Abbreviated Title: EPOCH-Campath in T Lymphomas
CC Protocol #: 03-C-0304 H
Version Date: 05/16/2018
NCT Number: NCT00069238

PHASE 2 TRIAL OF ALEMTUZUMAB AND DOSE-ADJUSTED EPOCH IN CHEMOTHERAPY NAÏVE AGGRESSIVE T and NK-CELL LYMPHOMAS

NCI Principal Investigator: Wyndham H. Wilson, M.D. Ph.D.
Lymphoid Malignancies Branch (LYMB)
Center for Cancer Research (CCR)
National Cancer Institute (NCI)
Building 10, Room 4N115
National Institutes of Health
Bethesda, MD 20892
Phone: 240-760-6092
Email: wilsonw@mail.nih.gov

Investigational Agents: None

Commercial Agents: Alemtuzumab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, Filgrastim

PRÉCIS

Background:

- The paradigm of combining therapeutic agents with non-overlapping toxicities for the treatment of malignancy produces clinical remissions and cures in a number of tumor types.
- A new class of agents, humanized and chimerized monoclonal antibodies, typically have little or no hematopoietic toxicity and can be readily combined with full doses of cytotoxic chemotherapy. It has become clear that in certain lymphomas and breast cancers, the combination of monoclonal antibodies and chemotherapy improves response rate and the quality of the response compared with that achieved by treatment with either agent alone.
- The clinical outcome for patients with T-cell non-Hodgkin's lymphoma is significantly inferior to the outcome of patients with B-cell non-Hodgkin's lymphoma. In most reports less than 20% of patients with T cell lymphoid malignancies remain free of disease at 5 years.

Objective:

- Determine the toxicity and maximum tolerated dose (MTD) of Alemtuzumab and EPOCH chemotherapy in untreated CD52-expressing T and NK lymphoid malignancies

Eligibility:

- CD52-expressing lymphoid malignancy.
- Patients with chemotherapy naïve aggressive T & NK lymphomas. Patients with alk-positive anaplastic large cell lymphoma and patients with T cell precursor disease are not eligible.
- Age ≥17 years.
- Adequate organ function, unless impairment due to respective organ involvement by tumor.
- No active symptomatic ischemic heart disease, myocardial infarction or congestive heart failure within the past year
- HIV negative
- Not pregnant or nursing

Design:

- Three dose levels of Alemtuzumab will be evaluated to determine the toxicity profile and in a preliminary fashion the antitumor activity of the combination with Dose-Adjusted EPOCH.
- Three dose levels of Alemtuzumab will be explored, in cohorts of three to six patients each. Patients will receive either 30, 60, or 90 mg of Alemtuzumab on day 1 of therapy, followed by dose-adjusted EPOCH chemotherapy days 1-5.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary

Determine the toxicity and maximum tolerated dose (MTD) of Alemtuzumab and EPOCH chemotherapy in untreated CD52-expressing T and NK lymphoid malignancies

1.1.2 Secondary

Determine in a preliminary fashion the anti-tumor activity of the combination of Alemtuzumab and EPOCH chemotherapy

1.2 BACKGROUND

1.2.1 Alemtuzumab Background

Alemtuzumab is a humanized antilymphocyte monoclonal antibody engineered by grafting the rodent hypervariable complementarity determining regions into a human immunoglobulin molecule. It is directed at CD52, a 12 amino acid protein that is highly glycosylated and linked to the cell membrane by phosphytidylinositolglycan linkage. It is expressed on lymphocytes and monocytes, but monocytes appear to be resistant to Alemtuzumab-mediated lysis. Monocytes disappear from the peripheral circulation but reappear shortly after treatment suggesting a sequestration without lysis or regeneration from a precursor pool that is CD52-negative. It is estimated that there are 5×10^5 antibody sites per lymphocyte and the antigen does not modulate from the cell surface. Alemtuzumab is thought to mediate cell lysis through complement or antibody-dependent cell-mediated cytotoxicity. The function of CD52 is not known but it may play a role in T-cell activation. Alemtuzumab has been used in clinical trials to suppress the immune system in patients undergoing allogeneic stem cell transplantation and in patients with autoimmune disease.

