**Abbreviated Title:** EPOCH/Rituximab NHL
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# Dose-Adjusted EPOCH Chemotherapy and Rituximab (CD20+) in Adults and Children with Previously Untreated Aggressive Non-Hodgkin's Lymphoma

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**Commercial Agents**:

EPOCH-R = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab

## PRÉCIS

### Background

- The treatment of the intermediate and aggressive non-Hodgkin's lymphomas in adults and children commonly induces complete responses in a sizable fraction of the treated population, and about 2/3 of the complete responders appear to have prolonged disease-free survival.
- The present study assesses the activity and tolerability in previously untreated patients of a regimen of EPOCH infusional chemotherapy given intensively with G-CSF support.

### Objective

- Assess complete response (CR) and progression-free survival (PFS) of dose-adjusted EPOCH-Rituximab (DA-EPOCH-R) with G-CSF in aggressive B-cell lymphomas.

### Eligibility

- Non-Hodgkin's lymphomas in the following categories: mediastinal gray zone lymphoma (MGZL) and primary mediastinal B cell lymphoma (PMBL).
- Patients ≥ 12 years old.
- Any Stage for PMBL and MGZL.
- No prior systemic chemotherapy.
- HIV negative.

### Design:

- This study will estimate the complete response rate of a group of previously untreated patients and the extent to which EPOCH infusional drug delivery accompanied by a hematopoietic growth factor can increase the dose intensity of treatment.
- Patients receive prednisone orally for 5 days, a 96 hour infusion of vincristine, doxorubicin, and etoposide, and a bolus of cyclophosphamide on day 5.
- Cycles are repeated every 21 days for a total of 6-8 cycles.
- Patients with CD20 expressing tumors (i.e. mature B-cell lymphomas) will also receive rituximab, the humanized monoclonal antibody against the CD20 receptor on day 1 of each cycle.
- A total of 348 patients will be enrolled on this protocol.

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## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on 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 OBJECTIVES

### 1.1.1 Primary Objective

- Assess complete response (CR) and progression-free survival (PFS) at five (5) years of follow-up of dose-adjusted EPOCH-Rituximab (DA-EPOCH-R) with G-CSF in aggressive B-cell lymphomas

### 1.1.2 Secondary Objectives

- Assess PFS in bcl-2 + lymphomas treated with dose-adjusted EPOCH-R, and determine if it is significantly better than dose-adjusted EPOCH alone at five (5) years of follow-up
- Obtain pilot information on the CR and PFS of dose-adjusted EPOCH with G-CSF in CD20 negative B cell lymphomas, anaplastic large cell lymphomas (ALCL) and peripheral T-cell lymphomas (PTCL)
- Assess toxicity of dose-adjusted EPOCH-Rituximab with G-CSF in aggressive lymphomas
- Characterize the patterns of mdr-1, bcl-2, MIB-1 and mutant p53 expression in previously untreated lymphoma patients
- Assess the effect of EPOCH-R on ovarian function and reserve in female patients with PMBL
- Determine if molecular monitoring of the peripheral blood before, during or after therapy is predictive of long-term progression-free survival

## 1.2 BACKGROUND

Over the past 15 years the treatment of the intermediate and aggressive non-Hodgkin's lymphomas has undergone considerable evolution. The initial demonstration that these diseases

were curable with combination chemotherapy [1] was followed by many attempts to improve the efficacy of treatment. After the general acceptance of CHOP [2] as an unofficial national standard, the development of newer regimens focused on the incorporation of additional active agents into combination regimens and a general increase in the dose intensity of therapy. Data from single institution studies strongly suggest that CR rates have risen from the 40-60% range historically reported with CHOP to about 80-85% [3,4,5], this despite the now widespread use of much more sensitive imaging modalities that should make CR more difficult to diagnose. Not surprisingly, in parallel with the rise in CR rates, these same studies suggest an apparent doubling (from about 30% to about 60%) in long-term survival over this period.

Over the past few years intramural studies in the diffuse aggressive NHL subtypes have focused on the evaluation of ProMACE-CytaBOM(PC)[5]. The original version of this regimen, which featured treatment for two weeks out of every three with alternating myelosuppressive and non-myelosuppressive components, produced CR in about 85% of patients and apparently long-term disease-free survival in about 2/3 of the treated population; in addition, PC proved superior to ProMACE-MOPP (PM) in a randomized comparative trial [5]. Although the basis for this superiority is not entirely clear, it seems most likely that the significantly increased dose intensity of PC compared to PM plays a role. To explore the effects of further increases in delivered DI, the PC regimen was subsequently altered by shortening the treatment cycle from 3 weeks to 2 and by administering the regimen for a planned total of 8 cycles, thus permitting comparable total doses of drug. This altered regimen ("short-course" PC), which also permits within-patient escalation to tolerance, appears highly active. At the time of last analysis, with 53 patients on study and 46 having completed therapy, 91% of patients have achieved CR and only 17% have relapsed. In terms of prognostic factors the patients on short-course PC were generally comparable to those on the previous PC trial. Analysis of DI for each constituent agent shows that 27-65% more drug can be given on the short-course schedule than on the original PC schedule. To the extent permitted by interim analyses, therefore, the results to date are consistent with the notion that further increases in delivered DI may convey further therapeutic benefit.

Formally, however, whether the alleged superiority of the newer regimens compared to CHOP is real or not can only be answered rigorously by studies such as the recently completed Intergroup trial, which compares the newer regimens (ProMACE-CytaBOM, m-BACOD, MACOP-B) with CHOP in a prospective randomized fashion. Interim results (median follow-up 31 months) of this study [6] reported at the 1992 ASCO meeting show no significant differences in overall response, complete response, disease-free survival, or overall survival between the various treatment arms and the CHOP control. Although numerically there is actually a 9 percentage-point difference in the estimated four-year DFS rate between ProMACE-CytaBOM (45.1%) and the CHOP control (36.4%), the difference is not statistically significant, and the curves appear nearly indistinguishable over their entire time-course. The apparent equivalence of the four regimens was seen in stages III and IV analyzed separately, as well as across the five prognostic groups recently defined in the Shipp-Harrington meta-analysis of trials results from many centers worldwide. The lack of superiority of ProMACE-CytaBOM to CHOP cannot be explained by failure of the study participants to give ProMACE-CytaBOM as written; as shown by Fisher during the presentation, the received dose intensity of ProMACE-CytaBOM in this trial is equivalent to that reported by the NCI in Reference 5, using, according to Fisher, identical techniques for the calculation (personal communication).

At present, therefore, these results are consistent with the essential therapeutic equivalence of

CHOP and ProMACE-CytaBOM, at least as both regimens are currently administered in a well-disciplined cooperative group. It is somewhat disturbing to note, however, that ProMACE-CytaBOM appears to do less well in the Intergroup trial than in the NCI experience (% alive without disease: NCI 62% at 5 yrs. versus Intergroup 45% at 4 yrs.). Comparison of the ProMACE-CytaBOM patient populations in the two studies reveals the following:

| | Intergroup | NCI |
|---|---|---|
| Median Age | 57 | 47 |
| Age Range | 19-79 | 18-80 |
| Age > 64 years | 24% | 15% (>65) |
| Positive BM | 27% | 26% |
| Bulky disease | 40% | 22% |
| LDH >250 | 42% | 56% |
| Working Formulation D or E | 14% | 6% |
| Working Formulation F, G, H | 82% | 89% |
| Working Formulation J | 4% | 5% |
| Unassessable | 21% | 5% |
| Median F/U | 31 mo. | 60 mo. |

Thus, the NCI cohort is younger, has fewer patients with bulk disease, but has a somewhat higher incidence of significant LDH elevation; distribution of histologies and prevalence of bone-marrow involvement appear quite comparable. Comparison of non-randomized groups in this way is hazardous at best, but it seems at least possible that differences in the patient population might well explain some of the apparent difference in therapeutic results between the NCI cohort and the Intergroup one. Although there may be subtle differences in how the regimens are administered between the cooperative group and the NCI, the dose-intensity comparisons would appear to rule out major differences in this parameter as an explanation of the differences in results. It seems likely that, if this issue is resolvable at all, it will only be by attempts to fit the ProMACE-CytaBOM raw data from each study into a multivariate model. Finally, although the Intergroup results will probably be stable with further follow-up, it remains possible that significant differences may emerge with the passage of time.

In summary, given these uncertainties, it seems reasonable to hypothesize that the essential equivalence seen in the Intergroup study results from a combination of two factors: (a) better results with CHOP than cooperative groups were able to achieve in the past, perhaps because oncologists are much more conscious now of the importance of dose intensity and delivering therapy on time than they were in the 1970's; and (b) results with ProMACE-CytaBOM that are numerically inferior to the NCI results, not because the regimen is being delivered incorrectly but because of probable differences in the patient population. Whether this latter point is correct or not will perhaps emerge from further analysis. It should also be noted that none of the intramural experience at NCI is directly relevant to the question of the relative merits of CHOP

and ProMACE-CytaBOM, since CHOP itself has never been tested systematically here, either alone or in comparison to either ProMACE-CytaBOM or ProMACE-MOPP.

Despite the interim Intergroup results, we also think it highly like that much, if not all, of the improvement in results within the intramural NCI's patient population over the past 15 years represents a real improvement in treatment rather than an altered pattern of case selection. As previously noted, we cannot say whether any improvement in results is due to the incorporation of additional active agents or to a general increase in the dose intensity of therapy, since both have occurred as new regimens have evolved here. Nevertheless, the case for the importance of treatment intensity in the diffuse aggressive lymphomas [(7)] seems sufficiently persuasive to lead us to hypothesize that further increases in treatment intensity will translate into additional benefit to the patient.

