < 40%, symptomatic coronary artery disease or symptomatic arrhythmias

3.2.6 Subjects with severe hepatic insufficiency Child-Pugh Score > 6 (see 11.3 Appendix C).

3.2.7 Subjects with severe renal impairment (i.e., creatinine clearance ≤ 30 mL/min; see Appendix B - Renal Impairment Guidelines).

3.2.8 Exclude patients with pre-existing neuropathy grade 2 or higher.

3.2.9 Patients receiving prohibited medications listed in the patient handout provided in **11.4 Appendix D:** Prohibited Medications or Those to be used with Caution (i.e.,

ketoconazole, itraconazole, ritonavir, macrolide antibiotics, erythromycin phenytoin, phenobarbital, carbamazapine, and valproic acid).

3.2.10 Patients with a parenchymal brain lesion thought to be consistent with active lymphoma on screening CT/MRI. Of note, patients with CSF involvement alone are not excluded.

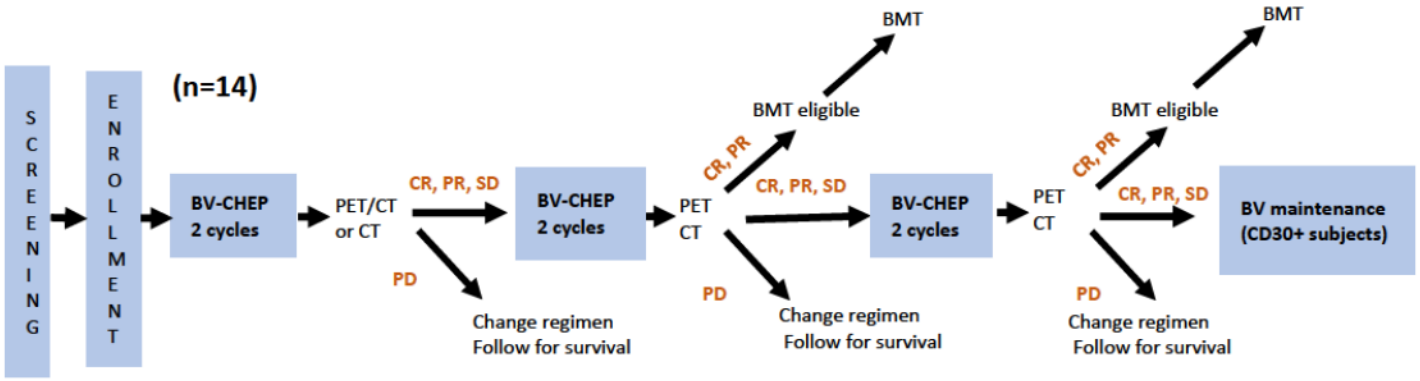
4.0 TREATMENT PLAN

4.1 Schema

Key Eligibility Criteria: Previously untreated ATLL or those with ATLL who have received a maximum of one cycle of combination chemotherapy (i.e. CHOP, CHOEP, DA-EPOCH, etc.) or antiretroviral therapy (i.e. AZT and/or IFN) within 4 weeks of signing the main consent form are eligible for enrollment.

Design: Open-label, Single Arm, Pilot Study

Primary Objective: Estimate Complete Response Rate to BV-CHEP in Patients with ATLL



Study Regimen: **21-day cycle**

Brentuximab vedotin	1.8 mg/kg,	IV	D1
Cyclophosphamide	750mg/m²,	IV	D1
Doxorubicin	50 mg/m²,	IV	D1
Etoposide	100 mg/m²,	IV	D1-3
Prednisone	100 mg	PO	D1-5

See Section 4.2.1 for further details and treatment options

Repeat BV-CHEP every 21 days for 2-6 cycles, followed by maintenance
brentuximab vedotin 1.8mg/kg IV every 21 days until

The study may enroll up to 16 subjects to ensure that 14 are evaluable for the primary endpoint. The BV-CHEP regimen will be considered safe if no treatment-related deaths (Grade 5 events) occur; and the proportion of subjects with Grade 3-4 non-infectious, non-hematologic and non-neuropathy-related toxicities associated with the infusion are lower than 0.20. Alopecia, electrolyte abnormalities, diarrhea, nausea, and vomiting AEs that can be managed with supportive care and do not persist as Grade 3-4 toxicities for > 2 weeks will not be considered DLTs. **See section 8.0 STATISTICAL CONSIDERATIONS for further details.**

We will collect preliminary data on the efficacy of a novel regimen, brentuximab vedotin with cyclophosphamide, doxorubicin, etoposide, and prednisone (BV-CHEP) in a pilot single-arm clinical trial. We will enroll a total of 14 evaluable subjects.

After completion or withdrawal of BV-CHEP therapy as depicted above, patients who complete 6 cycles of BV-CHEP and are CD30 positive but ineligible for transplant may continue study treatment with BV in the maintenance phase of the study.

4.2 Treatment Dosage and Administration

Patients will receive concurrent therapy with **BV + CHEP** [(brentuximab vedotin; 1.8 mg/kg IV, on D1 every 21 days) (cyclophosphamide 750 mg/m^2 on D1; doxorubicin 50 mg/m^2 on D1, etoposide 100 mg/m^2 IV infusion on D1-3 (oral etoposide at twice the dose of IV etoposide may also be used) ; prednisone 100 mg PO once daily on D1-5 (for subject that may have difficulty with oral drugs, an IV corticosteroid of equivalent dose to 100 mg prednisone may be substituted); cycle length every 21 days)] for 4 to 6 cycles. Disease assessment by imaging scans will be performed on day 1 of cycles 3 and 5 and at the end of cycle 6 to determine response to combination therapy: nonresponders (PD) will be withdrawn from study treatment but responders (CR, PR or SD) will receive additional treatment with BV + CHEP. Patients with a CR or PR after 4 or 6 cycles of BV + CHEP who are eligible for bone marrow transplant (BMT) will proceed to transplant which is the optimum therapy for treating ATLL. After 6 cycles of BV + CHEP, responders (CR, PR or SD) who are not eligible for BMT and have CD30-positive ATLL will continue maintenance therapy with BV alone (1.8 mg/kg IV, every 21 days) until disease progression, withdrawal due to toxicity or death. Subjects with CD30-negative ATLL will not be eligible for maintenance with BV alone. These subjects will be withdrawn from study treatment after completing BV-CHEP.

Subjects must meet eligibility criteria prior to cycle 1 of study therapy but changes that occur during therapy (e.g., elevations in bilirubin, renal function, etc.) should be addressed as noted in the table below, in section 4.4.1.2 and the prescribing information for each drug.