1.2.1.1 Phase 1 Clinical Trial Experience

A total of 519 patients have been enrolled in 18 phase I and II studies of Alemtuzumab sponsored by Wellcome. Based on the results of these studies a dose of 30 mg administered intravenously three times weekly for 12 weeks was selected for evaluation in phase II studies.

A total of 174 patients were evaluated in phase I dose-escalation trials in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia. In study 001, four cohorts of patients were evaluated with doses ranging from 2.5 to 80 mg intravenously three times weekly. In study 002, four cohorts were evaluated with doses ranging from 7.5 to 240 mg administered intravenously once per week. The administration of Alemtuzumab was associated with acute adverse events primarily related to the first dose or the first escalated dose during the period of antibody dose-escalation. The incidence of acute adverse events increased with doses over 3 mg but above this dose a dose-effect was less evident. Common adverse events seen in about half of the treated patients included chills/rigors, fever, nausea, and vomiting and skin rash. Hypotension occurred in about one third of patients but did not achieve grade 3 or 4 levels and dyspnea in about 25% of administrations. Bronchospasm occurred in about 10% of patients. In vitro data suggest that Fc-receptor crosslinking on NK cells may be responsible for these toxicities which are thought to be mediated by cytokine release [1]. Hypertension that achieved

grade 3 or 4 toxicity levels occurred in 17% of patients. Neutropenia emerged during treatment in about 24% of patients and was more common in patients treated with higher doses of Alemtuzumab (80 mg or higher). Transient thrombocytopenia occurred in association with early infusions in a course of treatment and typically became less pronounced with continued treatment. Thrombocytopenia emerged on treatment in about 15% of patients and was more common with higher individual doses. Thrombocytopenia was attributed to peripheral destruction as these patients had normal megakaryocyte numbers and failed to respond to platelet transfusions. Anemia occurred in about 16% of individuals. Hypoplastic bone marrow findings were seen in eight patients during these phase I studies. In three cases the patients were known to have pre-existing bone marrow abnormalities. In the remaining five cases, the patients were treated with 80 mg doses three times weekly. There were 27 deaths within 28 days of the final Alemtuzumab infusion. Fourteen deaths were attributed to disease progression, 6 were due to infectious complications. Other deaths were attributed to cardiac failure, renal failure in association with tumor lysis syndrome, hepatic failure, and respiratory failure. Two deaths occurred after administration of alternative chemotherapy.

Tumor responses were recorded in 16 patients; 8 occurred in patients with CLL or PLL, 2 in patients with small lymphocytic lymphoma, 2 in patients with mycosis fungoides, 2 in patients with small-cleaved cell lymphoma and 1 each in follicular and diffuse mixed cell lymphoma. The sites of tumor most likely to respond were blood, bone marrow and spleen. Lymph node enlargement, particularly bulky lymph node enlargements were less likely to respond.

1.2.1.2 Phase II Clinical Trial Experience

Eight phase II trials, enrolling 190 patients, were conducted by Wellcome (Investigator's brochure). These studies evaluated the three times weekly intravenous schedule of administration with a target dose of 25-30 mg and avoided the higher doses, which were associated with increased bone marrow toxicity. Subcutaneous dosing was evaluated in a subset of patients. An escalating dose regimen was used with attenuated doses of 3 and 10 mg during the first week of treatment. Patients with non-Hodgkin's lymphoma or CLL that was relapsed or refractory to initial therapy were eligible for the study. In one study, 125 patients with NHL or CLL were entered and in another study 24 patients with CLL refractory to fludarabine were entered. In the larger trial 8% of patients achieved a CR, 25% a PR and 37% stable disease. One third of fludarabine resistant patients with CLL responded to Alemtuzumab treatment. The investigators brochure indicates that seven patients with ATL have been treated but additional information on toxicity and response is not available.

1.3 THERAPY OF T CELL LYMPHOMA

The REAL classification has had a significant impact on the management of patients with lymphocytic neoplasms [2]. Previous classifications such as the working formulation did not account for lymphocyte phenotype in categorizing these disorders. As a result, B and non-B cell neoplasms were treated and categorized similarly. This has led to controversy with regard to the clinical outcome of patients with B and T cell neoplasms. Early studies evaluating outcome in small groups of patients suggested that there were no differences in outcome between the B and T cell subgroups. The REAL classification however makes clear that there are different subcategories within the T cell subgroup that have substantially different clinical outcomes and this difference combined with early stage disease likely account for the reported findings from earlier studies.