In considering the most promising avenues for future exploration, we are most interested in exploiting the opportunities presented by two separate sets of observations:

a) Intramural studies of infusional chemotherapy (EPOCH) in previously treated patients with lymphoma have yielded very promising results. This trial was motivated by two sets of considerations: (I) the laboratory observation that cell lines expressing P-glycoprotein are much more sensitive to cytotoxic natural products given for prolonged periods at very low concentrations than to the same drugs given for brief periods at much higher concentrations [(9)]; (ii) the finding that lymphoma cells can express PgP [(10)], though they frequently do so at quite low levels. Accordingly, a regimen (EPOCH) was devised to administer three natural products (vincristine, doxorubicin, and etoposide) by continuous infusion for several days, in combination with oral prednisone and a bolus of cyclophosphamide at the end of the infusion. Patients were to be treated with cycles of EPOCH until their tumor burden reached a plateau, at which time treatment with EPOCH would continue with the addition of the PgP antagonist r-verapamil. At a recent analysis, of 33 patients with intermediate or aggressive NHL at presentation, 14 (42%) experienced CR after EPOCH therapy, and 12 (36%) had PR. An additional 20 patients with histological conversion from an originally indolent lymphoma to a more aggressive subtype were also treated with EPOCH; of these, 4 had CR and 14 PR. We were very encouraged by these results, particularly since these patients were a very heavily pretreated group, having received a median of 8 (range 3-15) drugs and 2 (range 1-8) regimens prior to entry on study. Treatment was in general well tolerated; 51% of 345 cycles were complicated by neutropenia (ANC<500) but only 17% of total cycles (33% of those cycles for which ANC<500), involving 42% of the patients on study, were attended by hospitalization for fever in the presence of neutropenia. In comparison with ProMACE-CytaBOM, the delivered DI of the three natural products was significantly higher with EPOCH; that of cyclophosphamide was the same. We think, therefore, that the promising nature of these results justifies incorporation of infusional delivery of natural products into a regimen for previously untreated patients.

b) The isolation, cloning, characterization, production, and imminent availability for clinical use of a large number of hematopoietic growth factors (G-CSF, GM-CSF. M-CSF, EPO, IL1, 3, 4, 6, 11, and the stem-cell factor) have brought much closer the possibility of eliminating the bone marrow as a limitation on the dose intensity of cytotoxic treatment. Physiological studies have shown that myeloid growth factors appear to act in concert in the bone marrow micro-environment to stimulate the growth and differentiation of

hematopoietic stem cells and lineage-restricted progenitors. Although the clinical use of growth factors to ameliorate the myelosuppression of cancer treatment is still in its infancy, human trials have already established that the use of G-CSF or GM-CSF in combination with either conventional or transplant doses of chemotherapy can shorten significantly the duration of drug-induced granulocytopenia. Studies in cell culture systems and in animal models have given plausibility to the notion that combinations of growth factors will likely be able to shorten the duration of platelet nadirs in a clinically meaningful manner, though this has yet to be demonstrated in the clinical setting. Although the optimal sequencing of growth factors and cytotoxic chemotherapy has not been worked out in detail either in animal models or in the clinic, available data suggest that it is probably safer to separate temporally the administration of cytotoxic drugs from that of growth factors that cause progenitors to enter the cell cycle.

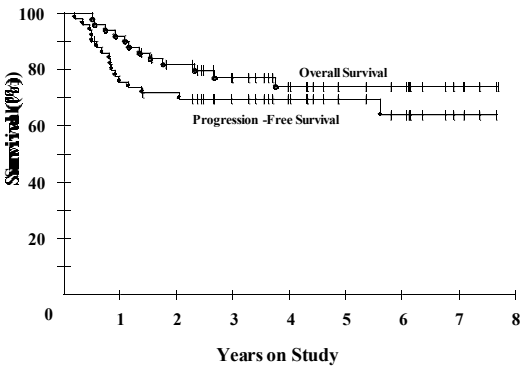
In vitro, rituximab has been shown to sensitize drug-resistant lymphoma cell lines to chemotherapy [(11)]. Additionally, preliminary results of CHOP and rituximab in untreated patients with aggressive lymphomas suggest that the combination is more active than CHOP alone [(12)]. In this trial of CHOP and rituximab, the response rate was 96% with 63% CR in 30 evaluable patients. Toxicities were those expected with CHOP or rituximab. Thus, there is significant evidence to suggest that rituximab may sensitize cells to the effects of chemotherapy and this may lead to an increase in cure rate. Based on these results and the lack of significant toxicity associated with combining rituximab with chemotherapy, we believe it important to rapidly gain experience in a pilot study with the combination of rituximab and EPOCH in patients with untreated aggressive lymphomas. The results of this pilot experience in 15 to 20 patients may be used by the cooperative groups to develop a protocol of rituximab and EPOCH.

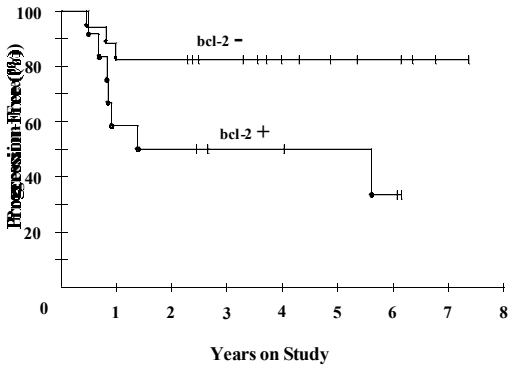
Rituximab has been well tolerated as a single agent. Of 315 patients treated in studies in which rituximab was administered as a single agent, 87% developed an adverse event. Common toxicities included fever (49%), chills (32%), nausea (18%), asthenia (16%), headache (14%), angioedema (13%), pruritus (10%), and rash (10%). Leukopenia occurred in 10.5%, but only six cases (1.9%) of grade 3 or 4 neutropenia were reported. Hypotension occurred in 10% of patients during rituximab infusion. This included a total of four grade 3 events and all recovered with saline administration and did not require vasopressors. Bronchospasm and urticaria associated with rituximab infusion each occurred in fewer than 10% of patients with grade 3 events occurring in only 1% of patients. Other toxicities occurring in fewer than 10% of individuals treated with rituximab included abdominal pain, vomiting, thrombocytopenia, anemia, myalgia, arthralgia, dizziness, and rhinitis. There have been eight reports of severe infusion-related adverse events associated with the use of rituximab, which have resulted in fatal outcomes. In 7 of the 8 cases, severe symptoms occurred during the first rituximab infusion. These symptoms included severe bronchospasm, dyspnea, hypotension, angioedema, hypoxia, pulmonary infiltrate and adult respiratory distress syndrome. Infections occurring during the treatment period and subsequently during follow-up were generally mild grade 1 or 2 adverse experiences. Infections that the investigator indicated were possibly or probably related to study treatment included pneumonia and herpes virus infection. Despite B-cell depletion, mean IgG, IgA, and IgM serum levels remained within the normal range throughout the study treatment period and during follow-up.

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 diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

A recent analysis of 50 patients with large B-cell lymphomas treated with dose-adjusted EPOCH showed an overall complete remission rate of 92%. Furthermore, progression-free (PFS) and overall survival (OS) were 70% and 74%, respectively, at a median follow-up of 52 months. Of potential importance, there was no relationship between any outcome measure and the risk factors identified in the International Prognostic Index (IPI) or the index itself, suggesting that dose-adjusted EPOCH has a different profile of cell kill compared with CHOP-based regimens.




These results suggest that dose-adjusted EPOCH may produce superior outcomes to CHOP-based regimens, even when adjusted for IPI. We were interested to assessing the relationship of markers of treatment failure, bcl-2, p53 and tumor proliferation rate (MIB-1), and outcome. This analysis showed that bcl-2 was the only factor associated with the outcome measure of PFS, with 50% and 82% PFS at 52 months, in the bcl-2 positive and negative cases, respectively [(13)]. These results suggest that bcl-2 expression may identify a subgroup of patients who will do poorly with dose-adjusted EPOCH and are consistent with the recent observations showing bcl-2 is increased in patients with activated B-cell genotypes. Based on these observations, we hypothesized that rituximab, potentially through its ability to modulate apoptosis, may increase the PFS and OS of patients with large B-cell lymphoma expressing bcl-2. Furthermore, we are interested in assessing the effects of dose-adjusted EPOCH-R in blc-2 negative cases, although to show a difference in outcome from dose-adjusted EPOCH alone will require a large number of patients and would not be the intent of this study.

Protocol update: One subset of patients with Primary Mediastinal B-cell Lymphoma was reviewed. The intent was to improve the rate of cure and eliminate the need for mediastinal radiation. There were 51 patients with untreated PMBL who were treated with DA-EPOCH-R. During a median of 5 years of follow-up, the event free survival rate was 93% and the overall survival rate was 97%. Therapy with DA-EPOCH-R obviated the need for mediastinal radiation. These results were published in the New England Journal of Medicine this year.

Another subset of patients with Burkitt Lymphoma was reviewed. They were followed for a median of 86 months. Rate of Progression Free Survival was 95% and Overall Survival was 100%. This was a comparator arm and these data were published in the New England Journal of Medicine this year.

# 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

## 2.1 ELIGIBILITY CRITERIA

2.1.1 Non-Hodgkin's lymphomas in the following categories: mediastinal gray zone lymphoma and primary mediastinal B cell lymphoma.

2.1.2 Diagnosis confirmed by staff of the Hematopathology Section, Laboratory of Pathology, NCI.

2.1.3 Patients ≥ 12 years old.

2.1.4 Stage of Patients: Any stage for MGZL and PMBL.

2.1.5 No prior systemic chemotherapy. Patients may be entered if they have had prior limited-field radiotherapy, a short course of glucocorticoids and/or cyclophosphamide for an urgent problem at diagnosis (e.g. epidural cord compression, superior vena cava syndrome).

2.1.6 HIV negative.

2.1.7 Not pregnant or nursing.

2.1.8 Adequate major organ function [in adults: serum creatinine ≤ 1.5 mg/dl or creatinine clearance > 60 ml/min; and in children serum Cr ≤ age-adjusted normal (See Table Below)]; bilirubin < 1.5 mg/dl; ANC > 1000 and platelets > 100,000) unless impairment is due to lymphoma or immune-mediated mechanism caused by lymphoma.

| Age(Years) | Maximum Serum Creatinine (mg/dl) |
|---|---|
| 12 - 15 | 1.2 |
| > 15 | 1.5 |

2.1.9 No active symptomatic ischemic heart disease, myocardial infarction or congestive heart failure within the past year. If MUGA is obtained, the LVEF should exceed 40%.

2.1.10 No other serious concomitant medical illnesses or uncontrolled active infection that would jeopardize the patient's ability to receive the regimen with reasonable safety.

