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SHORT-COURSE EPOCH-RITUXIMAB FOR UNTREATED CD-20+ HIV-ASSOCIATED LYMPHOMAS

NCI Principal Investigator: Christopher Melani, M.D.
Lymphoid Malignancies Branch (LYMB)
Center for Cancer Research (CCR)
National Cancer Institute (NCI)
National Institutes of Health (NIH)
Building 10, Room 3B38
9000 Rockville Pike
Bethesda, MD 20892
Phone: 240-760-6057
Email: christopher.melani@nih.gov

Commercial Agents: EPOCH-R = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab

PRÉCIS

Background:

- This is a study to investigate in a preliminary fashion the feasibility of short course chemotherapy to participants with HIV-associated non-Hodgkin's lymphoma (HIV-NHL).
- This study will investigate if the paradigm for treatment can be successfully changed from a standard of 6 cycles to one cycle beyond complete remission with 6 total allowable cycles.

Objective:

- To assess with 90% probability that at least 50% of participants treated with short-course EPOCH-R will be progression free at one year.

Eligibility:

- Aggressive CD20 positive DLBCL.
- HIV+ serology.
- All stages (I-IV) of disease.
- ECOG Performance status 0-4
- NHL previously untreated with cytotoxic chemotherapy.
- Age ≥ 18 years
- May not be pregnant or nursing
- May not have received previous rituximab

Design:

- Participants will be treated every three weeks with a combination of EPOCH and rituximab for one cycle beyond CR/CRu by CT scan of all detectable tumors for a minimum of three and maximum of six cycles. Following cycle 2, CT, positron emission tomography scans (PET), and bone marrow biopsies (if initially positive) will be performed.
- At the conclusion of the study, we will estimate whether the number of cycles can be reduced using the paradigm. If the cumulative number of participants to relapse exceeds 25% by 6 months, the study will be closed.
- Following the completion of chemotherapy, restaging will be performed 2 months following the end of treatment, then every 3 months for one year, every 6 months for one year, then every 12 months until relapse, death, or loss to follow up.
- Antiretroviral therapy (ART) will be given concurrently with treatment regimen.
- To study the effects of treatment approach on parameters of HIV disease, measurements of CD4 cells and viral loads will be made at baseline and at the completion of therapy, and then 2 months following the end of treatment, and then every 3-6 months for a total of 24 months following chemotherapy.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To assess with 90% probability that at least 50% of participants treated with short-course EPOCH-R will be progression free at one year

1.1.2 Secondary Objectives

- Assess toxicity of SC-EPOCH-R
- Assess response rate and duration of SC-EPOCH-R
- Assess the utility of PET scans to predict freedom from relapse with SC-EPOCH-R
- Assess effects of SC-EPOCH-R on CD4 cell depletion and recovery
- Assess response to antiretroviral therapy either following or concurrently with SC-EPOCH-R (effective with Amendment S, antiretroviral therapy will be given concurrently)
- Assess 5- year Overall Survival (OS)

1.1.3 Exploratory Objectives

- Explore molecular and genomic studies in tissue that may predict response and outcomes

1.2 BACKGROUND AND RATIONALE

HIV-associated lymphomas present unique treatment challenges compared with HIV negative lymphomas. Patients are often profoundly immunosuppressed and generally intolerant of aggressive chemotherapy, and have a median survival of 4 to 11 months with standard therapy[1, 2]. Additionally, HIV-associated lymphomas more frequently present with adverse prognostic features including multiple extranodal disease sites, elevated LDH, poor performance status and advanced stage3. Despite significant efforts to improve the outcome of HIV-NHL, it continues to limit the life expectancy of affected individuals more significantly than any single AIDS-defining condition except for multifocal leukoencephalopathy [4]. Median survivals for HIV-NHL are less than 18 months in most series, even for patients with good prognosis characteristics [1, 5-7]. To a large extent, efforts to improve treatment outcomes have had modest success at best. Treatment strategies primarily include low-dose chemotherapy regimens and given with multi-agent antiretroviral therapy in an effort to balance the antitumor and immunosuppressive effects of treatment.

Based on first principles, the strategy of low-dose chemotherapy given with antiretroviral therapy is appealing. Lower doses of chemotherapy may be less immunosuppressive relative to standard doses, and suppression of HIV may protect patients undergoing anti-lymphoma therapy from progressive HIV disease. However, there are a number of issues that raise concerns as to the likely effectiveness of such an approach. In non-HIV-associated lymphomas, some studies have suggested that chemotherapy dose-intensity (the amount of chemotherapy administered over time) is associated with curative potential [8]. Indeed, large studies of low- versus standard dose chemotherapy in HIV-NHL suggest that more patients in the low-dose groups die with active lymphoma than in the standard dose groups [1]. Also, attempts at preservation of CD4 cell

counts by utilizing concurrent anti-HIV therapy may not be very useful when lymphocytotoxic chemotherapy is administered to treat the lymphoma. In HIV-negative patients undergoing such therapy, CD4 cell depletion in excess of 80% of baseline can often occur[9], and recovery to baseline may not occur for greater than 12 months[10]. Thus, lymphocyte depletion occurs independently of HIV infection. Additionally, because of overlapping pharmacokinetic interactions and can adversely affect the therapeutic index of the various drugs, optimal treatment for both the lymphoma and the HIV infection may be compromised. Also, if chemotherapy-associated toxicity compromises compliance with the antiretroviral drugs, development of resistant HIV may be more likely to occur when this strategy is utilized.

However, studies have not shown improved survival, even though the complete response rates are generally somewhat higher in patients receiving standard dose chemotherapy [1, 5-7]. To a large extent, this is due to the inability of HIV-infected patients to tolerate the more intensive chemotherapy regimens, and death due to progressive complications of AIDS counterbalances the beneficial effects of such therapy on the lymphoma. Thus, strategies to successfully eradicate the lymphoma but with less immune damage may be one way of balancing these effects. The administration of short-course (2-3 cycles) chemotherapy as we propose would represent a significant change in the standard treatment paradigm, which typically employs 6 to 8 cycles. Such a strategy may result in significantly less chemotherapy related immune damage with better preservation of lymphocytes and potentially reduce the risk for AIDS-related mortality.

The concept of shorter course chemotherapy extends from our initial clinical research in HIV-associated lymphoma utilizing dose-adjusted EPOCH. This regimen appears to be effective and relatively well-tolerated when administered over 6 cycles[11]. Among 30 evaluable patients, 23 (77%) achieved a complete response, 100% of whom remain disease free with a median follow-up over 2 years. Of note, patients who achieved a complete response with EPOCH did so by cycle 4, and many had rapid resolution of all palpable tumor masses within 1 to 2 cycles. Indeed, the 100% disease free survival rate following 6 cycles of EPOCH alone suggests that 6 cycles of EPOCH may not be necessary in all patients. A unique aspect of this trial prior to Amendment S, was the suspension of all anti-retroviral treatment during EPOCH to reduce potential adverse pharmacokinetic interactions, and the emergence of resistant viral quasi-species due to sub-therapeutic antiretroviral drug concentrations[6, 12, 13]. Detailed assessment of immune status has demonstrated a loss of CD4 cells and increased viral loads, albeit transient, with return to baseline within 12 months after treatment[11]. However, it is likely that there is still a substantial risk of AIDS progression and opportunistic infections with this approach.

Beginning with Amendment S, antiretroviral therapy will be given concurrently with EPOCH. Concurrent therapy is felt to be in the best interests of the participants on study at this time. ART has been shown to be safe when administered concurrently with EPOCH and is no longer routinely stopped during the treatment of HIV-associated malignancies similar to those under study [40, 41].

Rituximab is a chimeric antibody, containing the human IgG1 and κ constant and murine variable regions, which targets the CD20 B cell antigen [14]. CD20 is expressed on the surface of normal and neoplastic B cells and is present from the pre-B cell stage through terminal differentiation to plasma cells [15, 16]. To date, the biological functions of CD20 remain uncertain, although incubation of B-cells with anti-CD20 antibody has variable effects on cell cycle progression, depending on the monoclonal antibody (MoAb) type. Ligation of CD20 by B1

MoAb inhibits B-cell progression from G_1 to the S/G_2+M phases of the cell cycle following mitogen stimulation, whereas IF5 MoAb, which binds to a different CD20 epitope, can deliver an activation signal and drive resting Go B cells into G1, but not into S phase [17-19]. Mechanistically, binding of MoAb to CD20 generates transmembrane signals that produce a number of events including autophosphorylation and activation of serine/tyrosine protein kinases, and induction of c-myc oncogene expression and major histocompatibility complex (MHC) class II molecules [18, 20]. Studies have shown that CD20 is also associated with transmembrane Ca^{2+} conductance, through its possible function as a Ca^{2+} channel, and may explain some of the differential effects of IF5 and B1 MoAb's on B-cells. The IF5 MoAb may activate resting B cells by facilitating rapid Ca^{2+} entry, while B1 MoAb does not have acute effects on Ca^{2+} currents. Both MoAb's, however, may lead to sustained intracellular Ca^{2+} levels over time with subsequent inhibition of cell cycle progression from G_1 into S phase [18, 20]. These studies demonstrate the importance of CD20 in B-cell regulation, but do not in themselves indicate how ligation of the receptor by MoAb produces cell death independent of ADCC or complement mediated pathways.

The clinically important mechanisms of rituximab cytotoxicity remain unclear. Although ADCC and complement mediated cytotoxicity can be demonstrated in vitro, accumulating evidence suggests that disruption of normal signal transduction by CD20 MoAb can directly induce apoptosis [21, 22]. Shan et al showed that proliferation of a B-cell line could be directly inhibited by the IF5 MoAb in heat-inactivated serum (i.e. inactivated complement) and that complement-replete serum further contributed to inhibition of proliferation [21]. Of note, in the absence of complement, the antiproliferative effect of IF5 MoAb was more dependent on CD20 saturation and cell density. The investigators further determined whether anti-CD20 MoAb's induced B-cell apoptosis following inhibition of cell growth through the use of three complementary assays. When used alone, neither IF5 nor B1 MoAb's induced significant apoptosis, but when cross-linked with a goat anti-mouse antibody (GAM), apoptosis occurred in 22% and 28% of cells at 24 hours, compared to 5% in the controls; similar results were also produced in tonsil B cells. These results suggest that similar cross-linking must occur in vivo for anti-CD20 MoAb to directly induce apoptosis. The investigators postulated that functional cross-linking may occur in patients through the binding of the MoAb's Fc domain to the FcγR of adjacent cells and showed, using a mouse fibroblast transfected with the human Fc receptor, a similar degree of apoptosis as observed with GAM cross-linking.

Accumulating evidence suggests there is an interplay of both pro and anti-apoptotic events in response to a cellular stress such as ligation of the CD20 receptor, which would result in either cell survival or death [23]. Although studies in other experimental have identified a number of cellular events associated with apoptosis, these pathways are poorly understood with anti-CD20 MoAb's. In a preliminary study, Mathas et al investigated the regulation of apoptosis in a human Burkitt-lymphoma cell line following exposure to the IDEC-C2B8 anti-CD20 MoAb [22]. Growth inhibition of cells occurred 4 hours after exposure to immobilized MoAb, followed by a significant rise in apoptotic cells as early as 6 hours later with 70% apoptotic cells after 20 hours. Study of major regulators of apoptosis failed to show a change in bcl-2, bax, bcl-x and bad protein levels after 20 hours of incubation. Of note, caspase-3 activation occurred following CD20 ligation, and the caspase-3 target proteins D4-GDI and PARP were shown to be cleaved; events that are similar to those observed with surface IgM-mediated (sIgM) apoptosis in human Burkitt lymphoma cell lines. Furthermore, these events could be abrogated by z-DEVD-fmk, an inhibitor of caspase-3. These observations suggest that both sIgM and ligation of CD20 by

MoAb share a similar apoptotic pathway and maybe clinically relevant mechanisms for rituximab-induced cell death.