Table 1 from the Non-Hodgkin's Lymphoma Classification Project summarizes the results from a worldwide survey of nine study sites that examined all newly diagnosed cases of lymphoma between 1988 and 1990 [3]. A cohort of 1403 cases of lymphoma was evaluated with an intensive histologic characterization of the neoplasms and immunologic phenotyping with review by an expert panel of five hematopathologists. Clinical correlations and survival analyses were performed. The report indicates the relative rarity of these malignancies compared with B cell lymphomas with only 7% of all diagnoses representing one of several different subgroups of T cell neoplasms. Anaplastic large cell lymphoma, an entity that frequently expresses T cell markers represented 2.4% of all lymphoma diagnoses.

Table 2 shows the survival analysis of these patients and emphasizes the poor outcome of patients with peripheral T cell neoplasms compared to that of patients with diffuse large cell lymphoma or anaplastic large cell lymphoma, a disease that is sometimes combined with the peripheral T cell neoplasms [3]. In the group with peripheral T cell neoplasm of all subtypes, the outcome is dependent upon the international prognostic index (IPI) score of the patient although the outcome is particularly poor in patients with high IPI scores with only 15% of patients with this diagnosis alive at five years and 5% of that group were alive with evidence of disease activity. Patients with low IPI scores fare better but still have only slightly over a fourth of these patients are alive with no evidence of disease at five years. In contrast, patients with anaplastic large cell lymphoma have a good outcome without reference to IPI score. Over 80% of patients are alive at 5 years regardless of IPI score. This emphasizes the potential for inaccuracy in comparing outcome between T and B cell lymphoma in older studies where patients with these two entities were combined for comparison purposes.

Three large series have recently been reported evaluating the incidence and clinical outcome of patients with T cell neoplasms [4-6]. The series reported from MD Anderson hospital identified 68 cases of T cell neoplasms among 560 patients (12%) with intermediate grade and immunoblastic non-Hodgkin's lymphoma treated between 1984 and 1995; GELA identified 288 cases of T cell neoplasms among 1883 patients (15%) with diffuse aggressive lymphoma treated between 1987 and 1993; and 174 cases of T cell lymphoma were diagnosed in nine Spanish institutions between 1985 and 1996. Peripheral T cell lymphoma not otherwise specified represented 49-66% of cases in these series with anaplastic large cell lymphoma representing 15-21% of cases and angioimmunoblastic lymphadenopathy 12-24% of cases. The complete remission rate for all patients with T cell neoplasm varied from a low of 49% in the Spanish series to 54% in the GELA study and 65% at MD Anderson. In each of these series the outcome for patients with anaplastic large cell lymphoma was significantly better than that of patients with peripheral T cell lymphoma otherwise unspecified. In the Spanish study the median survival of patients with anaplastic large cell lymphoma was 65 months versus 20 months for patients with peripheral T cell lymphoma and in the GELA study the five year overall survival was 64% for patients with anaplastic large cell lymphoma versus 35% for peripheral T cell lymphoma. The MD Anderson study contained only 10 patients with anaplastic large cell lymphoma and although not statistically significant, these patients had a better outcome. These studies and others [7]also emphasized the importance of the IPI score in outcome for patients with peripheral T cell lymphoma. The IPI score is generated by giving one point for each of five factors including age over 60, stage III or IV disease, elevated LDH, more than one extranodal site of disease, and poor performance status. As with other lymphomas, IPI score has an impact on outcome in peripheral

T cell lymphoma. Patients in the low risk group (IPI score 0,1) have a good prognosis with .5-year survival of 60-80% whereas patients in higher risk groups (IPI score 2, 3, 4, 5) have a bad prognosis with about 20% of patients alive at five years with scores of 2-3 and virtually all patients with scores of 4 and 5 dead with 5 years of diagnosis.