4.2.1 BV-CHEP and BV Maintenance Dosing Schedules

BV-CHEP Dosing Schedule			
Drug	**Dose & Route**	**Schedule**	**Cycles[1]**
Cyclophosphamide (C)	750 mg/m^2 IV over approximately 1 hr	Day 1	Every 21 days
Doxorubicin[2] (H)	50 mg/m^2 IV over approximately 3-5 minutes	Day 1	Every 21 days

Etoposide[3] (E)	100 mg/m^2 IV over approximately 1 hour each day for 3 days	Days 1-3	Every 21 days
	(Optional in the place of IV etoposide) Oral given at twice the IV dose rounded to the nearest 50 mg	Optional use in place of IV etoposide for any day or all days etoposide is administered	
Prednisone (P)[4]	100 mg, PO once daily for 5 days	Days 1-5	Every 21 days
Brentuximab Vedotin[5,6, 7, 8, 9] (BV)	1.8 mg/kg IV over approximately 30 minutes	Day 1	Every 21 days
Pegfilgrastim, filgrastim, or any G-CSF per institutional standard[10]	Peg: 6mg once or Fil: 5 µg/kg/day SC	Peg: 24-72hrs after chemo; Fil: Start ≥ 24 hrs after chemo	N/A

1. BV-CHEP will be administered for 2-6 cycles of therapy.
2. Doxorubicin adjustments after initial screening requirements are met: Serum bilirubin 1.2 to 3 mg/dL administer 50% of dose; 3.1 to 5 mg/dL administer 25% of the dose; Child-Pugh C or bilirubin >5 mg/dL use contraindicated. CrCl 15 to 50 mL/min administer 75% of dose; <15 mL/min administer 50% of dose
3. Etoposide adjustments after initial screening requirements are met: CrCl 15 to 50 mL/min administer 75% of dose; <15 mL/min administer 50% of dose. **For optional oral etoposide**: Doses ≤ 200 mg/day may be administered as a single once daily dose; doses > 200 mg should be given in 2 divided doses.
4. IV corticosteroid of equivalent dose to 100 mg prednisone may be used as clinically indicated for subjects that may have problems taking oral medications.
5. BV should not be mixed with, or administered as an infusion with, other medications, **AND MUST NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS.**
6. BV should be administered after and within approximately 1 hr of the cyclophosphamide infusion on day 1 of each cycle
7. CrCl<30 ml/min, permanently discontinue / Child-Pugh A, 1.2 mg/kg every 21 days, contraindicated for moderate or severe hepatic impairment
8. Maximum dose of BV is 180mg per cycle.*
9. Subjects with CD30+ disease will receive the commercial BV product and subjects with CD30- disease will receive investigational supply of BV. Subjects with CD30 expression above 1 percent will be considered to have CD30+ disease.
10. Filgrastim (5 µg/kg/day) should be administered ≥ 24 hrs after chemo for ≥ 3 days.

*The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

BV Maintenance Dosing Schedule[1,2]			
Drug	**Dose & Route**	**Schedule**	**Cycles**
Brentuximab Vedotin (BV)	1.8 mg/kg[3, 4] IV over approximately 30 mins	Day 1	Every 21 days until PD

1. BV maintenance will be given to patients with CD30+ expression only. Subjects with CD30 expression above 1 percent will be considered to have CD30+ disease.
2. BV maintenance will begin 21 days after last dose of BV-CHEP. Will allow for a one-week window.
3. Can start at DL-1 (1.2 mg/kg) or DL-2 (0.9 mg/kg) if necessary for toxicity.
4. Maximum dose of BV is 180mg per cycle. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg

4.2.2 Supportive Care

All patients are required to receive supportive care for acute or chronic toxicity, including blood components or antibiotics, and other interventions (e.g., correction of electrolyte abnormalities) as appropriate. Supportive care guidelines for administration of chemotherapy should be followed per institutional guidelines. Suggestions are:
1. PJP prophylaxis with Bactrim DS (or similar agent)
2. Antiviral prophylaxis for herpes simplex virus (HSV) and Varicella virus (VZV): Acyclovir or valacyclovir
3. Antifungal prophylaxis if ANC<500: Fluconazole at prophylaxis dosing
4. Bacterial prophylaxis if ANC<500: Fluoroquinolone at prophylaxis dosing
5. Tumor lysis prophylaxis for at least 1 week after treatment induction: Allopurinol
6. Transfusion of platelets if counts < 10,000 cells/mm^3

Intrathecal Chemotherapy:
CNS prophylaxis will be used for all patients starting with the first cycle of BV-CHEP. The agent(s) (methotrexate, cytarabine, or a combination of methotrexate and cytarabine) and dosing schedule will be at the discretion of the individual provider. Intrathecal chemotherapy will not be continued during the maintenance phase of BV.

If the patient has active CNS involvement, as evidenced by positive cerebrospinal fluid (CSF) cytology or flow cytometry, will need to increase schedule to weekly intrathecal chemotherapy until the lymphoma is cleared from the CSF. At that point, the schedule can return to a normal prophylactic schedule at the discretion of the provider.

Supportive Care for Hypercalcemia:
Intravenous fluids (IVF) and bisphosphonate therapy should be instituted in all patients to prevent complications from hypercalcemia according to institutional guidelines.

4.2.3 Premedication/Hydration

Premedication (including prophylactic antiemetics) and hydration should be provided as per institutional guidelines and per standard of care for CHOP or CHOEP administration.

Infusion-related reactions (including anaphylaxis) may occur during the infusion of BV. Therefore, the infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. Monitor patients during infusion. If anaphylaxis occurs immediately and permanently discontinue administration of BV and administer appropriate medical therapy per institutional standards. If a mild or moderate infusion-related reaction occurs, the infusion should be interrupted or the rate of infusion slowed and appropriate medical management instituted. Patients who experienced prior infusion-related reaction to BV should be pre-medicated for subsequent infusions per institutional standards. Premedication may include acetaminophen, an antihistamine and a corticosteroid.

4.3 Allowable Dose Level Reductions of Brentuximab Vedotin

4.3.1.1 Dose Level Reduction of BV

Dose Level	Brentuximab vedotin	Maximum dose
0	1.8 mg/kg	180 mg
-1	1.2 mg/kg	120 mg
-2	0.9 mg/kg	90 mg

*The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

4.4 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed regularly for the development of any toxicity according to the Time and Events table (Section 6.0). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility that the drug is the cause. See section 7.2 for additional information on SARs.

4.4.1.1 Dose Modifications/Delays for BV + CHEP

(Note: These dose modifications apply to BV only unless otherwise specified)

Toxicity	≤Grade 2	≥Grade 3
Nonhematologic (excluding neuropathy)	Continue at same dose level	Hold BV until toxicity has resolved to ≤Grade 2 or has returned to baseline[a]
Hematologic	Continue at same dose level	For neutropenia ≤500, manage by adding antimicrobial and antifungal prophylaxis. Must be antibiotic with gram-negative coverage (i.e. levofloxacin) and antifungal with Candida coverage (i.e. fluconazole) For thrombocytopenia, proceed according to institutional guidelines. For anemia, manage per institutional guidelines.

Peripheral Neuropathy	**Grade 1** Continue at same dose level	**Grade 2 or 3** Withhold BV until toxicity is ≤Grade 1, then reduce dose to 1.2 or 0.9 mg/kg and resume treatment or if already at 0.9 mg/kg, withhold BV until toxicity is ≤Grade 1 and resume at same dose. CHEP should be continued while holding BV.	**Grade 4** Discontinue BV. CHEP should be continued without BV.

a. Subjects who develop clinically insignificant Grade 3 or 4 electrolyte abnormalities should have any deficiencies replenished and may continue study treatment without interruption.

CHEP treatment should be modified or discontinued per applicable label/Summary of Product Characteristics (SmPc) instructions or per institutional chemotherapy standard.

4.4.1.2 Suggested Management of Renal and Hepatic Adverse Events Related to Study Treatments

Renal and Hepatic Impairment

Brentuximab Vedotin (BV):

- For severe renal impairment (creatinine clearance <30mL/min), BV should be discontinued.
- For moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment, BV should be discontinued (see Appendix C - Child-Pugh Hepatic Impairment Score)

Etoposide:

- CrCl 15 to 50 mL/minute administer 75% of dose; <15 mL/minute administer 50% of dose

Doxorubicin:

- Serum bilirubin 1.2 to 3 mg/dL administer 50% of dose.