2.1.11 No history of unrelated (non-lymphomatous) neoplasms within past 5 years other than non-melanoma skin cancer or in-situ cancer.

2.1.12 Ability to give informed consent.

## 2.2 RECRUITMENT STRATEGIES

This protocol may be abstracted into a plain language announcement posted on NIH websites on NIH websites and NIH Social Media platforms.

Study participants will be recruited from the population of patients screened in the lymphoid malignancy clinics of the National Institutes of Health. These will include both referrals from outside physicians as well as patient self-referrals. In addition, we participate in a locoregional consortium of eight academic institutions within the mid-Atlantic region that shares information

regarding active clinical protocols and aims to enhance patient recruitment across the region.

## 2.3 SCREENING EVALUATION

Note: Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols).

**Note:** Staging studies should be completed within 4 weeks and laboratory studies completed within 1 week to confirm study eligibility prior to the patient receiving any study intervention on the protocol.

2.3.1 Complete history and physical examination including formal documentation of measurable lesions.

2.3.2 Hgb, WBC, differential, platelets, prothrombin time, partial thromboplastin time.

2.3.3 SGOT, SGPT, LDH, alkaline phosphatase, bilirubin, albumin, calcium, phosphate, uric acid, BUN, creatinine, and electrolytes.

2.3.4 Creatinine clearance if serum creatinine > 1.5 mg/dl.

2.3.5 Computed tomography of chest, abdomen, and pelvis; and neck if indicated.

2.3.6 Bone marrow aspiration and biopsy.

2.3.7 Electrocardiogram.

2.3.8 Pregnancy test in women of childbearing potential.

2.3.9 HIV serology, hepatitis B IgG, core and surface antigen and anti-HCV Antibody.

2.3.10 MUGA or ECHO to assess cardiac ejection fractions as clinically indicated.

2.3.11 PET scan if clinically indicated or required for staging purposes.

## 2.4 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 here.

### 2.4.1 Treatment Assignment Procedures

#### 2.4.1.1 Cohorts

| Number | Name | Description |
|---|---|---|
| 1 | Cohort 1 | Patients with previously untreated aggressive non-Hodgkin's lymphoma (NHL) |

#### 2.4.1.2 Arms

| Number | Name | Description |
|---|---|---|
| 1 | Arm 1 | EPOCH-R every 3 weeks for 6 cycles |

#### 2.4.1.3 Arm Assignment

Subjects in Cohort 1 directly assigned to Arm 1.

### 2.5 BASELINE EVALUATION

2.5.1 Two 10 mL red top tubes for storage of serum in registered patients (NCI only). Samples will be sent to the Clinical Support Laboratory (CSL), Leidos Biomedical Research, Inc. in Frederick MD and stored as described in Section **5.2.1** Procedures for stored serum specimens.

2.5.2 One 10 mL cell-free DNA Tube (e.g. Streck collection tubes). Samples will be sent to CSL, Leidos Biomedical Research, Inc. in Frederick MD and stored as described in Section **5.2.1** Procedures for stored serum specimens.

2.5.3 Urinalysis

2.5.4 Lumbar puncture for CSF cytology and flow cytometry if bone marrow contains malignant cells or if there are neurological signs or symptoms.

2.5.5 Computed tomography of head if neurological signs or symptoms or if CSF cytology is positive. Use MRI with and without gadolinium if history of allergy to contrast.

2.5.6 Biopsy of accessible lymph node, where possible, for confirmation of histological diagnosis. Biopsies may be obtained for cytogenetics, immunophenotype, molecular analyses, and *mdr-1, p53, MIB-1* expression. At the NCI, biopsy of easily accessible lymph nodes should be performed for research purposes even if the diagnosis is clearly established from submitted material. Laparotomy, thoracotomy, or biopsy of relatively inaccessible lymph nodes (i.e. high axillary nodes) will only be performed if needed for definitive diagnosis and not for research purposes alone.

## 3 STUDY DESIGN

**Update**: As of January 3, 2017, the administrative hold has been removed for this protocol. Patient enrollment may begin after IRB Approval of Amendment CCC.

Please note that as of October 17, 2016 this protocol is on Administrative Hold. Amendment BBB (version date: 10/26/2016) serves as the formal notification to the IRB of the Administrative Hold. No new patients will be enrolled; however, patients currently on-study will continue to be followed per protocol.

### 3.1 STUDY DRUG ADMINISTRATION

All patients initiate therapy at Dose Level 1 of DA-EPOCH-R shown below. Doses are based on actual body weight for all patients. Future dose adjustments based on hematological toxicity as shown below.

| **Drugs** | **Dosages & Administration/Schedule** |
|---|---|
| Prednisone | 60 mg/m$^2$ PO BID days 1-5 (first dose should be given 60 minutes before starting rituximab) |
| Rituximab | 375 mg/m$^2$ day 1 (before etoposide+doxorubicin+vincristine infusion begins; see Section **11.7** for administration instructions)<br>Rituximab will only be given to patients whose tumor is CD20 +. |
| Etoposide[1] | 50 mg/m$^2$/day CIV days 1- 4 (96 hour infusion) |
| Doxorubicin[1] | 10 mg/m$^2$/day CIV days 1-4 (96 hour infusion) |

| Drugs | Dosages & Administration/Schedule |
|---|---|
| Vincristine[1] | 0.4 mg/m$^2$/day CIV days 1-4 (96 hour infusion) |
| Cyclophosphamide[2] | 750 mg/m$^2$ IV day 5 over 30-60 mins |
| Filgrastim | Body weight <75 kg: 300 mcg/dose<br>Body weight ≥75 kg: 480 mcg/dose<br>Starting on Day 6, doses are given once daily by subcutaneous injection until ANC > 5000/mcL after the neutrophil nadir. |
| Cycle Length[3] | Repeat cycle every 21 days |

[1]Begin the infusional agents immediately after rituximab is completed.
[1]Infusional agents should be administered through a central venous access device.
[2]Administer cyclophosphamide immediately after infusions are completed.
[3]Repeat cycles every 3 weeks (21 days). Delay cycle until ANC ≥ 1000/mcL **and** platelets ≥ 75,000/mcL. Use filgrastim to increase ANC and begin next cycle as soon as ANC recovers.

## 3.2 DOSE MODIFICATIONS

### 3.2.1 Goals and General Strategy

The aim of this protocol is to use neutrophil nadir as a means to normalize drug doses. Since we expect neutropenia to be the major manifestation of toxicity, we shall aim to adjust doses to achieve an acceptable level of neutropenia. If the patient has extensive bone marrow involvement at the start of therapy, the responsible physician has the option not to attenuate drug doses for unacceptable durations of neutropenia. If a patient has severe life-threatening complications, such as infection requiring intubation or pressor support, the responsible physician has the option not to escalate or to reduce doses. However, in the absence of severe complications, the dose-adjusted paradigm should be followed.

**Special Note: If a patient is unable to complete all 6 cycles of EPOCH chemotherapy and the PI determines that it is in the patient's best interest; the patient may receive all remaining doses of rituximab.**

### 3.2.2 Dose-Adjustment Paradigm for Hematologic Toxicities

- Dose adjustments above starting dose level (level 1) apply to etoposide, doxorubicin and cyclophosphamide
- Dose adjustments below starting dose level (level 1) apply to cyclophosphamide only.
- Drug Doses based on previous cycle ANC nadir:
  - If Nadir ANC ≥ 500/µl on all measurements: ↑ 1 dose level above last cycle
  - If Nadir ANC < 500/µl on 1 or 2 measurements: Same dose level as last cycle
  - If Nadir ANC < 500/µl ≥ 3 measurements: ↓ 1 dose level below last cycle

  Or

  - If nadir platelet < 25,000/µl** on 1 measurement: ↓ 1 dose level below last cycle.
- If ANC ≥ 1000/µl and platelets ≥ 75,000/µl on day 21, begin treatment.
- If ANC < 1000/µl or platelets < 75,000/µl** on day 21, delay up to 1 week. G-CSF may be started for ANC < 1000/µl and stopped 24 hours before treatment. If counts still low

after 1 week delay, ↓ 1 dose level below last cycle.

**Important: Measurement of ANC nadir based on twice weekly CBC only (3 days apart). Only use twice weekly CBC for dose-adjustment, even if additional CBC's are obtained.**

****Please Note: This does not apply to patients who have low platelets at baseline due to lymphoma or immune-mediated mechanism caused by lymphoma. In those cases, no delay or dose reduction is required. The dose adjustments for these patients will be based solely on the ANC nadir and the PI or designee's clinical judgment.**

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**Table of doses per level for adjusted agents:**

| Drugs | Drug Doses per Dose Levels | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6 |
| Doxorubicin (mg/m$^2$/day) | 10 | 10 | 10 | 12 | 14.4 | 17.3 | 20.7 | 24.8 |
| Etoposide (mg/m$^2$/day) | 50 | 50 | 50 | 60 | 72 | 86.4 | 103.7 | 124.4 |
| Cyclophosphamide (mg/m$^2$/day) | 480 | 600 | 750 | 900 | 1080 | 1296 | 1555 | 1866 |

3.2.3 Ileus

Constipation commonly occurs in patients receiving vincristine so patients should receive stool softeners as indicated. Occasionally, symptomatic ileus may occur and this should be treated with a vincristine dose reduction. Because the severity of ileus is dose related, it is usually unnecessary to stop the vincristine altogether. Furthermore, because the therapy administered in this study is potentially curative, every effort should be made to not unnecessarily reduce vincristine doses. The following guidelines for symptomatic ileus on a previous cycle should be followed.

1. Clinical ileus < 8 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting >2 days: Reduce vincristine dose 25%.
2. Clinical ileus 8-12 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting > 2 days: Reduce vincristine dose 50%.
3. Clinical ileus > 12 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting > 2 days: Hold vincristine on next cycle. May restart at 50% reduction on subsequent cycle.

3.2.4 Neurological Toxicity

- Sensory neuropathy

| Grade | % Dose of Vincristine |
|---|---|
| 2 | 100 |
| 3 | 50 |

- Motor neuropathy

| Grade | % Dose of Vincristine |
|---|---|

| | |
|---|---|
| 1 | 100 |
| 2 | 75 |
| 3 | 25 |
| 4 | 0 |

3.2.5 Hepatic and Renal Dysfunction

No dose modifications are required for hepatic dysfunction. Specifically, our results have shown no clinically significant changes in doxorubicin or vincristine drug clearance.