We have limited experience with T cell neoplasms treated with EPOCH chemotherapy due to the rarity of this disease but in the small number of patients treated the outcome has been poor (Fig. 1). In contrast to anaplastic large cell lymphoma, a relatively newly described entity that was frequently included as a T cell neoplasm, which has a good prognosis, patients with other T cell neoplasms usually do not have durable disease control. These patients frequently respond to chemotherapy but as with low grade B cell neoplasms do not achieve durable complete remissions. A total of 13 patients with T cell neoplasms (2 gamma-delta hepatosplenic, 6 peripheral T cell not otherwise specified, 1 subcutaneous panniculitis-like T cell, 4 angioimmunoblastic lymphadenopathy) have been treated with EPOCH at the NCI. Eight of the 13 patients have died due to progressive disease. Five patients are alive (two patients with angioimmunoblastic lymphadenopathy and one patient with peripheral T cell not otherwise specified). Two additional patients are alive but both had disease progression on EPOCH chemotherapy; one achieved a complete remission with depsipeptide and the other is undergoing allogeneic transplantation. We also treated six patients with adult T cell lymphoma/leukemia with EPOCH chemotherapy in combination with Zenapax but all six patients were induction failures. All but one patient showed a transient response to treatment. Thus, in contrast to the good outcome in B cell lymphoma treated with EPOCH chemotherapy alone and the apparent improvement in outcome achieved with rituximab and EPOCH chemotherapy due to an improvement in outcome for patients with activated B cell phenotypes, progress is desperately needed in the treatment of T cell neoplasms. Potential approaches to the management of these patients have included stem cell transplantation with both autologous and allogeneic stem cells at the time of disease progression and the incorporation of these methods in patients in complete remission represents one avenue of investigation. Depsipeptide represents another interesting approach and has been successful in one patient with EPOCH-refractory disease. We plan to take advantage of the lymphocyte specific monoclonal antibody Alemtuzumab in combination with EPOCH chemotherapy in patients with peripheral T cell lymphoma and no prior therapy. Three dose levels of Alemtuzumab will be explored, in cohorts of three to six patients each. Patients will receive either 30, 60, or 90 mg of Alemtuzumab on day 1 of therapy, followed by dose-adjusted EPOCH chemotherapy days 1-5.

Table 1: Distribution of NHL cases by the Consensus Diagnosis

Consensus Diagnosis	No. of Cases	% of total cases
Diffuse large B-cell	422	30.6
Follicular	304	22.1
Grade 1	131	9.5
Grade 2	85	6.2
Grade 3	88	6.4
Marginal zone B-cell, MALT	105	7.6

Consensus Diagnosis	No. of Cases	% of total cases
Peripheral T-Cell	96	7
Medium sized, mixed, and large	51	3.7
Angiocentric, nasal	19	1.4
Angioimmunoblastic	17	1.2
Intestinal	5	<1
Lymphoepithelioid	2	<1
Hepatosplenic	1	<1
Adult T-cell leukemia/lymphoma	1	<1
Small B-lymphocytic (CLL)	93	6.7
Mantle cell lymphoma	83	6
Primary mediastinal large B-cell	33	2.4
Anaplastic large T/null-cell	33	2.4
High grade B-cell, Burkitt-like	29	2.1
Marginal zone B-cell, nodal	25	1.8
Precursor T-lymphoblastic	23	1.3
Lymphoplasmacytoid	16	1.2
Marginal zone B-cell, splenic	11	<1
Mycosis fungoides	11	<1
Burkitt's lymphoma	10	<1
All other types	84	6.1

Table 2: Survival by Histologic Type and International Prognostic Index

Consensus Diagnosis	% 5-yr OAS	% 5-yr FFS	Index 0/1	Index 4/5
Follicular, all grades	84	17	55	6
Mantle cell	57	0	27	0
Marginal zone B-cell, MALT	89	40	83	0
Marginal zone B-cell, nodal	76	50	30	0
Small	76	38	35	13

Consensus Diagnosis	% 5-yr OAS	% 5-yr FFS Index 0/1		Index 4/5
lymphocyctic (CLL)				
Diffuse large B-cell	73	22	63	19
Primary mediastinal large B-cell	77	0	69	0
High grade B-cell, Burkitt-like	71	0	71	0
Precursor T-lymphoblastic	29	40	29	40
Peripheral T-cell, all types	36	15	27	10
Anaplastic large T/null cell	81	83	49	83

Abbreviations: IPI: International Prognostic Index; OAS: overall survival; FFS: failure-free survival; CLL: chronic lymphocytic leukemia