It is well established that combinations of biologic and/or cytotoxic agents can potentiate tumor cell sensitivity through synergistic interactions or possibly reversal of drug resistance [24, 25]. In this regard, it is of great interest to explore such interactions with rituximab because of its unique mechanisms of action and targeted approach. Demidem et al undertook such a study to examine the sensitizing effect of C2B8 (rituximab MoAb) to cytotoxic agents on a human B-cell line [26]. For these studies, the DHL-4 tumor cell line was used because of its relative resistance to multiple agents under study including cisplatin, etoposide, doxorubicin, ricin and tumor necrosis factor (TNF-α), compared to a control T-cell line (CEM). Incubation of the DHL-4 cells with 4 μg/ml C2B8 for 72 hours sensitized the cells to all agents tested except etoposide. Using a MTT cell kill end-point, pre-treatment with C2B8 produce an approximate 1-log increase in cell kill with ricin, TNF-α, and cisplatin compared to each agent alone. There was only a modest doubling of doxorubicin cytotoxicity. Of note, the kinetics of C2B8 preincubation revealed that the maximum sensitization was achieved between 2 and 5 days, depending on the agents tested, with ricin only requiring 2 days and doxorubicin and cisplatin requiring 4 days of C2B8 exposure. The investigators studied several possible mechanisms of sensitization but found no effect of C2B8 on expression of the multidrug resistance (MDR-1) protein (gp-170) or bcl-2. In contrast, C2B8 did significantly inhibit TNF-α secretion whose expression has been associated with resistance to cisplatin and doxorubicin.

The clinical study of rituximab and chemotherapy is at the phenomenological stage with results available from a few single armed phase II trials. Nevertheless, these early trials in indolent and aggressive lymphomas suggest the presence of potentially important positive interactions [27-29]. The interpretation of the results, however, is confounded by the activity of rituximab alone and the absence of a control group. As a single agent in relapsed lymphomas, rituximab has an overall response rate of 48% with a median time to progression of 13 months in indolent histologies and a response rate of 31% with a median time to progression of over 8 months in aggressive histologies [30, 31]. In both studies, fewer than 10% of patients achieved complete responses.

When rituximab was combined with CHOP (bolus cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy, there appeared to be a significant increase in overall response rate and duration, compared to CHOP alone. In one study of 35 patients with either relapsed or untreated indolent lymphomas, 100% of patients responded with 63% complete and 37% partial responses [27]. Of significance, a recent update reported that the median for duration of response and time to progression had not been reached with a median follow-up of 46 months[32]. By comparison, the median response duration for doxorubicin-containing regimens alone in indolent lymphomas is approximately 18 months (39). There was also no difference in either response rate or duration of response among naïve and previously treated patients. Furthermore, among 8 patients who were bcl-2 positive at baseline, 7 converted to negative in both bone marrow and peripheral blood, and 5 remain negative at between 36 and 51 months.

The combination of CHOP and rituximab has also been tested in previously untreated patients with aggressive B-cell lymphomas (36). In a preliminary report of 33 patients, 97% responded with 61% complete and 36% partial responses. Because of the frequent difficulty in interpreting the significance of residual masses, the progression-free survival provides an indication of the

potential rate of cure for a regimen. In the present study, 82% of participants have remained progression-free at a median follow-up of 24 months. By comparison, approximately 48% of patients treated with CHOP alone remain progression-free at 2 years [33]. Although these results suggest that rituximab may significantly improve the treatment of aggressive lymphomas, they should be tempered by the knowledge that 72% of patients had low (0-2) risk International Prognostic Indices (IPI).

In a third phase II trial, rituximab has been combined with dose-adjusted EPOCH (infusional etoposide, vincristine and doxorubicin with bolus cyclophosphamide and prednisone) (EPOCH-R) chemotherapy in patients with previous untreated aggressive lymphomas [29]. Although the results of the trial are early, among the 10 patients enrolled, none had progressed. Furthermore, of 8 evaluable patients, 6 achieved complete responses within 2 cycles, suggesting the combination has a high fractional cell kill. The majority of these patients (70%) also had high IPI scores. These investigators also treated 11 patients with relapsed aggressive lymphomas, including 6 with refractory disease, and achieved complete and partial remissions in 6 and 2 patients respectively, suggesting EPOCH-R has a high response rate in poor prognostic patients. Two additional cases with refractory lymphomas demonstrated significant responses to the addition of rituximab to EPOCH after progressing on EPOCH alone, suggesting that rituximab may have sensitized the patients to the effects of chemotherapy[34].

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

Positron emission Tomography (PET) using F-18 fluorodeoxyglucose (FDG) has been studied as a predictive tool for treatment outcome in NHL[35]. Pre-chemotherapy FDG-PET standardized uptake values (SUV) were compared with those determined 7 and 42 days post initiation of chemotherapy in a study of 11 patients. FDG uptake parameters at day 7 and day 42 were correlated with long-term treatment outcome. The group of patients with long-term remission had significantly lower mean values at these time points as compared to those with disease relapse. Thus, early in the chemotherapy of lymphoma, FDG-PET uptake decreases but does not necessarily resolve.

Beginning with Amendment O, there will be no further enrollments for children younger than 18 years old.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Aggressive CD20 positive Diffuse Large B-cell lymphoma confirmed by Laboratory of Pathology, NCI. **NOTE:** Participants with aggressive B-cell lymphoma of the plasmablastic lymphoma sub-type who do not have surface CD20 expression, are also eligible.

2.1.1.2 HIV+ serology

2.1.1.3 All stages (I-IV) of disease

2.1.1.4 ECOG Performance status 0-4

2.1.1.5 NHL previously untreated with cytotoxic chemotherapy; however, participants may be entered if they have had prior cyclophosphamide for an urgent problem at diagnosis (e.g. epidural cord compression, superior vena cava syndrome) and/or a single dose of intrathecal methotrexate (MTX) at the time of the pre-treatment diagnostic lumbar puncture

2.1.1.6 Age ≥ 18 years

2.1.1.7 Laboratory tests (unless impairment due to respective organ involvement by tumor):

- Creatinine ≤1.5 mg/dl or creatinine clearance ≥ 50 ml/min
- Bilirubin < 2.0 mg/dl, or total bilirubin ≤ 4.5 mg/dl with direct fraction ≤ 0.3 mg/dl in participants for whom these abnormalities are felt to be due to protease inhibitor therapy
- AST and ALT ≤ 3x ULN (AST and ALT ≤ 6x ULN for participants on hyperalimentation for whom these abnormalities are felt to be due to the hyperalimentation)
- ANC ≥ 1000/mm^3
- Platelet ≥ 75,000/mm^3 (unless impairment due to ITP)

2.1.1.8 Ability of participant to provide informed consent

2.1.2 Exclusion Criteria

2.1.2.1 Previous rituximab

2.1.2.2 Pregnancy or nursing

- Doxorubicin, etoposide, vincristine and cyclophosphamide are teratogenic and may be excreted in milk

2.1.2.3 Current clinical heart failure or symptomatic ischemic heart disease

2.1.2.4 Serious underlying medical condition or infection other than HIV that would contraindicate SC-EPOCH-R

Examples include, but are not limited to:

- Severe AIDS-related wasting
- Sever intractable diarrhea
- Active inadequately treated opportunistic infection of the CNS

- Primary CNS lymphoma

2.1.2.5 Primary CNS lymphoma

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

A waiver of consent for these activities has been requested in section **10.6.2**.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the study consent. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

To be completed within 2 weeks prior to initiation of therapy, except imaging studies, which must be completed within 4 weeks of initiation of therapy. Note: no time limit on previous HIV serology.

2.2.2.1 Complete history and physical examination with documentation of abnormalities, measurable disease, and assessment of performance status

2.2.2.2 Laboratory tests

- CBC/differential
- Prothrombin time, partial thromboplastin time
- Hepatic Panel (Alkaline phosphatase, AST, ALT, Total and direct bilirubin)
- LDH
- Mineral Panel (Albumin, Calcium, Magnesium, Phosphate)
- Uric acid
- Acute Care Panel (Sodium, Potassium, Chloride, Total CO2, Creatinine, Glucose, Urea Nitrogen)
- Creatinine clearance if serum creatinine > 1.5 mg/dl
- Urinalysis
- Urine pregnancy test in women of childbearing potential

2.2.2.3 Serology

- HIV (documented from outside lab or obtained at the NIH through standard procedure viral serology testing consent.)
- Hepatitis B surface and core antigen

- Hepatitis C
- Toxoplasma antibodies

2.2.2.4 Imaging Studies

- CT chest, abdomen, and pelvis
- CT or MRI of head
- Positron Emission Tomography -may be obtained after initiation of EPOCH-R if medically inadvisable treatment delay is required

2.2.2.5 Bone marrow aspiration and biopsy

2.2.2.6 Lumbar puncture for culture, chemistry, cytology, and HIV viral load following head CT or MRI scan

2.2.2.7 Electrocardiogram

2.3 Participant Registration and Status Update Procedures

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

Please Note: As indicated in Section **10.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	*Cohort 1*	*Up to 80 subjects with HIV-associated non-Hodgkin's lymphoma*

Arms

Number	Name	Description
1	*Arm 1*	*EPOCH-Rituxan+ filgrastim in 3-week treatment cycles for a minimum of 3 cycles and a maximum of 6 cycles*

2.3.2 Arm Assignment

Subjects in Cohort 1 directly assigned to Arm 1.

2.4 Baseline Evaluation

Studies performed during Screening Evaluation will be used for Baseline Evaluation if they were completed in the time frame noted in Section **2.2.2. Exception:** Pregnancy test must be completed within 3 days prior to initiation of therapy.