- CrCl 15 to 50 mL/minute administer 75% of dose; <15 mL/minute administer 50% of dose

4.4.1.3 Dose Modifications/Delays for BV Maintenance Therapy

Toxicity	≤ Grade 2	≥ Grade 3
Nonhematologic (excluding neuropathy)	Continue at same dose level	Skip 1 Brentuximab vedotin (BV) dose, then resume treatment at the next scheduled BV administration if toxicity is ≤ Grade 2 or has returned to baseline.[a] If ≥ Grade 3 toxicity persists for > 2 weeks, reduce the dose to 1.2 mg/kg. If ≥Grade 3 toxicity persists for >2 weeks at 1.2mg/kg then, dose reduce to 0.9mg/kg. If ≥Grade 3 toxicity continues, discontinue BV.
Hematologic	Continue at same dose level	Add growth factor support (G-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles. For unresolved Grade 4 neutropenia despite G-CSF prophylaxis, dose reduce to 1.2 mg/kg. If ≥Grade 3 toxicity persists for >2 weeks at 1.2mg/kg then reduce the dose of BV,to 0.9mg/kg. If ≥Grade 3 toxicity continues, discontinue BV.

Peripheral Neuropathy	**Grade 1** Continue at same dose level	**Grade 2 or 3** Dosing should be withheld until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. If toxicity persists at 1.2mg/kg dosing, hold BV until neuropathy improves to grade 1 or baseline, and restart at 0.9mg/kg. If neuropathy recurs at dose of 0.9 mg/kg, do not resume BV. For maintenance only, if neuropathy does not improve by 6 weeks, permanently discontinue.	**Grade 4** Discontinue treatment with BV.

a. Subjects who develop Grade 3 or 4 electrolyte laboratory abnormalities should have these replenished and may continue study treatment without interruption.

4.5 Concomitant Medications/Treatments

Up-to-date vaccinations are suggested, but not mandatory, prior to a patient signing the main consent form. Vaccination(s) during study treatment must be approved by the treating physician.

The use of transfusions, platelet and/or colony-stimulating factors per institutional practice is permitted during therapy at the Investigator's discretion. Patients may not receive other investigational drugs, immunosuppressive medications (other than dexamethasone or prednisone for use as anti-emetics, or if steroids are needed to treat an infusion reaction), or antineoplastic therapy during the study. The routine use of steroids as premedication prior to BV is discouraged.

If an infusion-related reaction occurs, the infusion should be interrupted, and appropriate medical management instituted per institutional guidelines. Patients who have experienced a prior infusion-related reaction to any of the study medications should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

4.5.1 Contraindications (Warnings and Precautions)

In-vitro data indicate that monomethyl auristatin E (i.e., drug conjugate of BV) is a substrate and inhibitor of the P450 isoenzyme CYP3A4. Patients who are receiving strong CYP3A4 inhibitors such as ketoconazole with BV should be closely monitored for adverse reactions. Co-administration with potent CYP3A4 inducers, such as rifampin, should be avoided. BV is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes. A frequently updated list of CYP3A4 inhibitors and inducers can be found at http://medicine.iupui.edu/clinpharm/ddis/.

Drugs which induce CYP3A4 (e.g., barbiturates, phenytoin, carbamazepine, rifampin) may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP3A4 (e.g.,

ketoconazole, itraconazole, ritonavir, indinavir, macrolide antibiotics such as erythromycin) have the potential to increase plasma concentrations of corticosteroids. Coadministration of other drugs that are metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentration. Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin.

Increased hematotoxicity and/or immunosuppression may result from the combined effect of cyclophosphamide administered with other cytotoxic agents. Increase cardiotoxicity may result when cyclophosphamide is given with anthracyclines (i.e., doxorubicin). Furthermore, concurrent treatment with cyclophosphamide with doxorubicin has been reported to exacerbate cyclophosphamide-induced hemorrhagic cystitis.

Concomitant use of antiepileptic medications including phenytoin, phenobarbital, carbamazepine, and valproic acid is associated with increased clearance and reduced efficacy of etoposide.

Please refer to the FDA-approved package inserts for BV, cyclophosphamide, doxorubicin, etoposide and prednisone for more extensive product information and a comprehensive list of adverse events, warnings and precautions and potential drug interactions.

4.6 Other Modalities or Procedures

There are no other modalities that are included within the study parameters. Of note, it is highly suggested that patients who are eligible, receive an allogeneic stem cell transplant in first remission.

4.7 Duration of Therapy

Patients should continue protocol therapy as described above until:

- Eligible for BMT therapy (i.e., after 2 - 6 cycle of BV+CHEP)
- Disease progression
- Inter-current illness prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.8 Duration of Follow Up

All patients will be followed for up to 5 years or until death (whichever occurs first) after removal from study treatment (i.e., BV-CHEP or BV maintenance). Patients removed from study treatment for unacceptable AEs will be followed until resolution or stabilization of the event(s). See Time and Events tables in section 6.0 and section 6.6 for additional details on Post study treatment/Follow up Assessments.

4.9 Removal of Patients from Protocol Therapy

Patients will be removed from treatment when any of the criteria listed in Section 4.7 apply, if the interaction cannot be resolved by a medication change or stopping the non-protocol treatment. Notify the Principal Investigator, and document the reason for study treatment removal and the date the patient was removed in the electronic Case Report Form (e-CRF). The patient should be followed-up per protocol.

4.10 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit 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 withdrawal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

4.11 Off-Study Criteria

Subjects will be considered off study by any of the following criteria:

- Subject has completed all study activities including any needed follow-up activities and no further data collection from the subject is needed
- Subject withdraws consent to be in the study (Section 4.10)
- Death
- Lost to follow-up
- Situations in which the treating physician feels it is in the best interest for the subject to not continue in the study.

5.0 DRUG INFORMATION

5.1 Brentuximab vedotin (Adcetris®)

See the BV Investigator's Brochure (IB) and the prescribing information for Adcetris® (brentixumab vedotin) for more detailed information.

5.1.1 Description

BV is a sterile, preservative-free, white- to off-white lyophilized cake or powder, supplied in single-use vials containing 50 mg each for reconstitution for

intravenous (IV) administration. It will be supplied by Pfizer at no charge to study subjects

5.1.2 Packaging and Labeling

Investigational drug supply of BV will be supplied by Pfizer for CD30- patients supplied for free by Pfizer. CD30+ patients will receive commercial supply.

5.1.3 Storage and Handling

Vials containing BV must be refrigerated at 2–8°C in a controlled location accessible only to the pharmacist, the Investigator, or a duly designated person. It is recommended that BV vials and solutions be stored protected from direct sunlight until the time of use.

5.1.4 Dose, Schedule and Administration

See Section 4.2. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

5.1.5 Preparation

See the BV prescribing information for preparation instructions. The dose of BV in this study will be 1.8 mg/kg with allowable dose reduction to 0.9 mg/kg.

The prepared dosing solution must be stored at 2-8°C (DO NOT FREEZE) and must be used within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight. See package insert for additional details.

5.1.6 Stability

BV for Injection does not contain preservatives; therefore, opened and reconstituted vials of BV must be used within the same day when stored under refrigeration at 2–8°C. Reconstituted vials must not be shaken.

5.1.7 Accountability, Return and Retention of BV

The investigator is responsible for keeping accurate records of the investigational supplies received from Pfizer or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, unused vials of investigational lot will be handled per instructions from Pfizer. The sponsor may request that 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.