Etoposide should be reduced 25% on cycle one for creatinine clearance < 50 cc/min. If the creatinine clearance remains low on subsequent cycles, etoposide should remain at the reduced level as in the previous cycle. Etoposide should be returned to full dose (or escalated if indicated) once creatinine clearance > 50 cc/min. No other dose modifications for abnormal renal indices will be made for enrolled patients.

3.2.6 Dose Modification for Obese Patients

All dosing is based on the patient's BSA as calculated from actual weight. There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight.

3.2.7 Rituximab Infusion related Adverse Events

Side effects of rituximab may be infusion rate related and may be reduced by slower administration or premedication. Thus, dose reductions of rituximab will not be made. Rituximab will be discontinued for the duration of the cycles in patients with grade 4 allergic reactions. At the discretion of the local PI, rituximab may be administered on the following cycles using slower infusion rates.

### 3.3 STUDIES DURING THERAPY

3.3.1 On day 1 (or Day-1) of each cycle: Physical exam, Hgb, WBC, diff, platelets, BUN, creatinine, alk P'tase, SGOT, SGPT, LDH, and one plain 10 mL red top tube for storage. Red top tubes will be sent to the Clinical Support Laboratory (CSL), Leidos Biomedical Research, Inc. in Frederick MD and stored as described in Section **5.2.1** Procedures for stored serum specimens.

3.3.2 Twice weekly [3 days apart (+/- 1 day)]: CBC/diff.

3.3.3 Twenty-four (24) hours after the start of chemotherapy in patients who start Cycle 1 Monday – Thursday: One 10 mL cell-free DNA Tube (e.g. Streck collection tubes). Samples will be sent to CSL, Leidos Biomedical Research, Inc. in Frederick MD and stored as described in Section **5.2.1** Procedures for stored serum specimens.

3.3.4 At the end of Cycle 6: One 10 mL cell-free DNA Tube (e.g. Streck collection tubes). Samples will be sent to CSL, Leidos Biomedical Research, Inc. in Frederick MD and stored as described in Section **5.2.1** Procedures for stored serum specimens.

3.3.5 At end of cycle 4 and cycle 6: Restage with physical examination, repeat of all initially positive imaging studies, repeat BM asp and biopsy if initially positive. PET scan should be performed in patients who have a residual mass after cycle 4 and 6 as clinically

indicated. If therapy is to stop at the end of cycle 6, See Section **4.8** for what to do with patients having residual masses.

3.3.6 In selected patients, restaging may be done after cycle 2 to obtain additional information on rapidity of response.

## 3.4 DURATION OF THERAPY

3.4.1 Patients in clinical CR

Patients in clinical CR: at the end of cycle 4 receive 2 more cycles for a total of 6 cycles.

3.4.2 Patients in PR

Patients in PR with an estimated >80% reduction in initial tumor bulk whose measurable disease does not change between cycles 4 and 6, and have negative imaging after cycles 4 or 6 will be considered to be in clinical CR and receive no further treatment after cycle 6. See Section **3.6** for guidance on biopsy of residual masses.

3.4.3 Responding patients

Responding patients whose disease continues to regress between cycles 4 and 6 may (at the discretion of the PI) receive 2 more cycles following cycle 6 with a restaging of residual disease sites following cycle 8.

## 3.5 RADIATION THERAPY ALLOWANCE

In the following specific situations, patients may receive Radiation Therapy. These patients will remain enrolled on this study as the vehicle for the radiation treatment so that we can obtain pilot information on these treatment approaches.

- Patients with mediastinal B cell lymphomas (PMBL and Gray Zone) who have evidence of disease progression and/or residual disease after completing DA-EPOCH-R may receive radiation therapy if it is determined by PI to be the best course for a curative treatment.
- As noted in Section **4.5**, Patients who fail to clear or relapse in the CSF will be considered for other intraventricular therapy and/or radiation.

## 3.6 STUDIES ON COMPLETION OF THERAPY

On completion of therapy, all initially positive or abnormal blood tests, radiologic imaging studies (i.e., CT and/or MRI) , and positive biopsies (bone marrow) will be repeated. Any persistent masses will ordinarily be carefully observed and a PET scan should be performed. Because PET scans are not performed routinely during initial staging, only positive results at the termination of therapy will be interpretable. For cases in which the investigators strongly suspect residual disease (e.g. abdominal masses is PET avid), imaging-guided needle biopsy may be performed. If this is negative or unsuccessful, laparotomy may also be considered. In view of the generally negative results with invasive restaging procedures in the past, observation alone will also be acceptable. Accessible residual nodes or accessible residual masses in extranodal sites should be biopsied to confirm disease-free status. It should be noted that the decision to perform PET scans or any additional work-up would be as clinically indicated.

End of treatment visit will occur approximately 30 days after the last dose of study drug. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect

required clinical labs (specify as needed) from a local physician or laboratory. If this is not possible, patients may be assessed by telephone for symptoms.

## 3.7 FOLLOW-UP

3.7.1 Patients who achieve remission should be seen every 3 months (+/- 4 weeks) during the first follow-up year, every 4 months (+/- 4 weeks) during the second year, every 6 months (+/- 4 weeks) during the third year, and annually for years four and five (+/- 4 weeks).

3.7.2 At each planned follow-up visit: Hgb, HCT, WBC, differential, platelets, electrolytes, BUN, creatinine, SGOT, SGPT, alkaline phosphatase, LDH one 10 mL plain red top tube for storage. Red top tubes will be sent to the Clinical Support Laboratory (CSL), Leidos Biomedical Research, Inc. in Frederick MD and stored as described in Section **5.2.1** Procedures for stored serum specimens.

3.7.3 At each planned follow-up visit for three years for selected patients: one 10 mL cell-free DNA Tube (e.g. Streck collection tubes). Samples will be sent to CSL, Leidos Biomedical Research, Inc. in Frederick MD and stored as described in Section **5.2.1** Procedures for stored serum specimens.

3.7.4 CT of chest, abdomen, and pelvis: every 3 months (+/- 4 weeks) during the first follow-up year, every 4 months (+/- 4 weeks) during the second follow-up year, every 6 months (+/- 4 weeks) during the third follow-up year and yearly (+/- 4 weeks) thereafter for 2 years.

## 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

3.9.1.1 Completion of protocol treatment

3.9.1.2 Inability to tolerate therapy as outlined in the protocol

3.9.1.3 Disease progression requiring new treatment

3.9.1.4 Extraordinary medical circumstances: if at any time the constraints of the protocol are judged to be detrimental to the patient's health, remove the patient from study and document the reason(s) for withdrawal.

3.9.1.5 Patient's refusal to continue treatment. In this event, document the reason(s) for stopping treatment

3.9.1.6 Positive pregnancy test

3.9.2 Off Study Criteria

3.9.2.1 Patient voluntarily withdraws from study

3.9.2.2 Physician’s determination that withdrawal is in the patient’s best interest

3.9.2.3 Death

3.9.2.4 Completed study follow-up period

# 4 ANCILLARY THERAPY

## 4.1 PROPHYLAXIS FOR PNEUMOCYSTIS JIROVECI (FORMERLY PNEUMOCYSTIS CARINII)

- Adult patients will receive prophylaxis for Pneumocystis Jiroveci during EPOCH chemotherapy. Trimethoprim/sulfamethoxazole 1 DS P.O. QD for three days each week. Monday, Wednesday, Friday is the preferred schedule. Children ages 12-17 receive the same Trimethoprim/sulfamethoxazole dose as adults.
- Patients allergic to either component may receive inhaled pentamidine 300 mg once a month or other standard treatments.

## 4.2 RECOMMENDATIONS FOR MANAGEMENT OF GASTROINTESTINAL ISSUES IN ADULTS

4.2.1 Prevention and/or treatment of nausea and vomiting prior to and during chemotherapy:

- Ondansetron 24 mg PO x1 dose 30–60 min prior to Cyclophosphamide, followed by Ondansetron 8 mg every 12 hours for 3 more days (5 or 6 doses)
- Prochlorperazine 10 mg PO every 6 hours PRN for nausea or vomiting

4.2.2 Prevention of symptoms of gastroesophageal reflux disease (GERD) and other conditions caused by excess stomach acid:

- Omeprazole 20 mg PO once daily

4.2.3 Prevention and/or treatment of constipation:

- Docusate Sodium 50 mg + Sennosides 8.6 mg 1 tablet PO twice daily.
- Lactulose 10-20 grams (15–30 mL) PO every 6 hours PRN for constipation

## 4.3 RECOMMENDATIONS FOR MANAGEMENT OF GASTROINTESTINAL ISSUES IN CHILDREN

4.3.1 Prevention and/or treatment of nausea and vomiting prior to and during chemotherapy:

- Ondansetron 24 mg PO x1 dose 30–60 min prior to Cyclophosphamide, followed by Ondansetron 8 mg every 12 hours for 3 more days PRN (5 or 6 doses)
- Prochlorperazine (oral or IV):
    - For children < 45 kg: 2.5-5 mg Q6-8H prn for nausea or vomiting (maximum 15 mg per day)
    - For adolescents >45 kg: 10 mg PO every 6 hours PRN for nausea or vomiting

4.3.2 Prevention of symptoms of gastroesophageal reflux disease (GERD) and other conditions caused by excess stomach acid:

- Omeprazole 20 mg PO once daily (except if <20 kg – use 10 mg once daily); this is especially important during the days of prednisone (Days 1-5 of every Cycle).