3 STUDY IMPLEMENTATION

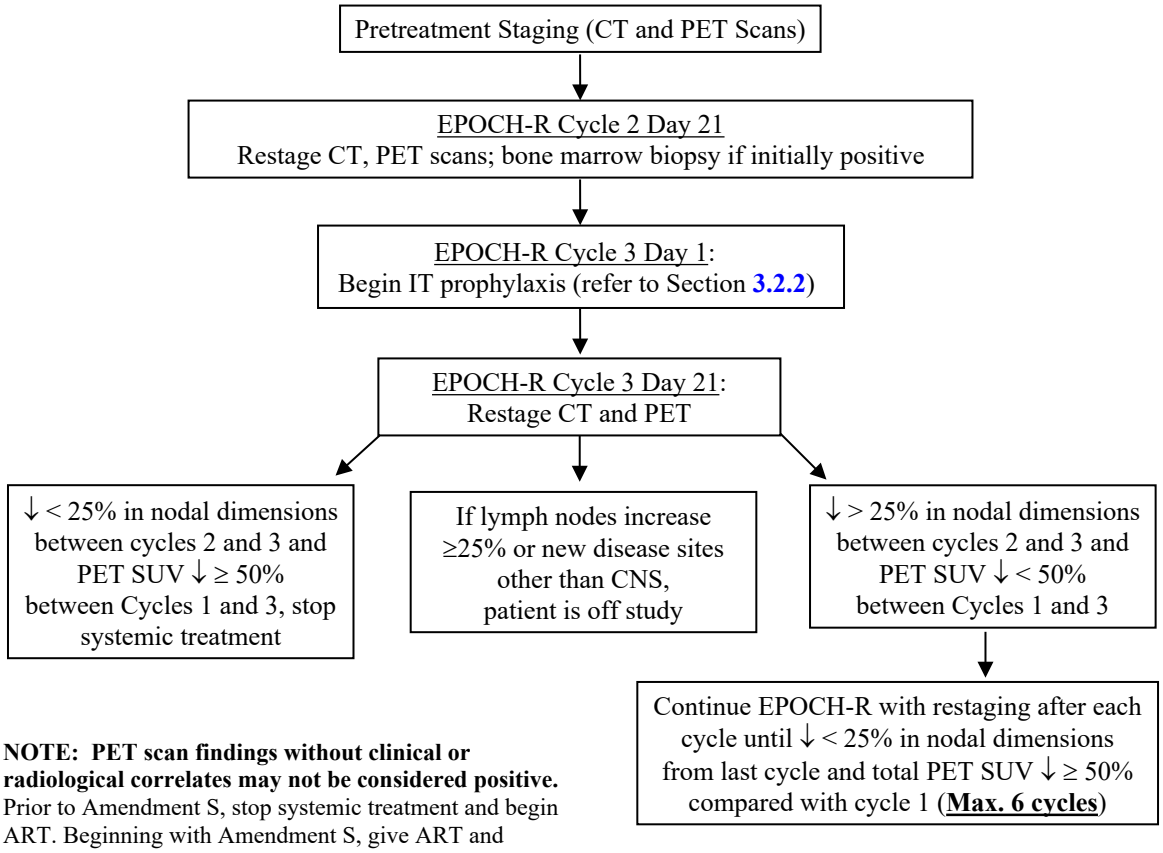
Please note that this protocol was on Administrative Hold from October 17, 2016 through December 27, 2016. Amendment Q served as the formal notification to the IRB of the Administrative Hold. During the time the protocol was on Administrative Hold, no new participants were enrolled; however, participants who were on-study were followed per protocol.

3.1 STUDY DESIGN

Participants undergo pretreatment evaluation with bone marrow biopsy, CT and FDG-PET scanning. Participants are treated every 3 weeks with SC-EPOCH-R. Treatment is for one cycle beyond complete remission (CR/Cru) - with a minimum of 3 and maximum of 6 cycles. CT and FDG-PET are repeated after cycles 2 and 3– bone marrow biopsy is repeated after cycle 2 if initially positive (and further repeated on subsequent cycles until negative).

Systemic therapy is stopped once there has been a decrease of < 25% in CT dimensions and/or a total PET SUV decrease of ≥ 50% in areas involved by lymphoma. These CT and PET parameters determine when a participant stops systemic treatment. NOTE: Prior to Amendment S, ART therapy was started 3 weeks after systemic chemotherapy had completed; ART therapy will now be given concurrently with systemic chemotherapy.

Intrathecal prophylaxis will begin on cycle 3 day 1 (refer to Section **3.2.2**). Restaging is repeated after every further cycle. If disease dimensions increase by ≥ 25% or new disease sites appear on therapy (excluding CNS disease), the participant is taken off study. Note that FDG-PET findings require clinical and radiological correlation before treatment decisions are made.



NOTE: PET scan findings without clinical or radiological correlates may not be considered positive. Prior to Amendment S, stop systemic treatment and begin ART. Beginning with Amendment S, give ART and EPOCH concurrently.

3.2 DRUG ADMINISTRATION

3.2.1 EPOCH-R Chemotherapy

- Rituximab 375 mg/m^2 IV days 1 and 5: (Day 1 dose immediately prior to infused agents and day 5 dose prior to administration of cyclophosphamide) – must be in separate port or IV line if any other cytotoxic agent is being infused.
- Etoposide 50 mg/m2 /day CIVI* over approximately 24 hours x 4 days (days 1 to 4)
- Doxorubicin 10 mg/m2 /day CIVI over approximately 24 hours x 4 days (days 1 to 4)
- Vincristine 0.4 mg/m2 /day CIVI over approximately 24 hours x 4 days (days 1 to 4)
- Prednisone 60 mg/m2/day PO x 5 days (days 1 to 5)
- Cyclophosphamide 750 mg/m2 IV (Day 5)
- Filgrastim 300 ug/day if participant weighs < 75kg or 480 ug/day if participant weighs ≥75kg SQ beginning day 6 until absolute neutrophil count recovery ≥ 5000 cells/mm^3

3.2.1.1 Rituximab administration

- See Section **12.1** for detailed information about rituximab.
- No other drugs should be added to or administered in the same IV line as rituximab.
- Consider administration of acetaminophen 500 mg PO prior to dose. Consider administration of diphenhydramine 25 – 50 mg IV prior to dose.

- Consider holding antihypertensive medication during the approximately 12-hour period prior to dosing

3.2.2 CNS Prophylaxis

3.2.2.1 Adult Guidelines:

- All participants will receive CNS prophylaxis beginning approximately day 1 cycle 3.
- Administer methotrexate (MTX) 12 mg IT days 1 and 5 every 21 days for a total of 6 doses.
- Administer leucovorin 25 mg PO (or IV) approximately 24 hours after each methotrexate dose.
- If signs or symptoms of chemical arachnoiditis occur, administer 10 mg of hydrocortisone (HDC) with the methotrexate.
- Cytarabine (Ara-C) 50 mg IT days 1 and 5 every 21 days for a total of 6 doses may be used in place of methotrexate after discussion with the principal investigator or protocol chair if methotrexate is contraindicated.

  NOTE: The days of treatment and associated supportive care may be adjusted 3 days to accommodate scheduling (e.g., holidays, vacations, etc.)

3.2.3 Antiretroviral therapy (ART)

- Prior to Amendment S:
  - Begin after final cycle of EPOCH-R. Recommend combination therapy based on Department of Health and Human Services Guidelines. However, participants may have extenuating circumstances requiring deviation from these guidelines. Additionally, referring physicians may manage this component of participant care.
- Beginning with Amendment S:
  - Generally, ART will be prescribed for HIV infected subjects.
  - Participants requiring modification of ART regimen due to contraindicated agents (e.g., cobicistat or ritonavir) or HIV resistance should generally have their ART regimen modified during the screening and baseline assessment period.
  - Integrase inhibitor-based regimens are preferred for co-administration with EPOCH.
  - Referring physicians may manage this component of participant care while liaising with study physician investigators, at the discretion of the Principal Investigator
  - Recommend combination therapy will be based on Department of Health and Human Services Guidelines for treatment of HIV infection: http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/0. However, participants may have extenuating circumstances requiring deviation from these guidelines. Certain antiretroviral agents with CPY3A4 inhibition are contraindicated.

3.3 TREATMENT MODIFICATIONS

3.3.1 Rituximab

For infusion related events or hypersensitivity reactions, the infusion rate should be slowed (e.g. for moderate flu-like symptoms of fever, chills, rigors; other infusion related reactions such as nausea, urticaria, pruritus, rash, fatigue, headache) or infusion of the drug should be interrupted or discontinued as clinically indicated (e.g. for reactions such as angioedema, hypotension, bronchospasm); following appropriate treatment and/or resolution of the reaction(s), administration of rituximab may be reinitiated at a slower infusion rate (one-half the previous infusion rate), and the rate of infusion may be incrementally increased as tolerated.

3.3.2 EPOCH

3.3.2.1 Hematological Toxicity

- Nadir Counts:

If ANC<500/mm^3 for 2 to 4 days or platelets < 25,000/mm^3 for 2 to 4 days reduce cyclophosphamide by 187 mg/m^2 (i.e. 25% of full dose). If ANC < 500/mm^3 ≥ 5 days or platelets < 25,000/mm^3 ≥5 days, reduce cyclophosphamide by 375 mg/m^2 (i.e. 50% of full dose). In the event that the cyclophosphamide dose had been reduced on the previous cycle, it may be increased on the next cycle if the following criteria are met: if ANC >500/mm^3 and platelets > 25,000/mm^3, then increase cyclophosphamide by 187 mg/m^2 each cycle, up to full dose (i.e. 750 mg/m^2).

- Day One Counts (takes precedent over nadir counts):

If ANC < 1000/mm^3 delay up to 2 weeks until ANC has increased (may use filgrastim 300 - 480 mcg SQ daily). If by day 14, ANC 750 – 999/mm^3, reduce cyclophosphamide by 187 mg/m^2. If ANC remains < 750/mm^3 on day 14, PI or protocol chair may adjust chemotherapy doses as clinically indicated.

- Bone Marrow Lymphoma and ITP:

These dose reductions do not necessarily apply to participants with bone marrow lymphoma. Reductions in these participants must be individually discussed with the PI. Platelet based dose reductions do not apply to participants with ITP: for participants with ITP, it is difficult to differentiate thrombocytopenia due to ITP from that caused by chemotherapy. Cyclophosphamide dose adjustments for thrombocytopenia in participants with ITP should be individually determined by the PI.

3.3.2.2 Non-Hematological Toxicity

Neurological toxicities:	Vincristine Dose
• Constipation > Grade 3	0.3 mg/m^2/day
• Neuropathy-sensory > Grade 3	0.3 mg/m^2/day
• Neuropathy-motor Grade 2	0.3 mg/m^2/day
• Neuropathy-motor ≥ Grade 3	none

- Grade IV toxicity: Treatment may be delayed up to 6 weeks or dose modified according to principles of best medical practice

- Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation.

3.4 ON STUDY EVALUATIONS

NOTE: See Sections **3.1** for the schema and **5** for the research blood sample collection details.

3.4.1 Research bloods and FACS analysis:

- Baseline/Cycle 1 Day 1 (up to 3 days prior to C1D1)
- Day 21 after each cycle of therapy (+7 days window)
- 2 months following treatment (±1 week window), then q 3 months x 1 year (±2 weeks window), then q 6 months x 1 year (±4 weeks window)

3.4.2 Day 1 (-3 days window) all cycles and day 21 (+7 days window) last cycle administered:

- CBC/differential; acute care panel; mineral panel; hepatic panel, LDH.

3.4.3 During cycles:

- CBC/differential BIW

3.4.4 Restaging:

- Complete by Day 21, cycles 2 through 6. Initially negative PET and/or bone marrow biopsy will not be repeated unless clinically indicated.

3.4.5 Optional blood draws

- Up to 100 ml of blood may optionally be drawn for immunological testing, establishment of cell lines, evaluation of hematologic parameters, or other studies that become clinically important during conduct of the trial. Subject consent to agreement of these optional samples will be documented in the records.
    - Blood and tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study. However, this research may only be done if the risks of the new questions were covered in the consent document or are of minimal risk. If new and significant risks are associated with the research (e.g. analysis of germ line genetic mutations) the principal investigator must obtain IRB approval. **NOTE:** Effective with Amendment R, the option for exploratory genetic testing was added and this protocol amended accordingly, including revised informed consent/procedures. See Section **5** for more information.
- Tests during Intrathecal Chemotherapy administration
    - On day one of each cycle of prophylactic intrathecal chemotherapy administration, send CSF for cell count, protein, glucose, and HIV viral load. If participant is receiving active treatment in the CNS, obtain these tests every 3-4 weeks.

3.5 CONCURRENT THERAPIES

3.5.1 Anti-retroviral therapy

Prior to Amendment S, suspend prior to SC-EPOCH-R commences. With Amendment S, anti-retroviral therapy will be given concurrently. See Section **3.2.3**.