1.4 RATIONALE FOR THIS TRIAL

The outcome of treatment of T cell non-Hodgkin's lymphoma is poor and new approaches to management are needed. The combination of monoclonal antibodies and chemotherapy has improved the outcome for patients with B cell NHL and this approach may be beneficial in T cell NHL. This is a pilot study to determine the toxicity of Alemtuzumab in combination with EPOCH infusional chemotherapy. Three dose levels of Alemtuzumab will be evaluated to determine the toxicity profile and in a preliminary fashion the antitumor activity of the combination. It is anticipated that the infusional toxicities of Alemtuzumab will be significantly reduced by the administration of steroids with dose-adjusted EPOCH. The plan for Alemtuzumab antibody administration will be similar to that used with rituximab with administration of the entire dose before chemotherapy is administered. The only change to this will be that steroid administration will begin on the evening before Alemtuzumab is to be given. It is our intent to administer a dose of 90 mg of Alemtuzumab in combination with dose-adjusted EPOCH at the highest dose level.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 CD52-expressing lymphoid malignancy, confirmed by pathology or flow cytometry staff of the Hematopathology Section, Laboratory of Pathology, NCI. Patients with T & NK cell malignancy without accessible tissue for flow cytometry analysis may be treated on this study.

2.1.2 Patients with chemotherapy naïve aggressive T & NK lymphomas, including but not limited to peripheral T cell lymphoma (nos), gamma-delta hepatosplenic T cell lymphoma, subcutaneous panniculitis-like T cell, NK-T cell lymphoma confirmed by pathology or flow cytometry staff of the Hematopathology Section, Laboratory of Pathology, NCI. Patients with alk-positive anaplastic large cell lymphoma and patients with T cell precursor disease are not eligible.

2.1.3 Age ≥17 years.

2.1.4 Laboratory tests: Creatinine ≤1.5 mg/dL or creatinine clearance ≥ 60 ml/min; bilirubin < 2.0 mg/dl unless due to Gilbert's, AST and ALT ≤ 3x ULN (AST and ALT ≤ 6x ULN for patients on hyperalimentation for whom these abnormalities are felt to be due to the hyperalimentation) and; ANC ≥ 1000/mm^3, platelet ≥ 75,000/mm^3; unless impairment due to respective organ involvement by tumor.

2.1.5 No active symptomatic ischemic heart disease, myocardial infarction or congestive heart failure within the past year

2.1.6 HIV negative, because of the unknown effects of combined therapy with chemotherapy and an immunosuppressive agent on HIV progression

2.1.7 Signed informed consent

2.1.8 Willing to use contraception

2.1.9 Not pregnant or nursing, because of the unknown effects of Alemtuzumab on the developing fetus and infant.

2.1.10 No serious underlying medical condition or infection that would contraindicate treatment. Patients with CNS involvement are eligible for treatment on this study.

2.2 RESEARCH ELIGIBILITY EVALUATION

Tests to be done within 4 weeks before study entry; the laboratory tests in Sections **2.2.2**, **2.2.6** and **2.2.7** must be done within 7 days of starting therapy.

2.2.1 Complete history and physical examination with assessment of performance status

2.2.2 Laboratory tests: CBC/differential; prothrombin time, partial thromboplastin time; total and direct bilirubin, AST, ALT, LDH, alkaline phosphatase; albumin, calcium, phosphate, uric acid, creatinine (creatinine clearance if serum creatinine > 1.5 mg/dl); and electrolytes.

2.2.3 Tumor biopsies will be obtained for flow cytometry for assessment of CD52 staining if accessible tissue is available. Laparotomy, thorachotomy, 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.

2.2.4 Serology: HIV; hepatitis B surface and core antigen; hepatitis C; HTLV-1 and HSV serologies

2.2.5 CMV serologies

2.2.6 Urinalysis

2.2.7 Serum pregnancy test in women of childbearing potential.

2.2.8 Imaging Studies: CT chest, abdomen, and pelvis; CT or MRI of head if neurological signs or symptoms suggestive of lymphomatous involvement are present.