4.3.3 Prevention and/or treatment of constipation:

- Docusate Sodium 50 mg + Sennosides 8.6 mg 1 tablet PO twice daily.
- Lactulose 10-20 grams (15–30 mL) PO every 6 hours PRN for constipation (except if <20 kg – use 1-1.5 mL/kg BID prn)

### 4.4 PROPHYLACTIC CENTRAL NERVOUS SYSTEM TREATMENT

- Up to 30% of patients with bone marrow involvement with large cell lymphoma, Burkitt's histology or DLBCL with c MYC-rearrangement may recur in the CNS. Thus, all patients with Burkitt's lymphoma, DLBCL with c MYC-rearrangement and all patients with other histologies who have bone marrow or disseminated bone involvement, or > 1 extranodal site and an elevated LDH will receive prophylactic CNS treatment with intrathecal methotrexate on the following schedule: methotrexate 12 mg IT on day 1 and 5 of cycles 3, 4, 5 and 6 (total of 8 treatments). Every effort should be made to administer IT therapy on Days 1 and 5. However, if scheduling or clinical constraints prohibit adhering to this schedule, it will not be considered a protocol deviation.
- Children ages 12-17 receive the same prophylactic CNS treatment as adults.

### 4.5 TREATMENT OF MENINGEAL LYMPHOMA

- If the CSF is cytologically positive for malignant cells at the start of therapy, the CSF should be treated with methotrexate and/or cytarabine as soon as possible. Suggested treatment as follows:
    - **Induction**- intrathecal methotrexate (6 mg by Ommaya or 12 mg by lumbar route) or cytarabine (70 mg by Ommaya or lumbar route). Alternatively, if combined with methotrexate, administer cytarabine 30 mg (by Ommaya or lumbar route) and hydrocortisone (15 mg by Ommaya or lumbar route). Administer induction treatment twice a week for 2 weeks past negative cytology with a minimum of 4 weeks treatment.
    - **Consolidation-**Following induction, change therapy frequency to weekly x 6.
    - **Maintenance**- Following consolidation, change therapy frequency to monthly x 4. Due to unforeseeable events, the above therapy may be modified as clinically indicated. In some cases, it may be necessary to administer radiation to the head

and/or spine or to administer intrathecal therapy using methotrexate 12 mg intrathecal (I.T.) two times a week. for 4 treatments beyond clearing, then once every other week for 4 treatments, and then once monthly for 6 treatments. Patients who fail to clear or relapse in the CSF will be considered for other intraventricular therapy and/or radiation.

- Children ages 12-17 receive the same CNS Induction, Consolidation and Maintenance treatment as adults.

### 4.6 MONITORING AND TREATMENT TO PREVENT HEPATITIS B REACTIVATION

Patients who are positive for either Hepatitis B core antibody (anti-HBc) or Hepatitis B surface antigen (HBsAg) and not acutely infected are at varying risk for reactivation of Hepatitis B, when treated with combination therapy and rituximab. These patients will have quantitative PCR testing performed for Hepatitis B virus.

Where indicated, patients will be treated with entecavir (or equivalent) to prevent hepatitis B reactivation and should have HBV DNA levels obtained monthly for at least 12 months after the last cycle of therapy by means of real-time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL.

If the HBV DNA assay becomes positive during combination therapy, study treatment should be held, and the patient should be immediately referred to a gastroenterologist or hepatologist for management recommendations.

If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving antiviral medication, study treatment must be permanently discontinued.

### 4.7 PREVENTION OF TUMOR LYSIS SYNDROME (CYCLE 1 ONLY)

- At the discretion of the PI, patients at risk of tumor lysis will receive allopurinol 600 mg 24 hours prior to the initiation of therapy followed by 300 mg daily for up to 7 days following administration of the first cycle of therapy. Additional measures such as hospitalization with aggressive IV hydration and urinary alkalization will be used at the discretion of the investigator.
- Children ages 12-17 receive the same dose of allopurinol as adults.
- Risk factors for tumor lysis include but are not limited to a diagnosis of Burkitt's lymphoma or large B-cell lymphoma with elevated LDH and uric acid.

### 4.8 TREATMENT OF PATIENTS WHO FAIL TO ACHIEVE COMPLETE RESPONSE

- Patients in PR, but with biopsy-proven residual disease should be considered for entry onto salvage therapy with high-dose chemotherapy.
- These patients will stay on this study and be followed for survival.

## 5 BIOSPECIMEN COLLECTION

### 5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

5.1.1 Assessment of Ovarian Function and Reserve

5.1.1.1 The following hormone levels will be measured, using stored serum samples, to assess the effect of EPOCH-R on ovarian function and reserve in female patients with PMBL:

- Luteinizing hormone (LH)
- follicle-stimulating hormone (FSH)
- inhibin B
- anti-Muellerian hormone (AMH)
- testosterone and 25-hydroxy-vitamin D

5.1.1.2 All hormone measurements will be performed by the Clinical Center Department of Laboratory Medicine, except inhibin B and AMH, which will be sent by the laboratory staff to American Esoteric Laboratories.

5.1.1.3 Stored samples from the following time points will be used:

- before treatment
- after the last cycle of DA-EPOCH-R (after cycle 6 or 8)
- 12 months after completion of chemotherapy

5.1.1.4 Female patients with PMBL may be contacted by telephone, by mail or in-person and asked to participate in an interview, using the questionnaire in **APPENDIX 2**, to assess the effect of EPOCH-R on fertility and psychosocial/emotional well-being in female patients with PMBL. Their consent to participate in this sub-study will be documented in the medical record.

5.1.2 Blood for serum storage

Blood will be drawn at the time points identified in Sections **2.4** Baseline Evaluation, **3.3** Studies During Therapy and **3.7** Follow-up and stored in the conditions described below.

5.1.3 Tissue biopsy

Tumor biopsies may be obtained for cytogenetics, immunophenotype, molecular analyses, and *mdr-1, p53, MIB-1* expression. For storage of tissue specimens see below.

5.1.4 Lymphomagenesis in HIV positive vs HIV negative individuals

[Beginning with Amend VV (version date: 04/14/2014)] **In select patients, per PI discretion.**

5.1.4.1 Rationale for lymphomagenesis correlative studies

The incidence of certain types of lymphomas in HIV positive patients 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 patients 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.

5.1.4.2 Methods

We plan to ex vivo expand T cell lines targeting both HIV and EBV antigens from HIV positive and HIV negative patients with any type of 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 patients and ultimately, to determine whether these T cells could have clinical efficacy in the setting of adoptive T cell therapy.

5.1.4.3 Sample collection time points

- After completion of chemotherapy
- One to 4 episodes in a 24 month period
- Minimum of 3 months between blood draws

5.1.4.4 Samples to be collected

- 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

5.1.4.5 Sample processing

- Samples collected from select patients 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<br>Phone #: 202-476-4776<br>Email: CBollard@childrensnational.org |
| Russell Cruz<br>Phone #: 202-476-2046<br>Email: ccruz@cnmc.org |
| Marcus Dean<br>Phone #: 202-476-4776<br>Email: MTDEAN@childrensnational.org |
| Lauren McLaughlin<br>Phone #: 202-476-3201<br>Email: LMcLaugh@childrensnational.org |

5.1.4.6 Clinical information to be provided with samples

- Samples and data will be coded
- The following patient 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

5.1.5 Detecting Minimal Residual Disease (MRD)

5.1.5.1 Rationale for MRD assessment

Detecting Minimal Residual Disease (MRD) can be a powerful tool to monitor patients' response to treatment and early detection of relapse.

Coded, frozen or formalin fixed and paraffin embedded (FFPE) human tissue, blood samples (serum, plasma and/or buffy coat) and data from select patients will be sent to Adaptive Biotechnologies Corp. 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.

5.1.5.2 Stored serum samples to be sent to Adaptive Biotechnologies Corp

Serum samples that were collected from select patients at the following collection time points:

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

The samples and data will be retrieved from the Clinical Support Laboratory, Leidos Biomedical Research, Inc., batched and sent to Adaptive Biotechnologies Corp at the address listed below.

Adaptive Biotechnologies Corp.
1551 Eastlake Ave E
Suite 200
Seattle WA 98102

5.1.5.3 Blood samples will be collected prospectively after approval of Amendment AAA (version date 8/11/2016) at the following time points:

- Baseline (pre-treatment)
- 24 hours after the start of chemotherapy (when feasible)
- After Cycle 6
- Each planned follow-up clinic visit for 3 years

The samples (plasma and/or buffy coat) and data collected prospectively will be stored in the Clinical Support Laboratory, Leidos Biomedical Research, Inc. and later sent in batches to Adaptive Biotechnologies Corp at the address listed below.

Adaptive Biotechnologies Corp.
1551 Eastlake Ave E
Suite 200
Seattle WA 98102

5.1.6 Systemic ALK-positive anaplastic large-cell lymphoma (ALCL) of adults: Meta-analysis of prognostic factors

5.1.6.1 Rationale for contributing data to this international study

Anaplastic large cell lymphoma (ALCL) is a rare T-cell lymphoma and in an effort to gain better understanding into the outcome and prognosis of this disease with standard approaches, we were invited to participate in an international study/meta-analysis led by David Sibon, MD, PhD and Kerry Savage, MD. They will use the data as above in a meta-analysis from various international centers and groups. This is a rare disease and few sites will be able to contribute. We have already published data on our patients and it will strengthen the results of meta-analysis if the samples size is large. Contributing our data to the study will increase the sample size.

The following coded data from adult patients with ALK+ ALCL will be sent:

Patient and disease characteristics at diagnosis:

- Age at diagnosis

- Sex
- Date of pathologic diagnosis or study entry
- B symptoms (yes or no)
- Performance status (0 to 4)
- Ann Arbor stage (I to IV)
- Extranodal sites more than 1
- Bulky disease ≥ 10 cm
- Site of involvement:
  - Mediastinum
  - Bone marrow
  - Bone
  - Liver
  - Spleen
  - Skin
  - Lung
  - Central nervous system
  - Soft tissue
  - Kidney
  - Adrenal
  - Gastrointestinal
  - Epidural

Labs at diagnosis

- Lactate dehydrogenase (LDH): normal vs elevated
- Beta2-microglobulin (< vs ≥ 3 mg/L)
- Hemoglobin (g/dL)
- Platelets (G/L)

Pathology (by definition all cases are CD30+ and ALK+):

- Morphologic variant (presence vs absence of a small cell/lymphohistiocytic component)
- CD2
- CD3
- CD4
- CD5
- CD8
- EMA
- TIA1 / granzyme B / perforin

First-line treatment (chemotherapy with or without radiotherapy):

- Anthracycline included in first-line chemotherapy regimen (yes or no).
- Etoposide included in first-line chemotherapy regimen (yes or no).
- Radiotherapy included in first-line treatment (yes or no).
- Chemotherapy regimen:
  - CHOP-14
  - CHOP-21
  - CHOEP-14
  - CHOEP-21

- HiCHOEP-14
- HiCHOEP-21
- MegaCHOEP
- ACVBP
- DA-EPOCH
- Other regimen (state regimen)

- Number of cycles of chemotherapy regimen
- Upfront autologous stem-cell transplantation (yes or no)

Outcomes after first-line treatment:

- Relapse/progression (yes or no)
  - If yes: date of relapse/progression
- Date of last follow-up
- Status at last follow-up (alive or dead)
  - If dead: cause of death:
    - ALCL
    - Other (state cause)

5.1.7 Comparison of methods of monitoring circulating tumor DNA

5.1.7.1 Rationale for comparing ctDNA methods

The detection of Minimal Residual Disease (MRD) in aggressive lymphomas can be a powerful tool to monitor patients' 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 patients 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.