3.5.2 Pneumocystis jiroveci prophylaxis

3.5.2.1 Bactrim DS PO 3x/week. Monday, Wednesday, Friday is the preferred schedule.

3.5.2.2 Alternatives include (other options may be considered at PI/designee discretion):

- Dapsone 50 – 100 mg PO qd or 100 mg PO 2x/week
- Aerosolized pentamidine 300 mg by inhalation.

3.5.3 MAC prophylaxis

- Consider for all participants with a historic CD4 nadir less than 100 cells/mm^3, for participants starting SC-EPOCH-R with CD4 cells 100/mm^3 or lower, or for participants whose CD4 cells fall below this level while on study. Recommend azithromycin 1200 mg once weekly, but other agents are acceptable.

3.5.4 Hepatitis B antigenemia

- For participants with serologic evidence of chronic persistent/active HBV infection, consideration will be given toward treating with lamivudine 150 mg PO daily, or other agents with demonstrated anti-HBV activity during protocol therapy
- Treatment with EPOCH-R will be modified or discontinued in any participant who develops active HBV infection or hepatitis as directed by the principle investigator to balance the risks of hepatitis reactivation with death from suboptimal treatment of lymphoma.

3.5.5 Leptomeningeal lymphoma

- If the CSF is positive for malignant cells by cytology or FACS, the participant should receive triple therapy with methotrexate, cytarabine and hydrocortisone.
    - Adult doses for IT administration: methotrexate (MTX) 12 mg, cytarabine (Ara-C) 50 mg, hydrocortisone (HDC) 50 mg. Doses for intraventricular per Ommaya administration: methotrexate 5 mg, cytarabine 50 mg, hydrocortisone 50 mg.
    - Administer leucovorin 25 mg PO (or IV) 24 hours after each dose of triple therapy (methotrexate, cytarabine and hydrocortisone).
    - In participants who cannot tolerate triple therapy, monotherapy with methotrexate and/or cytarabine may be used. Due to unforeseeable events, the above therapy may be modified as clinically indicated. All decisions should be discussed with the PI.
    - Administer leucovorin 25 mg PO (or IV) 24 hours after each dose of intrathecal single therapy with methotrexate or cytarabine) or triple therapy with methotrexate, cytarabine and hydrocortisone.
- Treatment Schedule:
    - Induction: Twice weekly for 2 weeks beyond negative cytology or FACS, for a minimum of 4 weeks (obtain CSF for cytology weekly);
    - Consolidation: Weekly for 6 weeks (obtain CSF for cytology weekly);
    - Maintenance: Monthly for 6 months (obtain CSF for cytology monthly).

3.6 RADIATION THERAPY GUIDELINES

For CNS involvement by lymphoma, radiotherapy should be considered for parenchymal brain or chemotherapy resistant leptomeningeal disease.

3.7 POST-THERAPY EVALUATION

3.7.1 Restaging:

- Chest, abdomen and pelvis CT scans two months following end of treatment, then q3 months x 12 months, then q6 months x 12 months, and then yearly thereafter. After five years, CT scans will no longer be performed.

3.7.2 Laboratory tests:

- CBC/differential, mineral panel, acute care panel, hepatic panel, LDH at restaging visits.
- HIV viral load 2 months following treatment, then q 3 months x 1 year, then q 6 months x 1 year.
- FACS lymphocyte analysis (including CD4, CD8,) 2 months following treatment, then q 3 months x 1 year, then q 6 months x 1 year. FACS analysis will be performed at the Clinical Center Laboratory as of amendment M.

3.7.3 Research blood samples will be collected at the same time points as FACS analysis (see Section **5** for collection information and schedule)

3.8 COST AND COMPENSATION

3.8.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.8.2 Compensation

Participants will not be compensated on this study.

3.8.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.9.1 Criteria for Removal from Protocol Therapy

- Completion of protocol treatment
- Inability to tolerate therapy as outlined in the protocol.
- Disease progression requiring new treatment.

- Extraordinary medical circumstances: if at any time the constraints of the protocol are judged to be detrimental to the participant's health, remove the participant from study and document the reason(s) for withdrawal.
- Participant's refusal to continue treatment. In this event, document the reason(s) for stopping treatment.
- Positive pregnancy test

3.9.2 Off Study Criteria

- Participant does not follow the instructions given by the study team
- Participant voluntary withdrawal
- Lost to Follow Up
- PI Discretion
- Study closes for any reason
- Death
- Completion of 5 year follow-up

3.9.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for three (3) consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 SUPPORTIVE CARE

4.1 CYTOMEGALOVIRUS (CMV)

Ganciclovir is usually the initial treatment choice, but due to its hematological toxicity, it should not be used without consulting the PI. Both cidofovir and foscarnet are effective in CMV, but are nephrotoxic, and will not be used if there is evidence of renal dysfunction. Urinalysis for proteinuria and creatinine clearance estimates or measurements made if these agents are to be used. All cases of CMV infection must be discussed with the PI.

4.2 FUNGAL INFECTIONS

4.2.1 Oral Candidiasis – if asymptomatic, recommend clotrimazole troches. If symptomatic, recommend oral fluconazole. Fluconazole interacts with many drugs, and can alter EPOCH pharmacokinetics and therefore must be held during chemotherapy infusions.

4.2.2 Esophageal Candidiasis – recommend oral fluconazole, but if no response, consider amphotericin B. Fluconazole interacts with many drugs, and can alter EPOCH pharmacokinetics and therefore must be held during chemotherapy infusions.

4.2.3 *Cryptococcus neoformans* infection may present as meningitis, pneumonia, or fungemia. Recommend amphotericin B and fluconazole.

4.3 MYCOBACTERIUM DISEASE

4.3.1 Mycobacterium tuberculosis – Inactive versus active infection must be distinguished. In participants with low CD4 counts, 2/3's present with extrapulmonary disease. Diagnosis may require biopsies in addition to culture. There is a high incidence of drug resistant strains. Consultation with the infectious disease service is mandatory for these participants. Combination therapy with isoniazid, rifampin, pyrazinamide, ethambutol and pyridoxine (vitamin B6) is usually initiated. These drugs may have a marked impact on EPOCH pharmacokinetics, and may cause hepatitis, bone marrow suppression, optic neuritis and peripheral neuropathy. Due to potential interactions with EPOCH pharmacokinetics, these drugs should be stopped during chemotherapy infusions, if possible.

4.3.2 Mycobacterium avium complex usually occurs in participants with CD4+ count $<100/mm^3$. Disseminated infection presents with fever, weight loss, night sweats, diarrhea, anemia, neutropenia, and thus may be difficult to differentiate from "B" symptoms. Sputum and blood cultures should be obtained. Clarithromycin or azithromycin in combination with clofazimine or rifampin are recommended. Due to potential interactions with EPOCH pharmacokinetics, these drugs should be stopped during chemotherapy infusions, if possible.

4.4 FEBRILE NEUTROPENIA

A life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics.

4.5 ANEMIA

If symptomatic or if the hemoglobin falls below 8 mg/dl erythropoietin may be considered. Red blood cell transfusions are sometimes associated with increased HIV replication and opportunistic infections, but if necessary, red blood cell transfusion support should be utilized.

4.6 THROMBOCYTOPENIA

Should be treated conservatively. In the absence of bleeding or a planned invasive procedure, platelet transfusions should be given for a platelet count below 10,000. If invasive procedures are planned or the participant develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count $> 50,000/mm^3$.

4.7 CENTRAL VENOUS ACCESS

Required for EPOCH administration. Temporary lines are preferred (removed after completion

of each infusion) and include: internal jugular line; PICC lines via the brachial vein. Other lines include semi-permanent HICKMAN, GROSHONG catheters or medi-port implanted devices. All devices will have nursing supervision to include participant self-care and cleaning/flushing of the devices.

4.8 OMMAYA RESERVOIRS

May be placed for participants requiring repeated CSF sampling and intrathecal chemotherapy. These devices will require nursing supervision to include participant self-care and cleaning of the devices.

4.9 NUTRITIONAL ASSESSMENT AND PSYCHOLOGICAL SUPPORT

AIDS is commonly complicated by malnutrition. Participants with weight loss or evidence of wasting syndrome should have a nutritional consult and nutritional intake should be optimized by either enteral or parental means. All participants on the study will be informed of and encouraged to see a NIH Social Worker for evaluation and support.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

Sample	Tube/ Volume*	Time Point(s)			Receiving/ Analyzing Lab^
		Baseline (up to 3 days prior to C1D1)	Each cycle, Day 21 (+7 days)	Post-Treatment 2 months (±1 week), q3 months x 1 year (±2 weeks), q6 months x 1 year (±4 weeks)	
Storage/ Future Use	1 x 8-10mL yellow top	X	X	X	Clinical Support Lab (Leidos)
Lymphomagenesis (optional)	4-10 x 10mL sodium heparin tubes (green top)		X	Up to 4 times over 24 months; ≥3 months between draws	Children's National Medical Center
HIV Genotyping (select subjects only)	2-4 x 10mL EDTA/ heparin tubes	X	X	X	Maldarelli Lab
*Tube type(s) may be adjusted based upon materials available and/or to ensure the best samples are collected for planned research analysis at the time of collection/procedure. ^The location of specimen processing or analysis may be adjusted with the permission of the PI or laboratory investigator Note: Platforms and procedures may be adjusted based upon current technologies and/or collaborations in place at the time of actual analysis.					

5.1.1 Blood and Tissue for Storage/Future Use

Blood will be drawn at the time points identified in Section **5.1**, processed per routine methods, and stored in the conditions described below in Section **5.2**. Tissues will be also accessed from biopsies or other procedures, no new biopsies are planned as part of this study. Portions of these samples will be used for the analyses outlined in Sections **5.1.4** and **5.1.5**, and for future identified projects upon regulatory approval (e.g., new amendment to this protocol), as appropriate.

5.1.2 HIV Genotyping

5.1.2.1 Scope of HIV Genotyping

HIV replication is rapid and error-prone in vivo, yielding a genetically diverse virus population in infected individuals. Combination antiretroviral therapy suppresses but does not eradicate HIV. The mechanism of HIV persistence is unknown, but better understanding of HIV persistence will lead to new strategies of HIV eradication. In order to investigate HIV persistence, we have been characterizing the genetics of HIV populations in infected individuals over time before and after introduction of antiretroviral therapy. It is of great interest to investigate the effects of cytotoxic chemotherapy on HIV populations. In this study, Wilson and colleagues[39] have demonstrated substantial frequencies of complete and partial responses with EPOCH and EPOCH-R chemotherapy delivered in the absence of antiretroviral therapy. In these

studies, participant viral RNA levels increased during chemotherapy, but were all suppressed to <50 copies/ml after chemotherapy was completed and antiretroviral therapy was introduced.

It will be of great interest to characterize HIV populations by performing sensitive HIV genotyping prior to, during, and/or following chemotherapeutic regimen. In these studies, we will obtain single genome sequences of HIV present in plasma. We will use phylogenetic and other population genetics analytic tools to compare the virus populations present during the course of the study period. We will determine whether chemotherapy results in change in overall genetic diversity of HIV, whether a shift in HIV populations occurs, and whether specific subpopulations of virus are affected more than others.

5.1.2.2 Methods

Starting with Amendment O (version date 08/08/2013), plasma samples collected from select participants will be sent to:

Frank Maldarelli, M.D. Ph.D.
Head, Clinical Retrovirology Section
HIV Drug Resistance Program
Building 535, Room 108E
1050 Boyles St.
Ft. Detrick
Frederick MD 21702
Phone: 301-846-5611

For each case, HIV RNA will be isolated from plasma samples taken before, during and after SC-EPOCH-R therapy. The isolated RNA will be genotyped using a detailed version of standard, commercially available HIV genotyping tests.