2.2.9 Electrocardiogram

2.2.10 Radionuclide bone and PET scans as clinically indicated.

2.2.11 Unilateral bone marrow aspiration and biopsy.

2.2.12 Lumbar puncture for cell count, chemistry, cytology and flow cytometry

2.3 Registration Procedures

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

3 STUDY IMPLEMENTATION

3.1 Study Design

This is a pilot trial of Alemtuzumab in combination with dose-adjusted EPOCH. Three cohorts of three to six patients will be treated. Patients in cohort 1 will receive 30 mg of Alemtuzumab. The second cohort, patients will receive 60 mg of Alemtuzumab and the final cohort will receive 90 mg of Alemtuzumab. Six to eight cycles of therapy will be administered based on clinical response evaluation. If a patient has progressive disease at any point during therapy, he/she will be removed from protocol treatment. For the purposes of dose-escalation of alemtuzumab the

toxicity observed during the first cycle will be used to determine escalation. All patients entered at a given dose level must have completed one cycle of treatment before the next dose level can begin. If an eligible patient requires therapy before the next dose level of the protocol is available the patient will be entered at the current dose level and will be used in the determination of the maximum tolerated dose. Toxicities observed during subsequent cycles will be used to determine the dose of Alemtuzumab that will be used in phase II trials.

3.2 DRUG ADMINISTRATION (VIA CENTRAL CATHETER)

3.2.1 Dose-adjusted EPOCH-Alemtuzumab Chemotherapy (Section **11**; Appendix 1):

Cohort 1 – Alemtuzumab 30 mg

Cohort 2 – Alemtuzumab 60 mg

Cohort 3 – Alemtuzumab 90 mg

3.2.2 Table for dose-adjusted EPOCH regimen

Drug	Dose	Route	Treatment Days
Infused Agents[1]			
Alemtuzumab	30, 60 or 90 mg	IV	day 1
Etoposide	50 mg/m2/day	CIV	1,2,3,4 (96 hours)
Doxorubicin	10 mg/m2/day	CIV	1,2,3,4 (96 hours)
Vincristine	0.4 mg/m2/day	CIV	1,2,3,4 (96 hours)
Bolus Agents			
Cyclophosphamide[2]	750 mg/m2/day	IV	day 5
Prednisone[3]	60 mg/m2/bid	PO	day 0-5[4]
Filgrastim	480 mcg	SC	days 6 to ANC recovery ≥ 5000/mm^3
Next Cycle	Day 21		

[1]Begin the infusional agents immediately after Alemtuzumab is administered.

[1]Infusional agents should be administered through a central venous access device.

[2]Administer cyclophosphamide immediately after infusions are completed.

[3]Begin Prednisone the evening before start of infusional chemotherapy and Alemtuzumab with second dose given on the morning of alemtuzumab

[4] The last dose of prednisone is given on the morning of Day 5 (10 total doses of 60 mg/m2 would be administered over 5 days).

3.2.3 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

3.2.4 Premedication for Alemtuzumab Infusion administration

Premedicate 30-90 minutes before ALEMTUZUMAB infusion with

- 650 mg acetaminophen PO
- 50 mg diphenhydramine PO
- Prednisone 60 mg/m2 PO. This would be the second dose of the 60 mg/m2 bid prednisone regimen that is part of the EPOCH therapy. The first dose is given the evening before (evening of day 0)

Patients will be treated with an escalating dose schedule of Alemtuzumab as detailed above. Patients should be premedicated as above. Alemtuzumab will be administered intravenously over twelve hours. If infusional toxicities are observed the infusion may be stopped for up to 60 minutes and resumed when toxicity has resolved to baseline, or to grade 1 or less. If the patient has not had resolution of infusional toxicities within 60 minutes, contact the investigator for guidelines on when to resume infusion.

3.2.5 Definition of Maximum Tolerated Dose (MTD)

If one of the three patients entered at a given dose-level experiences dose-limiting toxicity, up to three additional patients will be entered at that dose level. If 2 of 6 patients experience DLT at a particular dose level, the MTD has been exceeded. The preceding dose level will be the MTD, provided 6 patients have been entered at this level and no more than one has experienced DLT.

3.2.6 Definition of Dose-Limiting Toxicity

Infusional toxicities such as fever, chills, hypotension, shortness of breath, throat-tightness, or abdominal pain are common with monoclonal antibodies. Dose-limiting toxicity will be defined as grade 3 allergic toxicity (bronchospasm with wheezing, hypoxia and/or dyspnea) , any grade 3 non-hematologic toxicity lasting longer than 6 hours after infusion is completed or any grade 4 non-hematologic toxicity (except grade 4 dyspnea). If any grade 5 toxicity occurs the trial will be placed on hold to further patient accrual until the toxicity and plan for management for all patients is clarified. Patients who experience grade 3 non-hematologic toxicity may be retreated if the toxicity resolves to grade 1 or less before the next scheduled dose of treatment. If the

alemtuzumab toxicity does not resolve to grade 1 or less within 28 days from day 1 of treatment, the alemtuzumab will be removed from protocol treatment. Patients who experience infusional DLT may be retreated at the next cycle at the next lower dose level. If a patient experiences DLT at the first dose level, alemtuzumab will be discontinued on future cycles.