Coded, frozen or formalin fixed and paraffin embedded (FFPE) human tissue, blood samples (serum, plasma and/or buffy coat) and data from select patients will be sent to Alizadeh lab. 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 patients (and mutations per patient) 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 patients and mutations per patient. 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.

5.1.7.2 Stored serum samples to be sent to Alizadeh lab

Serum samples that were collected from select patients at the following collection time points:

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

The samples and data will be retrieved from the Clinical Support Laboratory, Leidos Biomedical Research, Inc., coded batched and sent to the Alizadeh lab at the following address.

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

5.1.8 Determining clinical significance of post-therapy positron emission tomography (PET) scans

5.1.8.1 Rationale for post-therapy PET imaging

The aggressive lymphomas included in this protocol are treated with curative intent. Dose-adjusted EPOCH-R has demonstrated the ability to cure a high proportion of patients with DLBCL subtypes, especially primary mediastinal B-cell lymphoma (PMBL). In the original series from this protocol, 51 patients were treated with DA-EPOCH-R and the 5-

year event-free survival was 93%. Importantly, this study demonstrated that many patients who were free of disease at the end-of-therapy had persistent areas of focal uptake on PET scans. Thus, the positive predictive value of end-of-therapy PET scans was limited. After more years of follow-up, it is critically important to update the series, demonstrate lack of late relapses, and validate these findings in a cohort of patients treated at an outside institution, Stanford University.

5.1.8.2 Clinical information to be sent to Stanford University

Coded clinical information including baseline demographics, clinical outcomes, and results of imaging scans (CT scans and PET scans, if done) will be sent to Ranjana Advani at Stanford University. She will collate the clinical information to determine if post-therapy PET scans are predictive of disease-free survival in PMBL and mediastinal gray zone lymphomas (MGZL).

- Age at diagnosis
- Sex
- Date of pathologic diagnosis or study entry
- B symptoms (yes or no)
- Performance status (0 to 4)
- Ann Arbor stage (I to IV)
- Extranodal sites more than 1
- Bulky disease ≥ 10 cm
- Site of involvement:
  - Mediastinum
  - Bone marrow
  - Bone
  - Liver
  - Spleen
  - Skin
  - Lung
  - Central nervous system
  - Soft tissue
  - Kidney
  - Adrenal
  - Gastrointestinal
  - Epidural
- Labs at diagnosis
  - Lactate dehydrogenase (LDH): normal vs elevated
  - Beta2-microglobulin (< vs ≥ 3 mg/L)
  - Hemoglobin (g/dL)
  - Platelets

## 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, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below for an indefinite amount of time. The PI will report any loss or any unanticipated destruction of samples as a deviation. Reporting will be per the requirement in section **7.2.**

5.2.1 Procedures for stored serum specimens

The Clinical Support Laboratory, Leidos Biomedical Research, Inc., processes and cryopreserves samples in support of IRB-approved, NCI clinical trials. All laboratory personnel with access to patient information annually complete the NIH online course in Protection of Human Subjects. The laboratory is CLIA certified for CD4 immunophenotyping 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 patient samples. Efforts to ensure protection of patient 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 patient information are kept in the locked laboratory or other controlled access locations.
- An electronic database is used to store information related to patient 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, typically 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 (generally 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 patient identifier information as part of the transfer process but may, at the discretion of the NCI investigator, group samples from individual patients 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.

5.2.2 Procedures for storage of tissue specimens

Tumor biopsies will be submitted in native condition to the Department of Pathology, NCI, NIH and handled according to routine procedures. Initial processing of samples for research will depend on the size of the tumor biopsy. For core biopsies the research sample will typically consist of 2 cores in a microcentrifuge vial snap frozen on dry ice. Surgical lymph node biopsies may in addition be processed for single cell suspension, additional vials of snap frozen tissue and OCT embedded tissue.

Tumor samples may be viably frozen, typically at concentrations of 20-100x106/mL in FCS with 10% DMSO using a temperature controlled freezing process to optimize sample viability. Samples will be transferred to Nitrogen tanks for long term storage.

Tumor samples may be further processed. Additional purification may be carried out by selection with magnetic beads binding to appropriate surface molecules, typically CD19. For analysis cells may be lysed to obtain RNA (using Qiagen manufactured kits or similar kit) or proteins (salt and/or triton containing buffers with addition of protease and phosphatase inhibitors). Integrity of RNA is monitored by gel electrophoresis and concentration of RNA or protein is measured spectrophotometrically.

5.2.3 Blood for Pharmacokinetic analysis

The blood that was collected for PK analysis is currently stored as plasma in screw-capped polypropylene vials in a -70 C degree freezer which is located in a common freezer room in the 1W lab area of the Pediatric Oncology Branch. The freezer temperature is continuously

monitored for +/- temperature differences of 10 degrees C. Samples are stored by patient initials as well as date and time of sample in individual boxes within this freezer. Records of samples stored are catalogued in a Filemaker database which is maintained by Pharmacology and Experimental Therapeutics research nurses and is password protected so that only members of the section have access to patient sample information. Results from the analyses of drug levels from these samples are maintained in an Excel database maintained on a password-protected computer in the laboratory of Dr. Brigitte Widemann. Both computers containing patient sample information are backed on a regular (at least one time per week) basis.

# 6 DATA COLLECTION AND EVALUATION

## 6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) 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 study intervention was administered. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

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 patient's outcome.

### 6.1.1 Special Considerations for Data Collection/Recording

- As the toxicity profile of EPOCH-R is well defined and published, grade 1 clinical adverse events will not be recorded in the database. Only the highest grade of each event during a cycle of treatment will be recorded in the database.
- No Concomitant therapy except intrathecal therapy and blood product transfusions will be recorded in the database.

### 6.1.2 Other Information

**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**.

## 6.2 RESPONSE CRITERIA

### 6.2.1 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 consider 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.

### 6.2.2 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, has a negative PET scan, 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.

### 6.2.3 Partial response (PR)

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.

- Patients in PR with an estimated >80% reduction in initial tumor bulk whose measurable disease does not change between cycles 4 and 6, and have a negative PET scan after cycles 4 or 6 will be considered to be in clinical CR.

### 6.2.4 Stable disease (SD)

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

### 6.2.5 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)

# 7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

## 7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found **here.**

## 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 **here.**

### 7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found **here**.

## 7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP/IRB in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

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

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

## 7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

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

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

The principal investigator will review adverse event and response data on each patient 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.

This study was monitored by the Clinical Data Update System (CDUS) version 1.1 through amendment dated 3-8-10. Cumulative CDUS data was submitted quarterly to CTEP by electronic means. Reports were due January 31, April 30, July 31 and October 31. The final report to CTEP via CDUS was submitted 3-31-2010.

# 8 STATISTICAL CONSIDERATIONS

The objectives of this amendment are to determine whether large B-cell lymphomas expressing BCL-2 (+) patients may experience an improved progression free survival with EPOCH-R compared to EPOCH alone, and to obtain a concurrent, precisely determined measure of

progression free survival in patients who are BCL-2(-) in order to provide a reliable target for the BCL-2 (+) patients to try to achieve. The sample size for this amendment will be guided by the number of BCL-2 (+) patients. In order to rapidly address this issue, patients entered with large B-cell lymphomas expressing CD20+ will all be assigned to receive EPOCH-R, and the determination of BCL-2 level will be made subsequent to commencement of treatment. It should also be noted that at this time 25 patients with CD20+ large B-cell lymphomas have been entered, and of 20 evaluable patients for response, 17 have achieved complete remission and none have relapsed (100% DFS), with a median follow-up of 12 months [(14)]. Of these, at least 8 are known to be bcl-2.

The Dixon-Simon method will be used to determine the number of BCL-2 (+) patients to enroll onto the trial, using the 8 patients enrolled on the prior EPOCH alone arm who are BCL-2 (+) as controls. For these calculations, it is assumed that the 5 of 12 patients who have not yet progressed on the EPOCH trial are still allowed to be followed, that we would have only 12 patients in this historical group, and that the median PFS for this group was reached by 2 years. We will assume 3 years of accrual of new patients, 4 years of follow-up, 0.05 one-sided significance, and 80% power.

Use of this method determined that a total of 33 new BCL-2 (+) patients would be required in order to detect a difference of 75% PFS at 2 years (EPOCH-R) vs. 50% at 2 years (EPOCH), while only 20 such patients would be needed to detect a difference of 80% PFS vs. 50% PFS at 2 years. We intend to accrue 20 newly identified, additional BCL-2 (+) patients, but to also use the (8) prior BCL-2 (+) patients, with the analyses being done in two ways. First, the most rigorous analysis with 21 future BCL-2 (+) patients on EPOCH-R will be done comparing their PFS, using Kaplan-Meier curves and a log-rank test, to the 12 EPOCH alone BCL-2 (+) patients. Then, an analysis using the (8) already accrued BCL-2 (+) patients plus the 20 newly accrued BCL-2 (+) patients will be done compared to the 12 with EPOCH alone; because it could be argued that this analysis includes patients who were already identified as doing well prior to the start of this amendment, this analysis will be considered secondary to the one with 20 prospectively enrolled patients.