5.1.3 Lymphomagenesis in HIV positive vs HIV negative individuals [Beginning with Amend P (version date: 04/16/2014)] **Optional**

5.1.3.1 Rationale for lymphomagenesis correlative studies

The incidence of certain types of lymphomas in HIV positive participants is significantly higher than in HIV negative individuals. Unlike other HIV-associated malignancies such as Kaposi's Sarcoma, the establishment of ART has not improved these statistics. The mechanism for lymphomagenesis in HIV positive vs HIV negative individuals and whether there is a difference in tumor response of T cells derived from these populations is largely unknown.

Cytotoxic T cells (CTL) play a major role in fighting viral infections, including HIV and EBV. They also play a role in anti-tumor immunity. The infusion of CD8, single-epitope specific T cells have been shown to be safe in HIV participants but currently has not shown long-term efficacy. In the cancer setting, the infusion of EBV-specific CTLs has been largely safe and successful. Over 90% of HIV-associated Hodgkin's Lymphoma is EBV+ and 30-40% of HIV-associated Burkitt Lymphoma is EBV+.

Therefore, we hypothesize that we can generate polyclonal CTL products that are specific for both HIV (gag, pol, and nef) and EBV latency antigens expressed in HL (LMP1, LMP2, and EBNA1). We hypothesize that these CTLs can effectively target both HIV infection as well as tumor cells which will (1) allow for immune reconstitution following HIV clearance and (2) provide direct anti-tumor activity.

5.1.3.2 Methods

We plan to ex vivo expand T cell lines targeting both HIV and EBV antigens from HIV positive and HIV negative participants with Burkitt Lymphoma or Hodgkin Lymphoma (either currently receiving treatment or completed treatment). We can achieve this by isolating T cells from 50-100mL of whole blood and stimulating them with antigen presenting cells pulsed with peptides from HIV gag, pol, nef and EBV LMP1, LMP2, and EBNA1. We will then use a variety of immunoassays to determine these T cells' specificity and function. Our goal is to determine whether there are differences in the anti-lymphoma response between HIV positive and HIV negative participants and ultimately, to determine whether these T cells could have clinical efficacy in the setting of adoptive T cell therapy.

5.1.3.3 Samples to be collected

- Up to 100 mL of blood per collection. If other research blood is being collected and the amount approaches the research blood limit, the amount of blood collected for CNMC may be adjusted. The CNMC collaborators need at least 40 mL of blood per collection.
- Blood should be collected in sodium heparin green top tubes and kept at room temperature
- Blood will be used as whole blood or processed to obtain plasma/serum, peripheral blood mononuclear cells, or lymphocyte subsets

5.1.3.4 Sample processing

- Samples collected from select participants will be coded and sent under an MTA to:

  Children's National Medical Center
  111 Michigan Ave NW
  Washington DC 20010

- For sample pick up, contact Marcus Dean. If not available, contact one of the other individuals as provided below.

Catherine Bollard Phone #:202-476-4776 Email: CBollard@childrensnational.org
Marcus Dean Phone #: 202-476-4776 Email: MTDEAN@childrensnational.org
Russell Cruz Phone #: 202-476-2046 Email: ccruz@cnmc.org
Lauren McLaughlin Phone #: 202-476-3201 Email: LMcLaugh@childrensnational.org

5.1.3.5 Clinical information to be provided with samples

- Samples and data will be coded
- The following participant details will be sent with the samples:

- Age and sex
- Lymphoma diagnosis and Stage at diagnosis
- EBV positivity of the tumor
- Lymphoma treatment received
- Date lymphoma treatment completed
- HIV serostatus
- HLA-type, if available
- CD4 Nadir before chemotherapy
- Peak HIV Viral Load, if available
- HIV viral load at or near time of sample collection, if available

5.1.4 Detecting Minimal Residual Disease (MRD)

5.1.4.1 Rationale for MRD assessment

Detecting Minimal Residual Disease (MRD) can be a powerful tool to monitor participants' response to treatment and early detection of relapse. It is of research interest to determine if circulating tumor DNA before, during or after therapy is predictive of long-term disease-free survival. Adaptive Biotechnologies Corp will assess whether immune repertoire data (B-cell immunoglobulin receptor sequences or T-cell receptor sequences) from the Human Material can be used as biomarkers that correlate with disease-free survival. Adaptive Biotechnologies Corp will use a proprietary method, Immune Cell Receptor Sequencing (ICRS) platform, for amplifying and analyzing immune cell receptor sequences, allowing unprecedented sensitivity and specificity. Data from experiments conducted by Adaptive Biotechnologies Corp using the human material will be provided to NCI and such data provided by Adaptive Biotechnologies Corp to NCI may be used by NCI for any purpose.

5.1.4.2 Samples to be sent to Adaptive Biotechnologies Corp

Bloods from the storage/future use samples collected from select participants at the following time points may be sent, if available:

- Baseline (pre-treatment)
- After each cycle of therapy
- At each planned follow-up clinic visit until disease progression

5.1.4.3 Sample collection and processing

Portions of the other samples collected, including blood (serum, plasma and/or buffy coat), frozen or formalin fixed and paraffin embedded (FFPE) human tissue, and data from select participants will be sent.

5.1.4.4 Shipping information

Only de-identified and coded samples will be shared as described below; see Section **5.2.1** for process of sample de-identification, coding, and sample request instructions. The samples and data will be stored in the Clinical Support Laboratory, Leidos Biomedical Research, Inc. and sent in batches to Adaptive Biotechnologies Corp at the address listed below.

Adaptive Biotechnologies Corp.
1551 Eastlake Ave E
Suite 200

Seattle WA 98102

5.1.5 Comparison of methods of monitoring circulating tumor DNA

5.1.5.1 Rationale for comparing ctDNA methods

The detection of Minimal Residual Disease (MRD) in aggressive lymphomas can be a powerful tool to monitor participants' response to treatment and early detection of relapse. The field of molecular monitoring of circulating tumor DNA (ctDNA) is an emerging field, however, and the most effective technique is unknown. Multiple methods that interrogate the peripheral blood for tumor-specific molecules are under development. Some technologies that assay for the VDJ region of the immunoglobulin receptor (i.e. Adaptive Biotechnologies) have been clinically validated, but newer technologies are capable of detecting multiple somatic mutations in the ctDNA in addition to detecting the VDJ gene sequence. The ctDNA genotyping method may provide additional information that captures a broader range of participants and may identify novel patterns of clonal evolution. One such technology is the Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq) method developed by the Alizadeh lab at Stanford University. The CAPP-Seq method is an ultrasensitive capture-based targeted sequencing method that can be used on lymphoid tissue and cell-free DNA in order to define key biological features from the tumor. It is of research interest to determine how the CAPP-Seq method compares with the Adaptive Biotechnologies method (i.e. clonoSEQ) for monitoring ctDNA before, during or after therapy.

The CAPP-Seq sequencing panel (i.e. 'selector') was designed to maximize the number of participants (and mutations per participant) detected, while simultaneously minimizing the panel size and sequencing cost. Genomic regions with recurrent somatic alterations in DLBCL were therefore prioritized for selector design. As an initial step, single nucleotide variants (SNVs) and indels were collected from multiple whole exome and whole genome sequencing studies, spanning a total of 102 DLBCL tumors. A bioinformatics approach was then applied to identify recurrently mutated regions of the genome harboring single nucleotide variants (SNVs) and/or indels that maximally cover both participants and mutations per participant. As a second step, the CAPP-Seq includes reported translocation breakpoints involving IGH, BCL2, BCL6 or MYC in order to identify hyper-localized and recurrent breakpoint regions. In order to capture MYC translocations, CAPP-Seq incorporates two IGH regions covering ~50% of MYC/IGH translocations and a single MYC hotspot encompassing 15% of MYC/non-IGH translocations as well as 2 more MYC breakpoint hotspots spanning ~5kb, yielding a final predicted coverage of 90% of all MYC translocations. As a third step, CAPP-Seq includes genomic regions encompassing Ig VDJ recombination sites and mutations arising from activation-induced cytidine deaminase activity (AID/AICDA). Specifically, it includes the 10 most commonly used IgVH regions in DLBCL along with the heavy joining cluster consisting of 6 IgJH regions. CAPP-Seq also incorporates several aberrant non-Ig AID target genes, including the region spanning the transcription start site and first exon of BCL6 as well as the transcription start sites of BCL2, MYC, PIM1 and CD83. The final selector design covers 1,053 genomic regions from 268 genes, totaling 242 kb (247 kb when including additional MYC regions.

The Alizadeh lab will use the CAPP-Seq method to determine whether the tumor-specific genetic aberrations from the human material can be used as biomarkers that correlate with disease-free survival. Alizadeh lab will use a proprietary method, CAPP-Seq, for analyzing

tumor genomic DNA. Data from experiments conducted by the Alizadeh lab using the Human Material will be provided to NCI and such data provided by Alizadeh lab to NCI may be used by NCI for any purpose.

5.1.5.2 Samples to be sent to Alizadeh lab

Bloods from the storage/future use samples collected from select participants at the following time points may be sent, if available:

- Baseline (pre-treatment)
- After each cycle of therapy (if collected)
- At each planned follow-up clinic visit until disease progression

5.1.5.3 Sample collection and processing

Portions of the other samples collected, including blood (serum, plasma and/or buffy coat), frozen or formalin fixed and paraffin embedded (FFPE) human tissue, and data from select participants will be sent.

5.1.5.4 Shipping information

Only de-identified and coded samples will be shared as described below; see Section **5.2.1** for process of sample de-identification, coding, and sample request instructions. The samples and data will be stored in the Clinical Support Laboratory, Leidos Biomedical Research, Inc. and sent in batches to Alizadeh lab at the following address:

Alizadeh Lab
Stanford Cancer Institute/Stanford University
1291 Welch Road
Lorry Lokey Building, SIM1 Rm. G2115
Stanford, CA 94305-5458

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

All specimens obtained in the protocol are used as defined in the protocol. Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements.

5.2.1 Procedures for stored specimens

5.2.1.1 Clinical Support Laboratory, Leidos Biomedical Research, Inc

- The Clinical Support Laboratory, Leidos Biomedical Research, Inc. -Frederick, processes and cryopreserves samples in support of IRB-approved, NCI clinical trials. All laboratory personnel with access to participant information annually complete the NIH online course in Protection of Human Subjects. The laboratory is CLIA certified for anti-IL15 and certain cytokine measurements and all laboratory areas operate under a Quality Assurance Plan with documented Standard Operating Procedures that are reviewed annually. Laboratory personnel are assessed for competency prior to being permitted to work with participant samples. Efforts to ensure protection of participant information include:

- The laboratory is located in a controlled access building and laboratory doors are kept locked at all times. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing participant information are kept in the locked laboratory or other controlled access locations.
- An electronic database is used to store information related to participant samples processed by the laboratory.
- The database resides on a dedicated program server that is kept in a central, locked computer facility.
- The facility is supported by two IT specialists who maintain up to date security features including virus and firewall protection.
- Program access is limited to specified computers as designated by the laboratory director. Each of these computers has a password restricted login screen.
- The database sample entry program itself is accessed through a password protected entry screen.
- The database program has different levels of access approval to limit unauthorized changes to specimen records and the program maintains a sample history.
- Upon specimen receipt each sample is assigned a unique, sequential laboratory accession ID number. All products generated by the laboratory that will be stored either in the laboratory freezers or at a central repository facility are identified by this accession ID.
- Inventory information will be stored at the vial level and each vial will be labeled with both a sample ID and a vial sequence number.
- Vial labels do not contain any personal identifier information.
- Samples are stored inventoried in locked laboratory freezers and are routinely transferred to the NCI-Frederick repository facilities for long term storage.
- Access to stored clinical samples is restricted. Investigators establish sample collections under "Source Codes" and the investigator responsible for the collections, the protocol Principal Investigator, specifies who has access to the collection. Specific permissions will be required to view, input or withdraw samples from a collection. Sample withdrawal requests submitted to approved laboratory staff by anyone other than the repository source code owner are submitted to the source code owner for approval. The repository facility will also notify the Source Code holder of any submitted requests for sample withdrawal.
- It is the responsibility of the Source Code holder (the NCI Principal Investigator) to ensure that samples requested and approved for withdrawal are being used in a manner consistent with IRB approval.
- The Clinical Support Laboratory does perform testing services that may be requested by clinical investigators including, but not limited to, immunophenotyping by flow cytometry and cytokine testing using ELISA or multiplex platforms.
- When requests are submitted by the NCI investigator for shipment of samples outside of the NIH it is the policy of the laboratory to request documentation that a Material Transfer Agreement is in place that covers the specimen transfer. The laboratory does

not provide participant identifier information as part of the transfer process but may, at the discretion of the NCI investigator, group samples from individual participants when that is critical to the testing process.