3.3 TREATMENT MODIFICATIONS

3.3.1 ALEMTUZUMAB (toxicity probably or definitely related)

Discontinue Alemtuzumab for:

- Grade 4 non-hematologic toxicity other than easily correctable metabolic toxicities or infection
- Grade 3 infusional dose-limiting toxicity

Reduce Alemtuzumab one dose level for:

- Grade 3 non-hematologic toxicity that does not resolve to ≤ grade 1 by the time the next administration of alemtuzumab is scheduled, except grade 3 infectious complications.
- Grade 4 neutropenia that persists for 3 or more biweekly measurements (maximum of approximately 10 days of neutropenia) despite G-CSF therapy.
- Grade 4 thrombocytopenia that persists for 3 or more biweekly measurements (maximum of approximately 10 days).

3.3.2 EPOCH Dose Adjustments:

HEMATOLOGICAL TOXICITY
Drug doses may be modified from the following algorithm at the discretion of the investigator for severe life-threatening toxicity such as ICU admissions for sepsis. When two different rules give different answers for a particular dose decision, use the lower of the two dose options.

Dose-Adjustment Paradigm

- Dose adjustments <u>above starting dose level</u> (level 1) apply to etoposide, doxorubicin and cyclophosphamide
- Dose adjustments <u>below starting dose level</u> (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 < 15,000/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 480 mcg every day 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.**

NON-HEMATOLOGICAL TOXICITY

a. Sensory neuropathy

Grade	% Dose of Vincristine
2	100
3	50

b. Motor neuropathy

Grade	% Dose of Vincristine
1	100
2	75
3	25
4	0

c. Hepatic dysfunction

Bilirubin on Day 1	% Dose of Vincristine
1.5-3.0	75
>3.0	50

d. 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. If the patient has severe ileus requiring hospitalization, reduce vincristine by 25%.

3.4 On Study Evaluation

3.4.1 Day 1 all cycles and day 21 last cycle: CBC/differential; electrolytes; mineral panel; AST, ALT, Bilirubin and LDH.

3.4.2 At the beginning of each cycle, and near Day 21 of the last cycle: CMV PCR, CD4, CD8 and NK cell counts.

3.4.3 During cycles: CBC/differential BIW.

3.4.4 Restaging: Day 21, cycles 4 and 6 and 8 (if administered). Repeat all initially positive staging tests.

3.4.5 Up to 50 cc of blood may optionally be drawn for immunological testing, evaluation of hematologic parameters, or other studies that become clinically important during conduct of the trial. (However, this should not be drawn if it brings the total amount of blood drawn to more than 450 ml during a 6-week period.)

3.4.6 16cc of blood in light blue citrate tubes or blue and black cell preservation tube (CPT) for polymerase chain reaction to define T cell receptor gene rearrangement

3.5 Concurrent Therapies (continued for 2 months post-treatment)

3.5.1 **Pneumocystis carinii prophylaxis:** Recommend Trimethoprim 160 mg/sulfamethoxazole 800 mg PO BID 3x/week. Alternatives include Dapsone 50 - 100 mg PO qd or 100 mg PO 2x/week; aerosolized pentamidine.

3.5.2 **Herpes Simplex prophylaxis** for herpes virus infection will be given (acyclovir 400 mg twice daily or famciclovir 500 mg twice daily).

3.5.3 **Fungal prophylaxis:** Fluconazole will be administered as prophylaxis for fungal infections (200 mg daily). Fluconazole should be held during EPOCH therapy.

3.5.4 **Prophylactic Central Nervous System Treatment.** All patients 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).

3.5.5 **Treatment of Meningeal Lymphoma**. If the CSF is positive for malignant cells at the start of therapy, the CSF should be treated with methotrexate and/or cytarabine as soon as possible. **Induction**- intrathecal methotrexate (6 mg by Ommaya or 12 mg by lumbar route) or cytarabine (70 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.