Accrual of CD20 large B-cell patients to the dose-adjusted EPOCH-R arm will be halted after 20 prospectively enrolled (20+(8) = 28 total) evaluable BCL-2 (+) patients have been accrued. Since it is expected that slightly more than half of all patients will be BCL-2 (-), this is expected to require up to 50 newly accrued patients. The prior EPOCH alone arm demonstrated that the BCL-2 (-) patients had a significantly longer PFS than the (+) patients. As such, the large B-cell lymphomas do not necessarily comprise a completely homogeneous group prognostically, and the outcome for the BCL-2 (-) patients would constitute a valid target for the (+) patients. Since BCL-2 status cannot be determined until several weeks after enrollment, and delay of therapy would negatively impact outcome and recruitment, the BCL-2 (-) patients will enrolled and analyzed, both to provide a more precise estimate of the overall PFS experience in these patients than would be realized by the limited number of such patients enrolled already, and will also be used in a formal comparison with the BCL-2 (+) patients in order to determine whether the two groups now have similar prognosis, which would signify improvement for the (+) group. While the sample size will not be set precisely for the BCL-2 (-) patients, a group of approximately 30 or more BCL-2 (-) patients would be useful for a statistically useful comparison with the BCL-2 (+) patients. Since the evaluation of the BCL-2 (+) patients between EPOCH and EPOCH-R is based on a historical comparison, some caution must be exercised in the interpretation of the

comparison. In its favor, however, is that the historical group is recently accrued from the same institution, using the same eligibility criteria, and is treated by the same principal investigator.

We have met the original accrual goal and have treated 33 patients with BCL-2(+) DLBCL. The overage in number of accrued BCL-2+ cases is due to the delay in obtaining tissue blocks for analysis. Our results have been extremely favorable, with 94% CR and 82% PFS. As a result of this study, a phase 3 study of CHOP-R vs. EPOCH-R will be opened, and we will be a participating site. In order not to disturb our critically important accrual stream, we wish to increase the accrual of DLBCL patients by 15 to bridge the time gap until the phase 3 study opens. These additional patients will be included in the overall analysis and will contribute to the overall confidence of the data when published.

This trial also aims to establish the CR rate and toxicities of dose-adjusted EPOCH in other subsets of aggressive T-cell lymphomas which have been historically combined with large B-cell lymphomas. Hence, the present trial has already enrolled 13 patients with ALCL and 11 patients with peripheral/aggressive T-cell lymphomas. At this time, the PFS of ALCL is 80% with dose-adjusted EPOCH. Thus, to adequately establish the CR rate and survival outcomes of dose-adjusted EPOCH in these groups, we wish to treat up to 30 patients each with ALCL and peripheral/aggressive T-cell lymphomas. We will also occasionally encounter a CD20 negative B-cell lymphoma or gray zone lymphoma which may be treated on this study at the National Cancer Institute. Such patients would be enrolled because it would not be in their best medical interest to deny treatment and non-protocol therapy is not allowed. Although they would not contribute to the primary research endpoints, they would provide pilot information.

As of March 2010, this study has accrued 266 patients, of which 21 have ALCL and 18 have PTCL. Furthermore, patients with mediastinal PBML and GZL are currently being enrolled onto the trial and are useful to increase the precision of the ongoing molecular, laboratory, and clinical evaluations of these latter groups. It is desirable to have this study remain open for approximately one more year in order to enroll further patients with GZL and PMBL. Since approximately 10-15 such patients will be enrolled in a year, and the intended ceiling for ALCL and PTCL is 30 patients apiece, the accrual ceiling will be increased from 277 to 298. This will permit the trial to enroll, approximately, 11 additional patients with GZL and PMBL, 9 additional patients with ALCL and 12 additional patients with PTCL. This will allow accrual of sufficient additional patients with GZL and PMBL to increase the precision of the estimates of values obtained on these patients, and will permit accrual to 30 in each of the other two categories.

As of June 2012, the study has accrued 290 patients. The trial continues to recruit and enroll patients with different aggressive lymphomas; and patients are typically having excellent clinical results. To allow the trial to remain open in order to increase the precision of the estimates of PFS in subsets of patients based on disease type, the accrual ceiling will be increased by 20 patients to a total of 318—28 more than are presently enrolled. This will allow patients to continue to enroll for approximately 2 more years and to permit better estimates of outcomes in patients with rare forms of NHL. Our plan is to replace this study with new trials that are dedicated to specific histologies (PMBL, Grey Zone Lymphoma, etc.). In the meantime, as we create these new disease-specific studies, we would like to continue to provide highly curative treatment on a clinical trial for these complex patients.

As of December 2014, the study has accrued 314 patients. The trial continues to recruit and

enroll patients with different aggressive lymphomas and patients are typically having excellent clinical results. To allow the trial to remain open in order to increase the precision of the estimates of PFS in subsets of patients based on disease type while awaiting new protocols dedicated to specific histologies (PMBL, Grey Zone Lymphoma, etc.), the accrual ceiling will be increased by 20 patients to a total of 338, which is 24 more than are presently enrolled. This will allow patients to continue to enroll for approximately 2 more years and to permit better estimates of outcomes in patients with rare forms of NHL. In the meantime, as we create new disease-specific studies, we would like to continue to provide highly curative treatment on a clinical trial for these complex patients.

As of April 2016, the study has accrued 335 patients. The trial continues to recruit and enroll patients with different aggressive lymphomas and patients are typically having excellent clinical results. To allow the trial to remain open in order to increase the precision of the estimates of PFS subsets of patients based on disease type while awaiting new protocols dedicated to specific histologies (PMBL, Grey Zone Lymphoma, etc.), the accrual ceiling will be increased by 10 patients to a total of 348, which is 13 more than are presently enrolled. This will allow patients to continue to enroll for approximately one more year and to permit better estimates of outcomes in patients with rare forms of NHL. In the meantime, as we create new disease-specific studies, we would like to continue to provide highly curative treatment on a clinical trial for these complex patients.

Effective with Amendment ZZ (version date 04-06-2016), the accrual ceiling will be set at 348.

Effective with Amendment FFF, all patients on trial will be followed for PFS for up to 5 years from the date they sign the consent form. Any future analysis will focus on evaluations taking place no more than 5 years after study entry. This will apply both to previously enrolled patients as well as to any patients who enroll after this amendment is in effect.

# 9 HUMAN SUBJECTS PROTECTION

## 9.1 RATIONALE FOR SUBJECT SELECTION

Non-Hodgkin's lymphomas affect all races and genders. However, males are more likely than females to be affected and this will be reflected in the gender distribution of our cases. Non-Hodgkin's lymphomas are the 9$^{th}$ leading cause of cancer death for men and the 6$^{th}$ leading cause of cancer death in women, and thus represent a significant public health risk. Although potentially curable, close to 50% of patients achieve a durable complete remission with standard R-CHOP chemotherapy, and most of the remaining patients die of their disease. Patients with HIV infection will be excluded as AIDS-related lymphoma is a distinct biological entity which is not being studied in this protocol, and pregnant or nursing mothers are excluded because of the potential teratogenic effects of therapy.

## 9.2 PARTICIPATION OF CHILDREN

The age range of pediatric patients eligible for this trial is 12 years and older. Physicians, nurses, and multidisciplinary support teams of the Pediatric Oncology Branch (POB), Lymphoid Malignancies Branch, and Clinical Center (CC) will provide patient care. The staff of the POB has expertise in the management of children with complex oncologic disorders and complications of therapy. Full pediatric support and subspecialty services are available at the NIH CC.

While participating in this protocol, children and their families can stay at the Children's Inn, located close to the Clinical Center on the NIH campus, which is a private, non-profit residence with the purpose of keeping children together with their families while they are in Bethesda to participate in research studies.

Minors who reach the age of consent while still on-study will be asked to sign the informed consent document to indicate that they agree to continue participating in the study.

## 9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit (Section **9.4**), 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 **9.5** for consent procedure.

## 9.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

### 9.4.1 Risks

#### 9.4.1.1 Biopsy collection

The risks associated with biopsies are pain and bleeding at the biopsy site. In order to minimize pain, local anesthesia will be used. Rarely, there is a risk of infection at the sampling site.

#### 9.4.1.2 Bone marrow aspirate and/or biopsy

Bone marrow biopsy is minimally invasive and is typically a very safe procedure. Usually hipbone is numbed with anesthesia. Using a needle, the solid and liquid portion of bone marrow is taken out. This procedure causes some pain. Very rarely, infection or bleeding may occur at the needle site.

#### 9.4.1.3 CT scans

In addition to the radiation risks discussed below, scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling.

#### 9.4.1.4 MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. There are no known long-term risks of MRI scans.

During part of the MRI patient will receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for research purposes.

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling. Participants undergoing gadolinium enhanced MRIs may also be at risk for kidney damage.

#### 9.4.1.5 Radiation

The study will involve radiation from the following sources in an annual maximum:

- Up to 1 CT (Head) scans
- Up to 4 CT (Chest, Abdomen, Pelvis, Neck) scans

Subjects in this study may be exposed to approximately 5.3 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 0.5 out of 100 (0.5%) and of getting a fatal cancer is 0.3 out of 100 (0.3%). The procedures for performing the CT will follow clinical policies, no special procedures will apply to these assessments for research purposes.

#### 9.4.1.6 Risks related to blood sampling

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

#### 9.4.1.7 Urine collection

There is no physical risk involved with urine collection.

#### 9.4.1.8 Lumbar puncture

Risks of lumbar puncture include headache, dizziness, infection, back discomfort, minor radicular numbness and brainstem herniation.

## 9.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided 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) 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.

### 9.5.1 Consent Process for Minors

Consent will be obtained from parent(s)/guardians of minor children as described in Section **9.5**.

Where deemed appropriate by the clinician and the child's parents or guardian, the child will also

be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. The assent process will take place in conjunction with consent; therefore, in person and remote assent are permitted under the same circumstances as in person and remote consent. Written assent will not be obtained from children as the study holds out the prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of the research. Verbal assent will be obtained as appropriate for children ages 12-17. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent.

All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

### 9.5.2 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require that consent be obtained from of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. We request waiver of informed consent for those individuals who become lost to follow up or who have been take off study prior to reaching the age of majority.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(3) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority.

### 9.5.3 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **9.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **9.5**.