- The NCI investigator responsible for the sample collection is responsible for ensuring appropriate IRB approvals are in place and that a Material Transfer Agreement has been executed prior to requesting the laboratory to ship samples outside of the NIH.

5.2.1.2 Maldarelli Laboratory

Under the direction of Dr. Maldarelli, all samples processed by the laboratory will be uniquely barcoded, with data entered using a secure computerized database and backup hardcopy process per standard laboratory practice.

Samples are stored in labeled boxes in secured freezers (i.e., -20ºC to -80ºC, or other, as appropriate) according to stability requirements; these freezers are located onsite. Access to stored clinical samples is restricted and limited to research personnel for approved analyses only (as per the IRB approved protocol).

Upon completion of planned analyses by the Maldarelli lab, leftover samples may be stored in the laboratory for future analyses or transferred to the Clinical Support Laboratory, Leidos Biomedical Research, Inc.in Frederick, MD.

5.2.2 Study Completion, Future Use and Sample Destruction

The study will remain open so long as sample or data analysis continues. Following completion of the planned analyses, samples will remain in storage as detailed above.

Tissue specimens and derived tissue lysates, RNA and DNA collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study that are not expressly stated in the present protocol. However, this research may only be done if the risks of the new questions and the proposed research have undergone prospective IRB review and approval. If new risks are associated with the research the Principal Investigator must amend the protocol and obtain informed consent from all research subjects.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved; additionally, the samples will be destroyed (or returned to the participant, if so requested) and reported per the requirements of section **7.2**

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**

5.3 GENETIC/GENOMIC ANALYSIS

5.3.1 Description of the scope of genetic/genomic analysis

At any point in the analyses, normal genome could be analyzed for comparison with other testing (e.g., HIV and/or cancer genome).

5.3.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Section **5.1.3.5** and **5.2**). In addition, a Certificate of Confidentiality has been obtained for this study.

5.3.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis.

5.3.4 Genetic Counseling

Subjects will be contacted with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Document AEs from the first study intervention, Study Day 1 through 30 days after the last agent was last administered.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

End of study procedures: Data will be stored according to HHS, FDA and NIH Intramural Records Retention Schedule regulations as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**

The following exceptions to data collection apply:

- As the toxicity profile of EPOCH-R is well defined and published, grade 1 clinical adverse events will not be recorded in the database.
- NOTE: The following was a prior data exception that no longer applies (effective with Amendment R) as it is contradictory to C3D guidelines, it is retained here for historical purposes only: *Only the highest grade of each event during a cycle of treatment will be recorded in the database.*

6.1.1 Additional Information

- All participants must have signed an Informed Consent and an on-study confirmation of eligibility form will be filled out before entering on the study.
- Data was submitted to CTEP using quarterly reports via CDUS. The final CDUS submission was for data collection through March 31, 2010. The CCR C3D database will be used to store and report data.
- Complete records must be maintained on each participant; these will consist of the hospital chart with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. A record of tumor measurements will be kept for each participant. These records will serve as the primary source material that forms the basis for the research record. All relevant data will also be entered on a computer database from which formal analyses are done. The primary source documentation will assure the following: on-study information, including participant eligibility data and participant history; flow sheets, specialty forms for pathology, radiation, or surgery; and off-study summary sheet, including a final assessment by the treating physician.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

How and where will the data be shared?

Data will be shared through:

_X_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov.

_X_ Another public repository. Insert name or names: dbGaP.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Publication and/or public presentations.

When will the data be shared?

_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

6.2.3 Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

6.3.1 Complete response (CR)

Disappearance of all signs and symptoms of lymphoma for a period of at least one month. All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse after treatment or by more than 75% in the sum of the products of the greatest diameters. The spleen, if considered to be enlarged before therapy on the basis of a CT scan must have regressed in size and must not be palpable on physical examination. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present.

6.3.2 Complete response unconfirmed (CRu)

A residual lymph node mass > 1.5 cm in greatest transverse diameter that has regressed by > 75% in sum of the products of the greatest diameters, does not change over the last two treatments, and any biopsies obtained are negative will be considered to be in CR. In organs involved by disease, any residual lesions that have decreased by > 75% in sum of the products of the greatest diameters or are < 1 cm, are consistent with scar, and stable over the last two treatments will be considered to fulfill criteria for CR.

6.3.3 Partial response (PR)

A 50% or greater decrease in the sum of the products of the longest perpendicular diameters of all measured lesions lasting for a period of at least one month. No individual lesions may increase in size and no new lesions may appear.

6.3.4 Stable disease (SD)

Tumor measurements not meeting the criteria of CR, PR, or PD.

6.3.5 Progression (PD)

Increase of 25% or more in the sum of the products of the longest perpendicular diameters of all measured lesions compared to the smallest previous measurements, or the appearance of any new lesion(s). For progressive disease, a biopsy should be performed to determine if the lesion is a reactive lymph node or lymphoma.

6.4 TOXICITY CRITERIA

This study will utilize the NCI CTC version 2.0 for toxicity and adverse event reporting. Adverse events that occur in the follow up period will not be reported or recorded unless the investigator believes they are related to protocol treatment.

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at https://irbo.nih.gov/hrpp-policy-guidelines/.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at https://irbo.nih.gov/hrpp-policy-guidelines/.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at https://irbo.nih.gov/hrpp-policy-guidelines/.

7.3 NCI CLINICAL DIRECTOR (CD) REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 IND SPONSOR REPORTING CRITERIA

NOTE: This section no longer applies, information is retained for historical reasons only. The IND sponsor of this study was CTEP, with applicable reporting requirements ending 3/15/2010.

Events requiring report were sent to the Investigational Drug Branch by AdEERS @ http://ctep.info.nih.gov/AdEERS/default.htm.

7.5 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise

the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

8.1.1 Racial/sex make-up

Subjects from both sexes and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests differences in drug metabolism or disease response would be expected in any one participant group. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between participant safety considerations and limitations on the number of participants exposed to potentially toxic treatments on the one hand and the need to explore sex and ethnic aspects of clinical research on the other. If differences in outcome that correlate with sex or ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate these differences.

8.1.2 Determination of sample size

8.1.2.1 Summary and Original Design

The main parameter of interest is the proportion of participants who are progression free at one year. It would be desirable if 70% of participants were without progression after one year from starting treatment, and inadequate if this were only 50%. Because of the relatively long time required to evaluate this endpoint (potentially a full year after the last participant has been accrued), the study will be conducted as a one-stage trial. Twenty-eight participants will be entered into this study; if at least 18 are progression free at the one-year point, then this will suggest that the treatment is associated with 91% confidence of having at least 50% progression free survival at one year. (This sample size is determined by using a one stage design with alpha=0.1, beta=0.2, p0=0.5 and p1=0.7 [36]). Confidence intervals about the 12-month DFS point will be made, and a Kaplan-Meier curve of disease free survival will also be constructed.

According to the literature and our experience, 6 cycles of chemotherapy are normally required in order to obtain a CR or CRu in this patient population. Based upon data from the first 8 participants enrolled on the trial, the mean number of cycles has been reduced to 4. We would like to provide evidence that the treatment in this protocol is resulting in a marked decline in the amount of chemotherapy administered.

We plan to enroll an additional 20 participants onto the study, consistent with the overall ceiling of 28. If we hypothesize that the mean number of cycles of chemotherapy will be 4, then with 20 participants, there is 80% power using a 0.05 level two-sided significance test, to detect a difference between a mean of 4 and a mean of 5 cycles of therapy, when the standard deviation is 1.5. We will determine the overall mean number of cycles given until CR/CRu, and will form an appropriate confidence interval about this number, to demonstrate whether this represents a marked decrease from the norm.

In addition, for purposes of safety, we will monitor the times at which participants experience disease progression. If at any time, the cumulative fraction of participants who have progressed after achieving a CR/CRu by 6 months exceeds 25%, then consideration will be given to modifying the therapy or terminating further accrual to the trial.

No formal comparison with any other group of participants is planned for this particular study.

This study is being conducted as a small pilot in order to provide information as to whether an equivalence trial should be conducted by a multi-center AIDS malignancy trials consortium or other cooperative group. It is recognized that the results from this trial are limited by the lack of a concurrent control group, but this is being done deliberately as a precursor to such a study, which would require considerably more participants and more institutions in order to be completed expeditiously.

Since beginning this study, there has emerged controversy regarding the role of rituximab in the treatment of ARL. A recently published randomized study of R-CHOP versus CHOP in ARL (Kaplan et al.) concludes that while rituximab is associated with a better tumor response, it is associated with an inferior clinical outcome because of toxicity. In our present study, we have achieved our initial goal of PFS in favor of at least 70%; current data shows a PFS of 77% at one year. This has been achieved with no treatment related deaths and with a median of 3 treatment cycles, which is 50% fewer than standard treatment. Given these very favorable results, and the need to provide further precision regarding the efficacy and safety of rituximab in ARL, we are increasing our accrual ceiling by 15 participants, for a total accrual ceiling of 43 participants. This will also allow us to gain further information on the efficacy of SC-EPOCH-R in subgroups of participants with low CD4 < 100/mm^3 and in whom rituximab was associated with increased infectious deaths in the Kaplan et al study. Hence, this study is important to evaluate the role of rituximab, especially in a heavily immunosuppressed population.

The most recent analysis performed indicated an 81.5% PFS probability at 30 months, and 77.9% survival at that point. Since these results are favorable, it would be desirable to increase the precision of the estimates and to allow further participants to enroll into a study with promising results. As such, the accrual ceiling will be set at 50 participants, to permit the maximum confidence interval width for PFS to be approximately 22% (from 69% to 91%) if the results are maintained.

The projected accrual rate for the study is at minimum 6 participants per year. The most conservative estimate thus is that it would take at maximum 28 months to meet the accrual ceiling.

8.1.2.2 Revised Design

As of December, 2011: this study enrolled 56 participants. A replacement protocol has recently opened for accrual of participants with Burkitt's lymphoma. The present study has demonstrated successful outcomes for a population of participants with DLBCL, with 84% 5 year PFS and 68% 5-year OS[39]. Thus far, we have enrolled 45 participants with HIV+ DLBCL. To provide further information on the efficacy of limited treatment among participants with germinal center B-cell like diffuse large B-cell lymphoma (GCB) and non-GCB DLBCL (which has an inferior outcome), we wish to increase the accrual by an additional 20 participants to increase the precision of the estimates of clinical outcomes for participants with DLBCL and to maintain a referral pattern until a replacement protocol is made available to subsequent participants.