5.1.8 Adverse Events Associated with BV

The adverse events listed below have been reported in patients receiving BV. For further instruction on the management adverse events associated with BV therapy see section 4.3.

- Peripheral Neuropathy: BV peripheral neuropathy is cumulative. Patients experiencing new or worsening peripheral neuropathy may require dose delay, change in dose or discontinuation of BV
- Anaphylaxis and infusion reactions: If anaphylaxis occurs, immediately and permanently discontinue BV. Infusion-related reactions should be managed per institutional standards (see recommendations in section 4.5)
- Hematologic toxicity: Includes Grade 3 or 4 thrombocytopenia or anemia and febrile neutropenia
- Serious infections or opportunistic infections: Includes pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes). Patients should be closely monitored for the emergence of possible bacterial, fungal, or viral infections.
- Tumor lysis syndrome: Patients with high tumor burden or rapidly proliferating tumor may be at risk for tumor lysis syndrome.
- Increased toxicity in the presence of severe renal impairment: See section for further details.
- Increased toxicity in the presences of moderate or severe hepatic impairment: See section 4.4.1.2 for further details.
- Hepatotoxicity: Serious cases of hepatotoxicity have been reported consistent with hepatic injury, including elevations of transaminases or bilirubin.
- Progressive multifocal leukoencephalopathy (PML): John Cunningham virus resulting in PML has occurred in patients receiving BV. Hold BV dosing for suspected case of PML and discontinue BV if diagnosis is confirmed.
- Pulmonary toxicity: Events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported. In the event of new or worsening pulmonary symptoms, hold BV dosing during evaluation and until symptomatic improvement.
- Serious dermatologic reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes have been reported with BV
- Gastrointestinal (GI) complications: Fatal and serious GI complications including perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus have been reported with BV therapy. In the event of worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

5.2 Return and Retention of Study Drug

Investigational Lot

At the conclusion of the study, remaining drug will be destroyed according to UNC IDS (or multicenter site) institutional policy.

Commercial Supply
Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
http://intranet.unchealthcare.org/intranet/hospitaldepartments/safetynet/policies/hazardousdrugs.pdf

5.3 CHEP Chemotherapy

5.3.1 Description
CHEP consists of cyclophosphamide, doxorubicin, etoposide, and prednisone.

5.3.2 Method of Procurement
CHEP components are commercially available and approved by the US Food and Drug Administration for use in patients with multiple types of cancer. Commercial supplies of the individual components of CHEP will be used for this study and billed to patients and/or their insurance company.

5.3.3 Dose, Schedule and Administration
See section 4.2

5.3.4 Storage and Handling and disposal
The individual components of CHEP therapy should be stored and handled per institutional guidelines in accordance with the manufacturer's prescribing information.

Please see policy on hazardous drugs:
http://news.unchealthcare.org/empnews/att/2011/nov/admin0188/

5.3.5 Packaging and Labeling
The components of CHEP are commercially available.

5.3.6 Preparation
CHEP components should be prepared per institutional guidelines in accordance with the manufacturer's prescribing information.

5.3.7 Return and Retention of CHEP
Partially used and completely used vials will be destroyed per institutional guidelines.

5.3.8 Adverse Events Associated with CHEP
Please refer to the FDA-approved package inserts for cyclophosphamide, doxorubicin, etoposide and prednisone for product information, extensive

preparation instructions, and a comprehensive list of adverse events. The most common toxicities associated with each of the individual agents are listed below:

Cyclophosphamide:

- Hematologic: myelosuppression (leukopenia, neutropenia, thrombocytopenia, and anemia), severe immunosuppression, and bone marrow failure may be dose limiting
- Urinary bladder toxicity: hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported. Adequate hydration is essential prior to cyclophosphamide
- Cardiotoxicity: myocarditis, myopericarditis, pericardial effusion, including cardiac tamponade and congestive heart failure have been reported
- Pulmonary: pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease and other forms of pulmonary toxicity leading to respiratory failure have been reported
- Gonadal suppression and embryofetal toxicity: male and female reproductive function and fertility and fetal development may be impaired by cyclophosphamide
- Gastrointestinal: nausea, vomiting, diarrhea, abdominal discomfort and anorexia may occur
- Alopecia and skin rash: hair loss, hyperpigmentation of the skin and skin rash and impairment of wound healing
- Hyponatremia: associated with increase total body water, and syndrome of inappropriate secretion of antidiuretic hormone, which may be fatal has been reported

Doxorubicin:

- Hematologic: leukopenia (dose-limiting), thrombocytopenia, anemia; nadir in 10-14 days with recovery usually in 21 days
- Dermatologic: alopecia (usually complete; reversible); radiation recall reactions; increased sensitivity to sunlight
- Gastrointestinal: nausea and vomiting (doxorubicin is generally considered moderately to highly emetogenic), anorexia, diarrhea, mucositis (stomatitis, esophagitis)
- Cardiovascular: cardiomyopathy may occur and is related to total cumulative lifetime dose. The risk for cardiomyopathy increases with total doses > 450 mg/m^2. ECG changes and less often, arrhythmias are seen. Rarely, sudden death has occurred

Etoposide:

- Hematologic: myelosuppression is among the most common side effects, and may be dose-limiting
- Gastrointestinal: nausea and vomiting may occur with etoposide is generally considered mildly or moderately emetogenic. These symptoms can usually be controlled with standard antiemetic therapy

- Blood pressure changes: incidences of hypo or hypertension have been reported
- Anaphylactic/allergic reactions: etoposide may cause anaphylactic-type reactions characterized by chills, rigors, tachycardia, bronchospasm, dyspnea, diaphoresis, fever, pruritus, hypertension or hypotension, loss of consciousness, nausea and vomiting have been reported. Skin rashes and facial flushing was reported in patients receiving etoposide
- Other: reversible alopecia, sometimes progressing to total baldness may occur in up to 66% of patients

Prednisone:

- Hematologic: anemia, neutropenia and febrile neutropenia
- Cardiovascular: bradycardia, cardiac arrest, arrhythmias, enlargement and other circulatory events may occur.
- Dermatologic: acne, acneiform eruptions, allergic dermatitis, alopecia, dry and scaly skin, hirsutism, etc. are associated with prednisone.
- Endocrine: adrenal insufficiency, fatigue weakness amenorrhea, postmenopausal bleeding and other menstrual irregularities, decreased carbohydrate and glucose tolerance, hyper or hypothyroidism, etc.
- Fluid and electrolyte disturbances: fluid retention, sodium retention resulting in edema, hypokalemic alkalosis, metabolic alkalosis and congestive heart failure in susceptible patients
- Other: negative nitrogen balance due to protein catabolism, arthralgias, loss of muscle mass, gastrointestinal disturbances including increase appetite and weight gain, neurologic and psychiatric disturbances, blurred vision and cataract, and increases in intraocular pressure, immunosuppression and masking of infections, insomnia, moon face and pyrexia

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table (BV+CHEP)