# 10 REGULATORY AND OPERATIONAL CONSIDERATIONS

## 10.1 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 study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) 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, and IRB.

## 10.2 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 Conference on 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.

## 10.3 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 National Cancer Institute 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.

### 10.4 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 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 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.

## 11 PHARMACEUTICAL INFORMATION

There will be no IND obtained for 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.

### 11.1 CYCLOPHOSPHAMIDE

Commercially available in white crystalline formulation for intravenous injection, in vials containing 100 mg, 200 mg, 500 mg, 1 gm, or 2 gm. Intact vials are stable at room temperature storage (not to exceed 30ºC). Reconstitute with appropriate amounts of Sodium Chloride Injection (0.9% NS) to produce a solution with final concentration of 20 mg/ml. Discard solution after storage for 24 hours at room temperature. After reconstitution, cyclophosphamide is stable for up to 6 days if refrigerated (2º-8ºC). Cyclophosphamide will be diluted in 100 mL of 5% Dextrose Injection or 0.9%NS and infused over 30-60 minutes. Patients will be instructed to drink an adequate amount of fluids and empty their bladders frequently during cyclophosphamide administration.

- **Toxicities**: myelosuppression, nausea and vomiting, hemorrhagic cystitis, 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 guidelines. Please refer to the package insert for a complete listing of all toxicities.
- **Hydration Guidelines:** All patients 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 |

### 11.2 DOXORUBICIN

Commercially available as a lyophilized powder in 10, 20, and 50 mg vials with 50 mg, 100 mg, and 250 mg of lactose, respectively. Store unreconstituted, lyophilized product at controlled room temperature and protect from light. Once reconstituted, solution is stable for 7 days at room temperature under normal room light and 15 days under refrigeration (2º- 8ºC).

Also available as a 2 mg/mL solution for injection in 10, 20, 50, and 200 mg vials. Store 2mg/mL solution in the refrigerator at 2º- 8ºC and protect from light.

- **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/m$^2$. The drug causes local necrosis if infiltrated into subcutaneous tissue. Please refer to the package insert for a complete listing of all toxicities.

### 11.3 VINCRISTINE

Commercially available in 1 mg and 2 mg vial sizes. Each ml contains 1 mg of vincristine and 100 mg mannitol. Sulfuric acid or sodium hydroxide are added for pH control (pH ranges from 4 – 5). Drug should be stored at 2-8$^{o}$C and should be protected from light.

- **Toxicities:** peripheral neuropathy, autonomic neuropathy, alopecia. Local necrosis if injected subcutaneously. Please refer to the package insert for a complete listing of all toxicities.

### 11.4 ETOPOSIDE

Commercially available as a concentrate for parenteral use in 100 mg, 500 mg, and 1 gram sterile, multidose vials. The pH of the clear yellow solution is 3 to 4; 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. Drug should be stored at controlled room temperature.

- **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.

### 11.5 ADMINISTRATION OF VINCRISTINE/DOXORUBICIN/ETOPOSIDE.

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.

For more detailed description, see **APPENDIX 1**.

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.

### 11.6 PREDNISONE

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$^{o}$C.

- **Doses**: Prednisone utilization may be simplified by using only 20- and 50-mg tablets to produce individual doses and by stratifying prednisone doses by a patient's body surface area (BSA) according to the chart below. These are recommendations and not requirements.

| 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 |

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

### 11.7 RITUXIMAB

The NIH Clinical Center Pharmacy Dept. will purchase rituximab from commercial sources. Rituximab is provided in pharmaceutical grade glass vials containing 10 mL (100 mg) 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.

IDEC rituximab (IND # 7028) was being supplied by Genentech Inc. through the Division of Cancer Treatment, Diagnosis, and Centers, NCI, for this protocol through amendment dated 3-8-10. After that date, Rituximab will be supplied by the Clinical Center Pharmacy. Rituximab is a mouse/human antibody. The antibody is produced by a Chinese hamster ovary transfectoma.

- **Storage**: Rituximab for clinical use should be stored in a secure refrigerator at 2 to 8 degrees C.
- **Preparation**: Rituximab will be diluted with 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.
- **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 12 hours.
- **Administration:** A peripheral or central intravenous line will be established. During rituximab infusion, a patient'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. Patients will also receive their first dose of prednisone 60 mg/m$^2$ (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/m$^2$ on day 1 of each cycle of EPOCH, immediately prior to starting etoposide + doxorubicin + vincristine administration. Rituximab infusions will be administered to patients 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 patients with clinically significant cardiovascular disease or high circulating lymphocyte counts (≧5000/mcL).

***Standard Administration for Second & Subsequent Infusions***

Patients 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.

- **Toxicities:**

  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 ($\geq$25,000/$\mu$L) 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 ($\geq$25,000/mm$^2$) 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.

### 11.8 FILGRASTIM (NEUPOGEN[R])

CTEP supplied commercial over labeled vials of filgrastim until the supply was depleted (approximately 2-01-02), after which filgrastim will be obtained from commercial sources**.**

The filgrastim injection will be supplied in single use vials containing 300 mcg (1 ml/vial) and 480 mcg (1.6 mL/vial). Filgrastim will be stored at 2º- 8º C. DO NOT FREEZE and DO NOT SHAKE the drug product. Filgrastim will be given by subcutaneous injection; patient or other caregiver will be instructed on proper injection technique.

- **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.

### 11.9 METHOTREXATE

Only the preservative-free preparation should be used for intrathecal or intraventricular injection. Preservative-free methotrexate is commercially available as either a lyophilized powder or solution in 50, 100, 200, 250, and 1000 mg vial sizes. Sodium hydroxide and/or hydrochloric acid are also added to adjust the pH to 8.5 to 8.7. When reconstituted, each ml contains 25 mg of methotrexate; the commercially available preservative-free solution also contains 25 mg of methotrexate per 1 mL. Methotrexate should be stored at 15 – 30º C and protected from light. Prior to intrathecal or intraventricular injection, the prescribed dose of methotrexate should be further diluted with preservative-free 0.9% sodium chloride to a total volume of 3 to 5 mL. Prepared doses of methotrexate should be utilized within 4 hours of preparation.

- **Toxicities:** myelosuppression, headache, nausea, drowsiness, and blurred vision. A transient acute neurologic syndrome manifested by confusion, hemiparesis, seizures, and coma may also occur. Please refer to the package insert for a complete listing of all toxicities.

### 11.10 CYTARABINE

Only the preservative-free preparation should be used for intrathecal or intraventricular injection. Preservative-free cytarabine is commercially available as either a lyophilized powder or solution in 100, 500, 1000, and 2000 mg vial sizes. Sodium hydroxide and/or hydrochloric acid are also added to adjust the pH to 7.7. When prepared for intrathecal injection, each mL contains 100 mg of cytarabine. Intact vials of lyophilized powder should be stored at 20 – 25º C and intact vials of solution should be stored at 15 – 30º C. Prior to intrathecal or intraventricular injection, the prescribed dose of cytarabine should be reconstituted and diluted with preservative-free 0.9% sodium chloride to a total volume of 3 to 5 mL. Prepared doses of cytarabine should be utilized within 4 hours of preparation.

- **Toxicities:** myelosuppression, fever, nausea, dizziness, somnolence, and arachnoiditis. Please refer to the package insert for a complete listing of all toxicities.

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# 13 APPENDIX 1: 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).

# 14 APPENDIX 2: LETTER TO FEMALE PATIENTS AND QUESTIONNAIRE

## 14.1 LETTER TO PATIENTS


National Institutes of Health
Building 10 Room 4N115

Dear

Thank you for your participation in our study using EPOCH-R chemotherapy to treat primary mediastinal B-cell lymphoma. We are very happy that the treatment has been helpful to you.

As we continue to follow individuals on this study, we would like to learn if the chemotherapy had any effect on the hormone levels and/or fertility of female patients. To gather this information, we are asking our female patients to take part in a telephone interview during which we will ask for information about gynecologic and obstetric history, as well as symptoms and emotions that may have been experienced during the time of diagnosis with lymphoma and then during the treatment and follow-up phases. We will use the list of questions which is enclosed with this letter.

We would appreciate, if you would consider taking part in this very important portion of our study.

If you agree to take part, please contact your research nurse to set up a time that is convenient for you to undergo a 30-minute phone interview. You will then be contacted at the appointed time and interviewed, using the enclosed questionnaire for guidance.

We hope you will be willing to assist us with this important project and we look forward to hearing from you.

Sincerely,

Lymphoid Malignancies Branch
Center for Cancer Research

## 14.2 QUESTIONNAIRE

1. What was your menstrual history before chemotherapy?

   [ ] Regular (21-35 days) [ ] Irregular

2. Do you have a history of thyroid disorder?

   [ ] Yes - What type of disorder? When were you diagnosed with it? [ ] No

3. Do you have a positive family history of infertility?

   [ ] Yes - Who is/was affected? [ ] No

4. Did you ever attempt to become pregnant before your diagnosis of lymphoma?

   [ ] Yes - successful [ ] Yes - unsuccessful [ ] No

5. Did you become pregnant naturally?

   [ ] Yes [ ] No

6. Did you deliver at term?

   [ ] Yes [ ] No

7. Did you ever have a miscarriage?

   [ ] Yes - How many times? During which trimester of pregnancy? [ ] No

8. Did your menstrual periods stop while undergoing chemotherapy?

   [ ] Yes [ ] No

9. Did your menstrual periods recur after completion of chemotherapy?

   [ ] Yes - How many weeks/months after completion of chemotherapy? [ ] No

   If yes, were they: [ ] Regular (21-35 days) or [ ] Irregular

10. If your menstrual periods did not recur after completion of chemotherapy, did you/are you experiencing symptoms such as hot flashes, sleep disturbances, vaginal dryness and discomfort or pain with intercourse?

    [ ] Yes - What type of symptoms do you have? [ ] No

11. Have you attempted to become pregnant after chemotherapy was completed?

    [ ] Yes - successful [ ] Yes - unsuccessful [ ] No

12. Were you worried about the risk of infertility or early menopause due to chemotherapy?

    [ ] Yes [ ] No

13. Did you at any point in time consider pursuing fertility preservation before starting chemotherapy?

    [ ] Yes - What were the barriers to following through? [ ] No