Thus, the total accrual ceiling as of the amendment dated 12/28/2011 will be 80 participants.

8.1.3 Evaluation of Secondary Objectives

The secondary objectives will be primarily used to address measures of utility of CT and nuclear scans with respect to their ability to predict response outcomes by means of sensitivity, specificity and predictive value and percent correct. We recognize that the sample size will be

limited as it is being driven by the primary endpoint and thus these values will be interpreted cautiously. Non-parametric statistical tests such as the Wilcoxon signed rank test will be utilized to compared baseline CD4 cell counts and HIV viral loads with post-treatment values to test whether post treatment values differ from baseline. Although these evaluations will be considered exploratory, and no formal correction for multiple comparisons will be employed, the results will be interpreted cautiously in view of the number of potential comparisons being performed.

9 COLLABORATIVE AGREEMENTS

This study involves a number of Material Transfer Agreements (MTAs). The listing and numbers for these will be maintained outside of the protocol.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

Persons with HIV infection are at increased risk of aggressive non-Hodgkin's lymphoma. For the age group under 19 years, there is nearly a 300-fold excess in cases above that expected in the HIV-negative age-matched population, and a 60-fold excess overall for all age groups [37]. There are no established guidelines for treatment of the pediatric patient population with HIV-NHL. Maternal transmission of HIV has been substantially decreased as a result of antiretroviral therapy. Therefore, this protocol will include participants ≥ age 18 years. No selection will be based on race, ethnicity, or sex.

10.2 PARTICIPATION OF CHILDREN

Participants under the age of 18 are excluded because inclusion of an occasional younger participant will not provide generalizable information that would justify their inclusion on this study. Pediatric patients with B cell lymphoma are rare and are treated on pediatric studies.

10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. For this reason and because there is a prospect of direct benefit from research participation (Section **10.5**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR, as needed.

Please see section **10.6.1** for consent procedure.

10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts, potential benefits, and potential alternative therapies will be carefully explained to the participant or the participant's surrogate, and a signed informed consent document will be obtained.

The potential benefit is that the protocol therapy may result in long-term lymphoma remission without the high potential for lethal complications associated with standard therapy.

The potential risk is that the protocol therapy may not result in long-term lymphoma remission.

The potential risks of genetic testing are as outlined in the informed consent document (included/revised with Amendment R; version date: 04/26/2017). This study has a Certificate of Confidentiality, which helps to protect participant's research information. The researchers involved in this study cannot be forced to disclose the identity or any information collected in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the participant or the researcher may choose to voluntarily disclose the protected information under certain circumstances. Furthermore, federal agencies may review participant's records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others. The procedures involved in this protocol, with their attendant risks and discomforts and potential benefits will be carefully explained to the participant.

10.5 RISKS/BENEFITS ANALYSIS

As outlined in the introduction, standard therapy for HIV-NHL results in a median survival less than 18 months for good prognosis patients, and downwards of 6 months for poor prognosis patients. This study is aimed at developing a strategy to effectively eradicate the lymphoma without untoward damage to the immune system resulting from the therapy. Standard therapy is not effective at either of these goals. Based on preliminary evidence of EPOCH alone, and on preliminary data from rituximab plus CHOP, it is reasonable to predict that the strategy outlined in this protocol will have a high likelihood of greater anti-lymphoma activity while at the same time ameliorating therapy associated immune damage.

10.5.1 Risks of Exposure to Ionizing Radiation

This research study involves up to nine (9) CT scans (C/A/P) and up to six (6) PET/CTs. Subjects undergoing these scans will be exposed to up to 17.1 rem.

The CT scans that participant will get in this study will expose them to the roughly the same amount of radiation as 57 years of background radiation. The risk of getting cancer from the radiation exposure in this study is 1.7 out of 100 (1.7 %) and of getting a fatal cancer is 0.9 out of 100 (0.9%)

10.5.2 Risks related to Imaging

The radiation risks of the FDG and CT scans are discussed above. In addition to radiation risks, CT scans that employ contrast may cause allergic reactions, injection site reactions abdominal discomfort and fainting. MRIs carry no radiation risks but are contraindicated in participants with metal in their bodies. In patients that receive gadolinium contrast with MRIs, allergic reactions, injection site reactions and kidney damage may occur.

10.5.3 Risk related to blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

10.5.4 Risks related to Bone Marrow Biopsy

The risks associated with bone marrow biopsies are pain and bleeding at the biopsy site. Rarely, there is a risk of infection at the sampling site.

10.5.5 Risks related to Lumbar Puncture

The risks associated with lumbar puncture may include pain or bleeding at the site of needle insertion (the low back), infection, and headache. Most people tolerate this treatment without serious side effects.

10.6 CONSENT PROCESSES AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent

remotely) found at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

10.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **10.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **10.6.**

10.6.2 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

11.2 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study

management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

12 PHARMACEUTICAL INFORMATION

There is no IND associated with the use of any of the commercial agents used in this study.

This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the drugs are already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

12.1 RITUXIMAB

Refer to the FDA approved package insert for complete product information.

12.1.1 Supply

Commercially available:

- CTEP held IND until amendment dated 03-15-10
- CTEP supplied until amendment dated 03-15-10

Rituximab is provided in pharmaceutical grade glass vials containing 10 mL (100mg) or 50 mL (500) mg at a concentration of 10 mg of protein per milliliter. Please refer to the FDA- approved package insert for rituximab for product information, extensive preparation instructions, and a comprehensive list of adverse events.

12.1.2 Storage

Rituximab for clinical use should be stored in a secure refrigerator at 2º to 8°C.

12.1.3 Preparation

Rituximab will be diluted to a final volume of 0.9% Sodium Chloride or 5% Dextrose Injection to prepare a standard product with concentration of 2 mg/ml. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody

12.1.4 Stability

After dilution, rituximab is stable at 2-8 degrees C (36-46 degrees F) for 24 hours and at room temperature for an additional 24 hours.

12.1.5 Administration

A peripheral or central intravenous line will be established. During rituximab infusion, a participant's vital signs (blood pressure, pulse, respiration, temperature) should be monitored according to the standard of care. Medications readily available for the emergency management of anaphylactoid reactions should include: epinephrine (1:1000, 1 mg/mL) for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment.

Prophylaxis against hypersensitivity and infusion-related reactions associated with rituximab will include acetaminophen 650 mg and diphenhydramine hydrochloride 50-100 mg administered 30 to 60 minutes prior to starting rituximab. Participants will also receive their first dose of prednisone 60 mg/m2 (or a glucocorticoid equivalent dose of an alternative steroid) at least 60 minutes before rituximab treatment commences.

Rituximab will be administered as an intravenous infusion at 375 mg/m2 on day 1 of each cycle of EPOCH, immediately prior to starting etoposide + doxorubicin + vincristine administration. For Low Risk Participants receiving EPOCH-RR, Rituximab will also be administered on day 5 of each cycle, following etoposide + doxorubicin + vincristine but prior to cyclophosphamide administration. Rituximab infusions will be administered to participants primarily in an outpatient clinic setting.

First dose:

The initial dose rate at the time of the first rituximab infusion should be 50mg/hour (25 mL/hr) for the first 30 minutes. If no toxicity is seen, the dose rate may be escalated gradually in 50 mg/hour (25 mL/h) increments at 30-minute intervals) to a maximum of 400 mg/hour (maximum rate = 200 mL/h).

Second and Subsequent Doses (select the appropriate administration timing):

90-minute Administration

If the first dose of rituximab was well tolerated, subsequent doses may be administered over 90 minutes with 20% of the total dose given in the first 30 minutes, and remaining 80% of the total dose administered over the subsequent 60 minutes; e.g.:

Two-Step Rate Escalation	Volume to administer (X mL)
1st portion (0 – 30 minutes)	$\frac{\text{Total Dose (mg)}}{2} \times 0.2 = \text{X mL (over 30 min)}$
2nd portion (30 – 90 minutes)	$\frac{\text{Total Dose (mg)}}{2} \times 0.8 = \text{X mL (over 60 min)}$

Special Note: The 90-minute infusion scheme is not recommended for participants with clinically significant cardiovascular disease or high circulating lymphocyte counts (≧5000/mcL).

Standard Administration for Second & Subsequent Infusions

Participants who tolerate initial treatment without experiencing infusion-related adverse effects but for whom the 90-minute infusion scheme during subsequent treatments is considered inappropriate, may receive subsequent rituximab doses at the Standard Rate for Subsequent Infusions, which is as follows:

Begin at an initial rate of 100 mg/hour (50 mL/h) for 30 minutes. If administration is well tolerated, the administration rate may be escalated gradually in 100-mg/hour (50-mL/h) at 30-minute intervals to a maximum rate of 400 mg/hour (maximum rate = 200 mL/h).

CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

12.1.6 Safety Profile

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, asthenia, and hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate.

Fatal Infusion Reactions: Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.

Cardiac Events: Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

Tumor Lysis Syndrome: Tumor lysis syndrome, some with fatal outcome, has been reported and is characterized in patients with a high number of circulating malignant cells (≥25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

Renal Events: Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (≥25,000/mm2) or high tumor burden who experience tumor lysis syndrome and in patients administered concomitant cisplatin.

Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis and paraneoplastic pemphigus, have been reported in patients treated with rituximab. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported.

In addition, there have been a limited number of post-marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia.

Infectious Events: Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and was associated with decreased serum immunoglobulins in a minority of patients; the

lymphopenia lasted a median of 14 days (range, 1-588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

Hepatitis B Reactivation: Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

Other Serious Viral Infections: The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or post-marketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituxan and have resulted in death.

Progressive multifocal leukoencephalopathy (PML)

PML is a rare disease caused by the reactivation of latent JC virus in the brain. Immunosuppression allows reactivation of the JC virus which causes demyelination and destruction of oligodendrocytes resulting in death or severe disability. Rare cases of PML, some resulting in death, have been reported in patients with hematologic malignancies who have received rituximab. The majority of these patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Cases of PML resulting in death have also been reported following the use of rituximab for the treatment of autoimmune diseases. The reported cases had multiple risk factors for PML, including the underlying disease and long-term immunosuppressive therapy or chemotherapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Physicians should consider PML in any patient presenting with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, rituximab should be discontinued and reductions or discontinuation of any concomitant chemotherapy or immunosuppressive therapy should be considered.

Bowel Obstruction and Perforation: Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving Rituxan in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1−77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

Immunogenicity: Patients may develop a human anti-chimeric antibody (HACA) response with rituximab treatment. The clinical significance of this is unclear.

Pregnancy: B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in utero.

Immunization: Response rates may be reduced with non live vaccines.

Additional Safety Signals: The following serious adverse events have been reported to occur in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), eye disorders (uveitis and optic neuritis), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), that may result in fatal outcomes, and fatal cardiac failure.

See the rituximab Investigator Brochure for additional details regarding safety experience with rituximab.

12.2 DOXORUBICIN

Refer to the FDA approved package insert for complete product information.

12.2.1 Supply

Commercially available in 10, 20, 50, 100 and 150 mg vials with 50, 100, 250, 500 and 750mg, of lactose, respectively.