Study Assessments	Screening[1] (D-28 to 0)	BV+CHEP (21-Day Cycle) X 6 cycles[1]								
		D1	D2	D3	D4	D5	D8	D15	End of Txt Visit[1]	Follow up[19]
Signed Informed consent	X									
Medical history/Demographics	X									
Inclusion/exclusion criteria review	X									
Physical Exam (PE)[2]	X	X[2]							X	
Vital signs (BP, pulse and temperature)	X	X	X[3]	X[3]			X		X	
ECOG performance status	X	X							X	
Imaging studies [4]	X[4]	X[4] (Cycles 3/5)							X[4] (end of cycle 6)	X[19]
Bone marrow aspiration and biopsy[5]	X								X[5]	
Biopsy with CD30 testing (by flow or IHC)[6]	X									
HTLV-1 Serology/ HIV/HCV/HBV Testing	X									
Strongyloides via serology or stool	X									
G6PD	X									
Uric acid and phosphorus[7]	X	X					X			
Hematology (CBC w. differential)	X	X					X		X	X[19]
Clinical Chemistry (CMP/ LDH)[8]	X	X					X		X	
Soluble Interleukin 2 Receptor	X								X	
Serum or Urine pregnancy test (WOCBP)[9]	X[9]	X[9]							X	
Intrathecal Prophylaxis with CSF studies (cell count, cytology, flow)[10]		X							X[10]	
Intrathecal Treatment (for active CNS involvement) with CSF studies (cell count, cytology, flow)[11]		X[11]					X[11]	X[11]	X[11]	
CT or MRI Brain[12]	X								X[12]	
ECHO (MUGA)	X[13]	X[13] (prior to cycle 4)								
IV Brentuximab vedotin[14]		X								
IV Cyclophosphamide and Doxorubicin		X								
IV Etoposide[15]		X	X	X						

Study Assessments	Screening[1] (D-28 to 0)	BV+CHEP (21-Day Cycle) X 6 cycles								
		D1	D2	D3	D4	D5	D8	D15	End of Txt Visit[1]	Follow up[19]
PO Prednisone[16]		X	X	X	X	X				
Check patient diary		X							X	
Adverse event assessment[17]	X	X	X[17]	X[17]			X	X[18]	X	
Prior/concomitant medication review	X	X							X	
Initiate/Renew prophylactic medications		X								
Survival										X[19]

NOTE: After completion of BV-CHEP subjects who 1) progressed on BV-CHEP therapy, 2) received 2-6 cycles of BV-CHEP and go on to transplant or 3) received 6 cycles of BV-CHEP and are CD30 negative will enter follow up outlined in this table. Subjects with CD30-positive ATLL who complete 6 cycles of BV-CHEP, are ineligible for transplant, and are CD30+ will continue study treatment on BV maintenance therapy as outlined in Table 6.2.

Footnotes (BV+CHEP Treatment Cycles)

1. All screening assessments should be completed within 28 days before initiating study therapy unless otherwise specified. If screening labs are performed within 72 hours of initiating study treatment on D1/C1, they do not need to be repeated. Each scheduled visit should occur within ±2 days of the scheduled visit while the subject is receiving study treatment. The end of treatment visit should occur 21 days (+/-1 one week) after discontinuing study therapy and all ongoing AEs should be followed until satisfactory resolution to the lowest achievable toxicity grade based on the patient's health status.
2. A complete physical exam (PE) should be conducted at screening i.e., baseline including height (baseline only) and weight. A targeted physical exam including weight should be conducted on D1 of each cycle prior to administration of BV+CHEP therapy.
3. Vital signs will be taken if the subject is in clinic to receive IV etoposide.
4. Imaging should be obtained at screening within 21 days of initiating study treatment and at C3D1 (-7 days), C5D1 (-7 days) and day 21 of cycle 6 (+/-7 days) or as needed, if there are any clinical signs/symptoms of progression. A PET/CT scan is preferred for screening, C5D1, and C6D21 but a CT CAP is acceptable for screening in situations that would affect patient safety. A PET/CT or CT scan is required for C3D1.
5. The bone marrow exam will be done for staging. Only need to repeat at end of treatment if BM biopsy was positive initially at baseline to confirm CR (if applicable).
6. If the biopsy done for diagnosis is not available or the bone marrow biopsy done for staging is negative, a biopsy will be needed to confirm diagnosis and test for CD30.
7. Uric acid and phosphorus will be tested at screening and on Days 1 and 8 of Cycle 1 only.
8. Clinical chemistry will include a complete metabolic panel [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] + LDH. Note: Creatinine clearance, bilirubin, AST and ALT to be obtained within 3 days of starting study treatment. See criterion 3.1.7.
9. Pregnancy test must be performed within 72 hours before initiating study treatment on day 1 of cycle 1. For subsequent cycles, a pregnancy test will be done on day 1.
10. **IT prophylaxis** will consist of either cytarabine, methotrexate, and hydrocortisone, or methotrexate alone, or cytarabine alone. This will be administered per institutional guidelines. The suggested regimen is: starting with C1 will consist of 6 total treatments (1 treatment per cycle for 6 cycles). If the patient receives IT prophylaxis, the patient will not receive IT treatment. CSF will be obtained for all patients. CSF studies should occur within +/-4 days and will be sent starting with C1. The end of study CSF studies will only be sent for patients who had a positive finding and the CNS has not resolved.
11. **IT treatment** will consist of either cytarabine, methotrexate, and hydrocortisone, or methotrexate alone, or cytarabine alone. This will be administered to any patients with CSF findings consistent with CNS ATLL involvement (positive flow or cytology). This can be administered per institutional guidelines. The suggested schedule will consist of treatment on D1, D8, and D15 until clearance on CSF. Then the regimen will return to prophylactic dosing. If the patient is positive for CNS involvement, the patient will follow the treatment schedule not the prophylaxis schedule for IT chemotherapy. CSF studies will be obtained for all patients. CSF studies should occur within +/-4 days and will be sent starting with C1. The end of study CSF studies will only be sent for patients who had a positive finding and the CNS has not resolved.
12. CT/MRI of brain will be completed for all patients during screening. Repeat same test at end of BV-CHEP if baseline test was positive.
13. ECHO at screening excludes patients with LVEF <40%. Patients with baseline LVEF of 40% to 55% should have repeat assessment performed prior to cycle 4.

14. Subjects with CD30+ disease will receive commercial supply of Brentuximab vedotin. Subjects with CD30- disease will receive investigational lot. Subjects with CD30 expression above 1 percent will be considered to have CD30+ disease.
15. Oral etoposide may be substituted for IV etoposide for any or all days in which etoposide is administered. See Section 4.2.1 for Dosing and Administration of oral etoposide.
16. IV corticosteroid of equivalent dose to 100 mg prednisone may be substituted as clinically indicated.
17. Toxicity assessment per NCI-CTCAE criteria v.4.03. Toxicity assessment on days 2 and 3 of each cycle will be assessed only if the subject receives IV etoposide.
18. For Day 15, the adverse event assessment is only required when a subject is receiving IT treatment (not IT prophylaxis). The adverse event assessment may be done by the study team over the phone.
19. All subjects will be followed every 3 months (+/- 1 month) for survival for 5 years or until death, whichever occurs first, starting from time the subject discontinues study treatment. To document survival, subjects will either be contacted directly, or their medical record will be checked. Subjects that are removed from study therapy and change to a new anti-cancer regimen will be followed for survival only. All other subjects on follow up will also have imaging scans (PET or CT) and hematology laboratory tests (CBC with differential) every 6 months (+/-1 month) for 2 years or until death, whichever occurs first, from the time they discontinue study treatment. Subjects eligible for BV maintenance (i.e., ineligible for transplant and CD30+) should continue study treatment as described in table 6.2. See section 6.6 Post treatment/Follow up for additional guidance.

6.2 Time and Events Table (BV Maintenance Therapy)

Study Assessments	D1[1]	End of Study Txt Visit[1] see section 6.5.2	Follow up[8]
Targeted PE[2]	X	X	
Weight	X	X	
Vital signs (BP, pulse and temperature)	X	X	
ECOG performance status	X	X	
Imaging studies	X[3]	X[3]	X[8]
Hematology (CBC w. differential)	X	X	X[8]
Clinical Chemistry (CMP/ LDH)[4]	X	X	
Soluble Interleukin 2 Receptor		X	
Serum or Urine pregnancy test (WOCBP)	X[5]	X	
IV Brentuximab vedotin	X[6]		
Adverse event assessment[7]	X	X	
Prior/concomitant medication review	X	X	
Survival			X[8]

Note: To be eligible for BV maintenance therapy, patients must have CD30 positive ATLL. Subjects with CD30 expression above 1 percent will be considered to have CD30+ disease.

Footnotes (BV Maintenance Treatment Cycles 1-N)

1. Each scheduled visit should occur within ±2 days of the scheduled visit while the subject is receiving study treatment. The end of maintenance treatment visit should occur 21 days (+/- one week) after discontinuing study therapy and all ongoing AEs should be followed until satisfactory resolution to the lowest achievable toxicity grade based on the patient's health status.

2. A targeted physical exam including weight should be conducted on D1of each cycle prior to administration of BV maintenance therapy in patients with CD30 positive ATLL
3. A PET/CT scan or CT scan should be done every 8 cycles (+/-21 days) (or sooner, if there are any clinical signs/symptoms of progression) during maintenance therapy. A PET/CT scan or CT scan should also be done at the end of study treatment visit.
4. Clinical chemistry will include a complete metabolic panel [BUN, creatinine, Na, K, Cl, CO2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] + LDH
5. Pregnancy test (serum or urine) must be performed within 72 hours before initiating BV maintenance therapy for cycle 1. For subsequent cycles, a pregnancy test will be done on day 1.
6. BV (1.8 mg/kg IV) administration every 21 days until PD or withdrawal for toxicity or other reasons
7. Toxicity assessment per NCI-CTCAE criteria 4.03
8. All subjects will be followed every 3 months (+/- 1 month) for survival for 5 years or until death, whichever occurs first, starting from time the subject discontinues study treatment. To document survival, subjects will either be contacted directly or their medical record will be checked. Subjects that are removed from study therapy and change to a new anti-cancer regimen will be followed for survival only. All other subjects on follow up will also have imaging scans (PET/CT or CT) and hematology laboratory tests (CBC with differential) every 6 months (+/-1 month) for 2 years or until death, whichever occurs first, from the time they discontinue study treatment. Follow as outlined above. See section 6.6 Post treatment/Follow up for additional guidance.

6.3 Pre-Study Assessments

Screening tests and evaluation will be performed only after a signed, written Institutional Review Board (IRB) approved informed consent is obtained from each subject. Screening will include:

Clinical evaluation: complete history (including history of hepatitis B, C or HIV + HTLV serology and strongyloides test via serum or stool), physical examination (including height, weight and vital signs), ECOG performance status
Cardiac evaluation: MUGA or ECHO
Study Eligibility: Inclusion/Exclusion Criteria review
Laboratory studies:

- HTLV-1 Serology/ HIV/HCV antibody/HBV core antibody/surface antibody/surface antigen
- Glucose 6 phosphate dehydrogenase (G6PD), uric acid, and phosphorus
- complete blood count (CBC) with differential
- CMP + other test; CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus LDH
- Soluble interleukin-2 receptor
- Pregnancy test: serum β-HCG or urine (if applicable for WOCBP) within 72 hrs of initiating study treatment

Disease Measurements: PET/CT scan of chest, abdomen and pelvis or CT CAP (in situations that would affect patient safety) (obtained within 21 days of starting study medications)
CT or MRI of brain
Bone marrow exam: A bone marrow aspiration and biopsy will be done for staging.
Biopsy with CD30 testing (by flow or IHC): If CD30 testing was previously done on the biopsy sample from diagnosis, this information will be collected. If CD30 testing was not done, an archival sample from the biopsy used for diagnosis will be requested and tested for CD30. CD30 testing will also be done on the bone marrow tissue collected from the bone marrow exam. If we are unable to obtain an archival sample or if the bone marrow exam is negative, a new biopsy will be performed to confirm the diagnosis and test for CD30.
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.03
Concomitant medications: Review

6.4 Treatment Assessments (See Table 6.1)

6.4.1 D1 of Cycles 1-6 (BV-CHEP)

Clinical evaluation: targeted history physical examination (including weight and vital signs), ECOG performance status
Cardiac evaluation: MUGA or ECHO required prior to treatment in C4 for patients with baseline LVEF of 40% to 55%
Laboratory studies:

- complete blood count (CBC) with differential
- CMP + other test; CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus LDH
- Uric acid and phosphorus (cycle 1 only)
- Pregnancy test: serum β-HCG or urine (if applicable for WOCBP). For day 1 of cycle 1, the pregnancy test must be done within 72 hours of beginning treatment. For subsequent cycles, the pregnancy test will be done on day 1.

Disease Measurements (Cycle 3 and Cycle 5 prior to starting treatment, and at the end of Cycle 6 or as needed if signs of PD): PET/CT or CT scan required for Cycle 3 and a PET/CT scan of chest, abdomen and pelvis required for Cycle 5 and end of cycle 6.
CSF: cell count, cytology, and flow cytometry
Check patient diary
IT prophylaxis / IT treatment: See footnotes 10 & 11 in T&E table
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.03
Concomitant medications: Review
Prophylactic medications: initiate/renew as needed per standard of care
Administer Study Medications: (see section 4.2)

6.4.2 D2, 3, 4 and 5 of Cycles 1-6 (BV-CHEP)

Clinical evaluation: (vital signs only D2 and D3 if the subject is receiving IV etoposide)
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.03 (only D2 and D3 if the subject is receiving IV etoposide)
Administer Study Medications: (see section 4.2)

6.4.3 D8 Cycles 1-6 (BV-CHEP)

Clinical evaluation: (vital signs only)

- Laboratory Studies:
  - CBC with differential
  - CMP + other test; CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus LDH
  - Uric acid and phosphorus (cycle 1 only)

Intrathecal treatment: per standard of care (see footnote 11 in T&E)
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.03

6.4.4 D15 Cycles 1-6 (BV-CHEP)

Intrathecal treatment: per standard of care (see footnote 11 in T&E)
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.03 for subjects who are receiving intrathecal chemotherapy treatment.

6.4.5 End of Treatment (BV-CHEP)

Clinical evaluation: physical exam focused on toxicity, vital signs, ECOG performance status
Laboratory studies:
- complete blood count (CBC) with differential
- CMP + other test; CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus LDH
- Soluble interleukin-2 receptor
- Pregnancy test: serum or urine β-HCG (if applicable for WOCBP)

Check patient diary
CT or MRI of brain: (same test as performed at baseline if baseline test was positive)
CSF: cell count, cytology, and flow cytometry (if tested positive for CNS involvement during study treatment unless testing shows it has cleared see footnotes 10 & 11)
Bone marrow aspiration and biopsy- See footnote #5
Disease Measurements: PET/CT scan of chest, abdomen and pelvis (see footnote #4 under Table 6.1)
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.03. Subjects with ongoing study treatment-related toxicity should be followed until resolution of ≤ grade 1 or investigator determines event resolution to minimum level that can be achieved.
Concomitant medications: Review

6.5 BV Maintenance Treatment (CD30-positive ATLL only – see Table 6.2)

6.5.1 D1 of each cycle of BV Maintenance

Clinical evaluation: targeted physical examination (including weight and vital signs), ECOG performance status
Laboratory studies:
- complete blood count (CBC) with differential
- CMP + other test; CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus LDH
- Pregnancy test: serum β-HCG or urine (for WOCBP) within 72 hours of starting BV on day 1 of cycle 1. For subsequent cycles, the pregnancy test will be done on day 1.