12.2.2 Toxicities

Myelosuppression, stomatitis, alopecia, nausea and vomiting, and acute and chronic cardiac toxicity, manifested as arrhythmias or a congestive cardiomyopathy, the latter uncommon at total cumulative doses less than 500 mg/m2. The drug causes local necrosis if infiltrated into subcutaneous tissue. Please refer to the package insert for a complete listing of all toxicities.

12.3 VINCRISTINE

Refer to the FDA approved package insert for complete product information.

12.3.1 Supply

Commercially available in 1 mg, 2 mg, and 5 mg vial sizes. Each ml contains 1 mg of vincristine, 100 mg mannitol, 1.3 mg methylparaben, and 0.2 mg propylparaben. Drug should be stored at 2º-8ºC and should be protected from light.

12.3.2 Toxicities

Peripheral neuropathy, autonomic neuropathy, and alopecia. Local necrosis if injected subcutaneously. Please refer to the package insert for a complete listing of all toxicities.

12.4 ETOPOSIDE

Refer to the FDA approved package insert for complete product information.

12.4.1 Supply

Commercially available as a concentrate for parenteral use in 100 mg vials; each ml contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg of polyethylene glycol 300, and 30.5% alcohol.

12.4.2 Toxicities

Myelosuppression, nausea, vomiting, anaphylactoid reactions, alopecia, and hypotension if infusion is too rapid. Please refer to the package insert for a complete listing of all toxicities.

12.5 ETOPOSIDE/ DOXORUBICIN/VINCRISTINE ADMINISTRATION

Stability studies conducted by the Pharmaceutical Development Section, Pharmacy Department, NIH Clinical Center, have demonstrated that admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, USP (0.9%NS) at concentrations, respectively, of 1, 25, and 125 mcg/mL; 1.4, 35, and 175 mcg/mL; 2, 50, and 250 mcg/mL; and 2.8, 70, 350 mcg/mL are stable for at least 36 hours at room temperature when protected from light. Also, admixtures containing vincristine, doxorubicin, and etoposide concentrations of 1.6, 40, and 200 mcg/mL are stable for at least 30 hours at 32°C.

For this study, etoposide, doxorubicin, and vincristine comprising a daily dose (a 24-hour supply) will be diluted in 0.9%NS. Product containers will be replaced every 24 hours to complete the planned duration of infusional treatment. Product volumes will be determined by the amount of etoposide present in a 24-hour supply of medication. For daily etoposide doses ≤130 mg, admixtures will be diluted in approximately 500 mL 0.9%NS. For daily etoposide doses >130 mg, admixtures will be diluted in approximately 1000 mL 0.9%NS.

Etoposide + doxorubicin + vincristine admixtures will be administered by continuous IV infusion over 96 hours with a suitable rate controller pump via a central venous access device.

12.6 CYCLOPHOSPHAMIDE

Refer to the FDA approved package insert for complete product information.

12.6.1 Supply

Commercially available in white crystalline formulation for intravenous injection, in vials containing 100 mg, 200 mg, 500 mg, 1gm, and 2 gm.

12.6.2 Storage and preparation

Intact vials are stable at room temperature (not to exceed 30°C). Reconstitute with appropriate amounts of 0.9% NaCl to produce a final concentration of 20 mg/ml. Discard solution after 24 hours at room temperature. Stable up to 6 days if refrigerated (2°-8°C).

12.6.3 Administration

Cyclophosphamide will be diluted in 100 mL of D5W or 0.9% NaCl and infused over 30 minutes or according to institutional standard. Participants will be instructed to drink an adequate amount of fluids and empty their bladders frequently during cyclophosphamide administration.

12.6.4 Toxicities

Myelosuppression, nausea and vomiting, hemorrhagic cystitis, and alopecia. Cystitis can be largely prevented by maintaining a good state of hydration and good urine flow during and after drug administration using the following. Please refer to the package insert for a complete listing of all toxicities.

12.6.5 Hydration Guidelines

All participants should receive 0.9%NS at the following volumes (based on cyclophosphamide dose levels) and rates with half the specified volume given before starting cyclophosphamide administration and half the volume given after completion of the cyclophosphamide administration.

Cyclophosphamide Dosage Levels	Fluid Volume and Administration Rate
1 & 2	1000 mL 0.9%NS @ 300 – 500 mL/h
Levels 3, 4, & 5	2000 mL 0.9%NS @ 300 – 500 mL/h
Levels ≥6	2500 mL 0.9%NS @ 300 – 500 mL/h

12.7 PREDNISONE

Refer to the FDA approved package insert for complete product information.

12.7.1 Supply

Commercially available in a large number of oral dosage strengths including pills and liquid formulations. Tablets should be stored in well-closed containers at temperatures between 15-30°C.

- **Doses**: Prednisone utilization will be simplified by using only 20- and 50-mg tablets to produce individual doses and by stratifying prednisone doses by a participant's body surface area (BSA), as follows:

BSA (m^2)	Each Dose
1.25 – 1.49	80 mg
1.5 – 1.83	100 mg
1.84 – 2.16	120 mg
2.17 – 2.41	140 mg
2.42 – 2.6	150 mg
2.61 – 2.69	160 mg
2.7 – 3	170 mg

12.7.2 Toxicities

Proximal muscle weakness, glucose intolerance, thinning of skin, redistribution of body fat, Cushingoid facies, immunosuppression, and propensity to gastrointestinal ulceration. Please refer to the package insert for a complete listing of all toxicities.

12.8 FILGRASTIM (G-CSF)

Refer to the FDA approved package insert for complete product information.

12.8.1 Supply

Commercially available in single use vials containing 480 mcg/vial (300 mcg/ml, 1.6 ml vial). Should be stored at 2°-8°C (do not freeze and do not shake) and is stable for at least 1 year at this temperature. Filgrastim will be given by subcutaneous injection; participant or other caregiver will be instructed on proper injection technique.

12.8.2 Toxicities

Rare anaphylactic reactions with the first dose; bone pain at sites of active marrow with continued administration. Local reactions at injection sites. Constitutional symptoms, increased alkaline phosphatase, LDH, uric acid; worsening of pre-existing inflammatory conditions. Please refer to the package insert for a complete listing of all toxicities.

12.9 HYDROCORTISONE, DEXAMETHASONE

These drugs are commercially available.

12.9.1 Hydrocortisone is a commercially available corticosteroid available as preparations that should be stored at less than 40°C (preferably between 15 - 30°C). Reconstituted solutions should be stored at 25°C or below, and unused reconstituted solutions should be discarded after 3 days.

12.9.2 Dexamethasone is a synthetic glucocorticoid. Preparations for intravenous injection should generally be stored a temperature less than 40°C (preferably between 15 - 30°C). It must be protected from light and freezing. It may be administered parenterally, or orally as tablets, elixir, solution, or concentrate.

12.10 METHOTREXATE

Refer to the FDA approved package insert for complete product information

12.10.1 Supply

Commercially available folic acid antagonist, and only the preservative-free preparation may be used for intrathecal injection.

12.10.2 Storage

It should be stored at 15-30°C and protected from light. Prior to intrathecal or intraventricular injection, the prescribed dose of methotrexate should be reconstituted/diluted with preservative-free 0.9% sodium chloride to a total volume of 5 mL. Prepared methotrexate doses should be utilized within 4 hours of preparation.

12.10.3 Toxicities

It can cause leukopenia, and as such leucovorin may be administered 24 hours after each dose. It can cause headaches, drowsiness, and blurred vision. It can also cause a transient acute neurologic syndrome manifested by confusion, hemiparesis, seizures, and coma. Please refer to the package insert for a complete listing of all toxicities.

12.11 CYTARABINE

Refer to the FDA approved package insert for complete product information

12.11.1 Supply

A commercially available pyrimidine nucleoside antimetabolite.

12.11.2 Storage

Cytarabine should be stored at –15-30°C, and used within 2 years of the date of manufacture. Prior to intrathecal injection it is reconstituted with preservative free 0.9% sodium chloride, and should be utilized within 4 hours of preparation. Prior to intrathecal or intraventricular injection,

the prescribed dose of cytarabine should be reconstituted/diluted with preservative-free 0.9% sodium chloride to a total volume of 5 mL.

12.11.3 Toxicities

It can cause myelosuppression, fever, dizziness, somnolence, and arachnoiditis. Please refer to the package insert for a complete listing of all toxicities.

12.12 LEUCOVORIN

A commercially available calcium salt of folinic acid, which is a metabolite of folic acid. Leucovorin calcium powder for injection and tablets should be stored at 15-30°C and protected from light. When reconstituted with sterile water for injection, it should be used immediately, or when reconstituted with bacteriostatic water, within 7 days. It must not be given intrathecally. Given IV or orally, it is usually non-toxic in therapeutic doses. Hypersensitivity reactions have been reported.

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14 APPENDICES

14.1 APPENDIX A: EVALUATIONS ROADMAP

NOTE: See Section **5** for applicable windows and additional information.

Evaluations Roadmap

Pre treatment	During treatment	Post treatment
Confirmation of aggressive histology NHL Confirm HIV serology Laboratory eligibility assessment HIV viral load Lymphocyte FACS analysis Research bloods Staging: CNS Bone marrow Peripheral sites PET CT	Restage following cycles 2-6 See Schema in Study Design (Section **3.1**) End of therapy research studies/samples: HIV viral load Lymphocyte FACS analysis Research bloods	Restage with CT at two months, then q3 months x 1 year, then q6 months x 1 year, and then yearly thereafter. CT scans stop after 5 years. HIV viral load Lymphocyte FACS analysis Research bloods at same time points FACS is obtained.

14.2 APPENDIX B: EPOCH ADMIXTURES: PREPARATION AND ADMINISTRATION

Preparation

All 3-in-1 admixtures dispensed from the Pharmacy will contain a 24-hour supply of etoposide, doxorubicin, and vincristine, *PLUS* 40 mL overfill (excess) fluid and a proportional amount of drug to compensate for volume lost in parenteral product containers and administration set tubing**.**

Etoposide Dose	**Volume of Fluid Containing a Daily Dose**	**Volume of Overfill** (fluid + drug)	**Total Volume in the Product** (including overfill)
≤ 130 mg	528 mL	40 mL	568 mL
> 130 mg	1056 mL	40 mL	1096 mL

Before dispensing 3-in-1 admixtures, Pharmacy staff will:

[1] Purge all air from the drug product container,
[2] Attach an administration set appropriate for use with a portable pump,
[3] The set will be primed close to its distal tip, and
[4] The set will be capped with a Luer-locking cap.

Pre-printed product labeling will identify the 'Total Volume To Infuse' and the 'Volume of Overfill (fluid + drug)'.

Bags will be exchanged daily for four consecutive days to complete a 96-hour drug infusion (unless treatment is interrupted or discontinued due to un-anticipated events).

Administration

Portable pumps used to administer etoposide + doxorubicin + vincristine admixtures will be programmed to deliver one of two fixed volumes at one of two corresponding fixed rates based on the amount of etoposide and fluid that is ordered (see the table, below).

Etoposide Dose	**Total Volume to Infuse per 24 hours**	Volume of Overfill (drug-containing fluid)*	**Administration Rate**
≤ 130 mg	528 mL	40 mL	22 mL/hour
> 130 mg	1056 mL	40 mL	44 mL/hour

* DO NOT attempt to infuse the overfill.

At the end of an infusion, some residual fluid is expected because overfill (excess fluid and drug) was added; however, nurses are asked to return to the Pharmacy for measurement any drug containers that appear to contain a greater amount of residual drug than expected.

Example at right: The amount of fluid remaining in a bag after completing a 24-hour infusion (1056 mL delivered).