Disease Measurements (Repeat every 8 cycles (+/- 21 days) or as needed if signs of PD): PET/CT or CT scan of chest, abdomen and pelvis (see footnote #3 of Table 6.2)
Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.03
Concomitant medications: Review
Administer BV: (see section 4.2)

6.5.2 End of BV Maintenance Treatment

Clinical evaluation: targeted physical examination (including weight and vital signs), ECOG performance status

Laboratory studies:

- complete blood count (CBC) with differential
- CMP + other test; CMP [BUN, creatinine, Na, K, Cl, CO_2, glucose, calcium, albumin, total protein, total bilirubin, ALT, AST, alkaline phosphatase] plus LDH
- Soluble interleukin 2 receptor
- Pregnancy test: serum β-HCG or urine (if applicable for WOCBP).

Disease Measurements): PET/CT or CT scan of chest, abdomen and pelvis

Toxicity: Toxicity will be assessed according to the NCI CTCAE, version 4.03. Treatment related toxicity. Subjects with ongoing study treatment-related toxicity should be followed until resolution of ≤ grade 1 or investigator determines event resolution to minimum level that can be achieved.

Concomitant medications: Review

6.6 Post-Treatment Follow-up Assessments

Subjects who are withdrawn from study treatment (i.e., BV-CHEP or BV maintenance) with ongoing toxicity should be followed until resolution of symptoms to grade ≤1 or investigator determines event resolution to minimum level that can be achieved.

Note: After completion or withdrawal of BV-CHEP therapy, patients will segregate into 4 separate groups:

1) Those who progressed on BV-CHEP therapy (Group 1);
2) Those who complete 2-6 cycles of BV-CHEP and are eligible to go to allogeneic transplant (Group 2);
3) Those who complete 6 cycles of BV-CHEP but are CD30 negative (Group 3); and
4) Those who completed 6 cycles of BV-CHEP, are CD30 positive and continue study treatment with BV in the maintenance phase of the study (Group 4). Subjects on BV maintenance will continue study treatment until disease progression or withdrawal for other reasons e.g., toxicity.

All subjects will be followed every 3 months (+/- 1 month) for survival for 5 years or until death, whichever occurs first, starting from time the subject discontinues study treatment. To document survival, subjects will either be contacted directly or their medical record will be checked. Subjects that are removed from study therapy and change to a new anti-cancer regimen will be followed for survival only. All other subjects on follow up will also have imaging scans (PET/CT or CT) and hematology laboratory tests (CBC with differential) every 6 months (+/-1 month) for 2 years or until death, whichever occurs first, from the time they discontinue study treatment.

6.7 Correlative Studies Procedures

CD30 expression will be determined at baseline by immunohistochemistry. We expect to show a "dose-response" effect, with increasing efficacy of our experimental regimen, BV-CHEP, in patients with a higher percentage of CD30 expression for ATLL.

6.8 Assessment of Safety

Any patient who receives at least one dose study therapy on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events tables. Toxicity will be assessed according to the NCI CTCAE v4.03.

6.9 Assessment of Efficacy

The ORR will be evaluated as the rate of complete responses (CR) + partial responses (PR) as defined by the International Workshop to standardize response criteria for malignant lymphomas (i.e., Lugano Criteria per Cheson, et al. J Clin Oncol. 2014;32(27):3059-68); see Appendix A: Revised response criteria for lymphoma**.**

Additionally, for subjects with a leukemic component to their disease at baseline peripheral blood will be assessed per Adult T-Cell Leukemia/Lymphoma NCCN guidelines version 2.2017 outlined in the table below.

Response	**Peripheral Blood**
Complete remission*	Normal†
Uncertified complete remission*	Normal†
Partial remission*	≥50% decrease
Stable disease*	No change
Relapsed or progressive disease	New or ≥50% increase#

* Required that each criterion be present for a period of at least 4 weeks.
† Provided that <5% of flower cells remain, complete remission is judged to have been attained if the absolute lymphocyte count, including flower cells, is $<4 \times 10^9$/L.
# Defined by ≥50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells $>4 \times 10^9$/L.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

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

associated with the use of a medicinal product, whether or not related to the medicinal product.

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

7.1.2 Suspected Adverse Reaction (SAR)

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

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

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

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

7.1.4 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 drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

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

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

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued.

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

7.3 SAEs or Serious SARs

7.3.1 Timing

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

SAEs that are subject to these reporting requirements are those that (i) occur from after the first dose of the Pfizer Product or the Study subject's enrollment in the Study (whichever is later) through twenty-eight (28) days after the last administration of the Pfizer Product or the subject's last Study visit (whichever is earlier), or longer if so specified in the Protocol; or (ii) occur any time after the

28-day period if Institution or Principal Investigator suspects a causal relationship between the Pfizer Product and the SAE.

7.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within OnCore™ for that patient within 24 hours of learning of its occurrence. Additionally, the Multicenter Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence. The Regulatory Associate and Medical Monitor must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

7.3.3 Reporting

IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem. Please note, these events must be reported to the sponsor within 24 hours of learning of the occurrence.

Multicenter sites:

- For multicenter sites using a local IRB of record, please submit adverse events per local IRB policy.
- For multicenter sites relying on the UNC-IRB, any SAEs that qualify as an Unanticipated Problem will be entered into OnCore™ and reported to the UNC IRB by the Multicenter Regulatory Associate using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

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 should be recorded as SAEs. The patient is to be discontinued immediately from the study.

For multicenter sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the assigned Multicenter Project Manager immediately (within 24 hours) via email or call Multicenter main line 919-966-7359. The Multicenter Project Manager will then report the event to the Funding Source (see requirements below). The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the Multicenter Project Manager. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

Laboratory Test Abnormalities
The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Overdose
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Funding Source (e.g. Manufacturer) Reporting Requirements:

Pfizer Reporting Requirements:
The Principal Investigator is responsible for ensuring that safety data are reported to Pfizer as outlined in the table below.

*Expedited SAE reports must include all the information outline on the FDA form 3500A form.
**SAE log must include SAEs reported expeditiously to the FDA and Pfizer. Pfizer SAE form and sample SAE aggregate listing are available at https://www.pfizersafetyreporting.com/. All SAE forms should be emailed to USA.AEReporting@pfizer.com

FDA Expedited Reporting requirements for studies conducted under an IND:
A sponsor must report any suspected adverse reaction that is both serious and unexpected to the FDA. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The sponsor must submit each IND safety report on FDA Form 3500A. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division that has the responsibility for review of the IND. For this study, the review division is the Center for Drug Evaluation and Research. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

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 drug 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 as per 21 CFR 312.32. Unexpected adverse events or adverse reaction

refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch form should be emailed to the assigned Multicenter Project Manager and also to CPOMulticenter@med.unc.edu, along with supporting documentation defining the event and causality. The Multicenter Project Manager will then send the report to the Funding Source. The MedWatch 3500a form can be accessed at http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500a, and not form 3500).

Once the UNC Principal Investigator determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA.

The Multicenter Project Manager will also be responsible for informing each multicenter site of all serious and unexpected SARs reported to the FDA via fax as soon as possible.

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 drug.
- *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 drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity t 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.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient 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. These meetings will include the investigators as well as study coordinators, data coordinators, regulatory associates, clinical data management associates, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

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

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients 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.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

This is a single-arm non-randomized pilot study to examine the efficacy and safety of BV-CHEP for the treatment of Adult T-Cell Leukemia/Lymphoma and the primary efficacy outcome is complete response (CR).

In this pilot single-arm study, we will accrue 14 patients to get preliminary data on efficacy of a novel regimen, brentuximab vedotin with cyclophosphamide, doxorubicin, etoposide, and prednisone (BV-CHEP). *We expect the complete response rate will be about 45%. The study may enroll up to 16 patients to ensure 14 are evaluable for the primary endpoint.*

8.2 Sample Size and Accrual

Accrual will take place at UNC. Additional sites of patient accrual will include BMC, DFCI, BIDMC, and MGH and potentially additional sites that participate in this study. Based on a previous study conducted with a similar population, we anticipate averaged accrual of 1 patient per month, corresponding to 12 months to accrue the 14 desired patients for this study. The CR rate of this population under the new treatment is expected to be approximately 45%, about 25% higher than the CR rate under current practice[6,7,11,12]. The design as proposed in the above section leads to 95% confidence interval with half length about 20%, as shown in the following table.

Number of CR/Total	Estimated CR	95% Wilson Score CI
4/12	33%	(14%, 61%)
5/12	42%	(19%, 68%)
5/13	38%	(18%, 64%)
6/13	46%	(23%, 71%)
5/14	36%	(16%, 61%)
6/14	43%	(21%, 67%)

Assuming a 10% patient drop-out (non-evaluable) rate, we will plan to enroll 16 patients in order to achieve 14 evaluable patients in this study.

Sequential boundaries will be used to suspend the trial if excessive toxicity is seen. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the Data and Safety Monitoring Committee with a description of the failures to date and a rationale for why the study should be continued. A dose-limiting toxicity (DLT) is defined as all grade 5 toxicities and any grade 3-4 non-infectious, non-hematologic and non-neuropathy-related toxicities (exceptions include alopecia and electrolyte abnormalities, diarrhea, nausea, and vomiting AEs that can be managed with supportive care and do not persist as Grade 3-4 toxicities for > 2 weeks) attributed to BV-CHEP. The accrual will be halted if the number of DLTs is equal to or exceeds bn out of n patients with full toxicity follow-up (see table below). This is a Pocock type stopping boundary that assumes that **a DLT rate of 0.20** is acceptable. If the true DLT rate is equal to 0.20, the probability of crossing the boundary is 0.20. For a few DLTs below or above 0.20, we found that the probability of crossing/reaching the boundary is approximately 0.5% at true toxicity 5%; 3% at toxicity 10%; 48% at toxicity 30%; 77% at toxicity 40%; 93% at toxicity 50%.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16				
Boundary, b_n	-	2	3	3	3	3	4	4	4	5	5	5	5	6	6	6				

8.3 Data Analysis Plans

For the primary objective of complete response rate, the estimated rate will be reported with 95% exact confidence intervals in the final analysis.

Time-to-event outcomes like PFS, duration of response and overall survival will be analyzed using the Kaplan Meier method for time-to-event outcome, with median duration of response reported with 95% confidence intervals. Descriptive statistics (frequencies) of the toxicity and tolerability (assessed via NCI-CTCAE v. 4.03) of BV-CHEP will also be reported. Proportion of overall response rate (ORR) will be reported with an exact 95% confidence interval.

Exploratory analyses will be conducted to examine the associations between CD30 expression and PFS using Cox proportional hazard regression.

9.0 STUDY MANAGEMENT

9.1 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 patient 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 patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

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

9.2 Required Documentation

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

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.

- Form FDA 1572
- Financial disclosures
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the LCCC CPO Multicenter group at the University of North Carolina before enrollment to study. To register a patient call the Multicenter Project Manager at 919-966-7359 Monday-Friday 8:30 am – 5:00 pm EST. Email the registration form, signed informed consents and all source documents to confirm eligibility to the assigned Project Manager (if unknown, email CPOMulticenter@med.unc.edu). When sending registration request with eligibility documentation, please allow 24 hours for source documents to be reviewed.

9.4 Data Management and Monitoring/Auditing

The CPO Multicenter Office of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). Clinical Data Management Associates will review clinical data entered in the eCRFs and coordinate with Multicenter Personnel to ensure data quality and integrity with queries issued on an ongoing basis.

All data will be collected and entered into OnCore® by research coordinators from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The Clinical Data Management Associate (CDMA) can be reached at LCCC_OnCore@med.unc.edu or 1-877-668-0683.

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

As an investigator initiated study, the LCCC compliance committee or their designee will audit trial sites every six or twelve months while still enrolling or subjects are still on treatment.

9.5 Adherence to the Protocol

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

9.5.1 Emergency Modifications

UNC and multicenter 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 Institutions Relying on UNC's IRB:
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.

For Institutions Relying on Their Own IRB:
For multicenter investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The multicenter institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the Multicenter Regulatory Associate).

9.5.2 Single Patient/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.

9.5.3 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:

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

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

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the Multicenter Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the Multicenter Regulatory Associate.

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

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

9.6 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 patient, a revised consent form might be required.

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

For Institutions Relying on Their Own IRB:
Investigators must submit the amendment to their institution's IRB for approval. For multicenter studies, any multicenter site must submit their informed consent revisions to the Multicenter Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

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

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

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

9.8 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 patients. 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 at each institution or site 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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11.0 APPENDICES

11.1 Appendix A: Revised response criteria for lymphoma (Cheson, et al. J Clin Oncol. 2014;32(27):3059-68)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	*Complete metabolic response*	*Complete radiologic response (all of the following)*
Lymph nodes and extra-lymphatic sites	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 (e.g., 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 f initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	*Partial metabolic response*	*Partial remission (all of the following)*
Lymph nodes and extra-lymphatic sites	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	≥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
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared 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	Not applicable

Revised Criteria for Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (Lugano Criteria)
Continued from previous page

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

Revised Response Criteria continued from previous page (Table Key)

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

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 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. Nonmeasure 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 (e.g., 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 (e.g., 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.

11.2 Appendix B - Renal Impairment Guidelines

Group	Description	Estimated Creatinine Clearance (mL/min)
1	Normal renal function	80 mL/min
2	Mild renal impairment	50-80 mL/min
3	Moderate renal impairment	30-50 mL/min
4	Severe renal impairment	<30 mL/min
5	End-stage renal disease	Requiring dialysis

Cockcroft-Gault

$$\text{Estimated creatinine clearance (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

For females, use 85% of calculated creatinine clearance value.

11.3 Appendix C - Child-Pugh Hepatic Impairment Score

Factor	1 point	2 points	3 points
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	Class B	Class C
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Available at: http://www.2minutemedicine.com/the-child-pugh-score-prognosis-in-chronic-liver-disease-and-cirrhosis-classics-series/ (Last updated August 4, 2015).

11.4 Appendix D: Prohibited Medications or Those to be used with Caution

Several study medications you are receiving during this clinical trial 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**.

- **Some of the study medications** are processed by a certain enzyme in the liver called CYP3A4. Drugs that increase the activity of this enzyme are called "inducers", and drugs that decrease the activity of this enzyme are called "inhibitors". Some of the study medications must be used very carefully with other medicines that are **inducers** or **inhibitors** of CYP3A4.
- 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: ketoconazole, itraconazole, ritonavir, macrolide antibiotics, erythromycin phenytoin, phenobarbital, carbamazapine, and valproic acid.
- 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.
- If you drink grapefruit juice or eat grapefruit, you should avoid these until the study is over.
- 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 _____.