3.6 Post-Study Evaluation

3.6.1 For patients with response: Restage sites of disease q3 months for the first year, then q4 months for the second year, and then q6 months for the next three years, and yearly thereafter. Laboratory tests: CBC/differential, mineral panel, electrolytes, AST, ALT, Bilirubin, and LDH. The timing for these visits may be adjusted $\pm$ 2 months.

3.6.2 All patients will be followed, at restaging visits, with CMV PCR levels until the CD4 count is greater than 200

3.7 Criteria for Removal from Protocol Therapy and Off Study Criteria

3.7.1 Criteria for removal from protocol therapy

- Institution of another therapy
- Patient non-compliance.
- Patient voluntary withdrawal.
- Excessive toxicity (as defined in section **3.2.6**)

3.7.2 Off-Study Criteria

- Participant requests to be withdrawn from study
- Death

3.7.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 SUPPORTIVE CARE

4.1 Pneumocystis carinii Pneumonia

Patients who develop PCP will receive standard of care including trimethoprim-sulfamethoxazole, steroids when appropriate and alternative standard agents such as IV Pentamidine, atovaquone, or trimetrexate in combination with leucovorin when TMP-sulfa cannot be used.

4.2 CMV antigenemia

Patient management will be handled on a case-by-case basis in conjunction with the infectious diseases service.

4.3 Febrile neutropenia

Febrile Neutropenia is a life-threatening complication requiring urgent broad-spectrum antibiotics. Management may be as an inpatient or outpatient depending on the clinical situation.

4.4 SYMPTOMATIC ANEMIA

Symptomatic anemia should be treated with appropriate red blood cell support, and is recommended if the hemoglobin falls below 8 mg/dl. Only irradiated leukodepleted blood products should be used.

4.5 THROMBOCYTOPENIA

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

4.6 CENTRAL VENOUS ACCESS

Central venous access is required for EPOCH administration. Possible lines include: temporary internal jugular line (preferred); PICC lines via the brachial vein; semi-permanent HICKMAN, GROSHONG catheters or medi-port implanted devices. All devices will have nursing supervision to include patient self care and cleaning/flushing of the devices.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

Data will be prospectively collected and entered into the NCI database.

The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. Patients will be followed for adverse events for 30 days following the last dose of study drug or until off-study, whichever comes first.

An abnormal laboratory value will be considered an AE 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.

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

Exceptions for data collection/recording on case report forms:

- All adverse events that represent known reactions of grade 1 toxicity will not be recorded in the database.

5.2 RESPONSE CRITERIA

Response criteria for lymphomas: From the International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphomas. Responses must last for at least 4 weeks off treatment.

Complete Remission (CR): Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease related symptoms if present before therapy and normalization of those biochemical abnormalities (for example LDH) definitely assignable to the lymphoma. All lymph nodes must have regressed to normal size (less than or equal to 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in greatest diameter must have decreased to less than or equal to 1 cm or by more than 75 percent in the sum of the products of the greatest diameters. The spleen, if considered to be enlarged before therapy, must have regressed in size and not be palpable on physical examination. The bone marrow must show no evidence of disease by histology. Flow cytometry, molecular or cytogenetic studies will not be used to determine response. Response must persist for 1 month.

Complete response unconfirmed (Cru): As per complete remission criterion except that if a residual node is greater than 1.5 cm, it must have decreased by greater than 75 percent in the sum of the products of the perpendicular diameters.

Partial Response (PR): ≥ 50% decreased in SPD of 6 largest dominant nodes or nodal masses. No increase in size of nodes, liver or spleen and no new sites of disease. Splenic and hepatic nodules must regress by ≥ 50% in the SPD. Bone marrow is irrelevant for determination of a PR. Relapsed disease (CR, Cru) requires the following: Appearance of any new lesion or increase by ≥ 50% in the size of the previously involved sites. Greater than or equal to 50% increase in greatest diameter of any previously identified node > 1 cm in its shortest axis or in the SPD of more than one node.

Progressive disease (PR, nonresponders) requires the following: ≥ 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders. Appearance of any new lesion during or at the end of therapy.

Stable Disease (SD): is defined as less than a PR but not progressive disease.

ALL assessment of clinical response will be made according to the NCI guidelines. The major criteria for judging response will include physical examination and examination of blood and bone marrow. All laboratory studies that are abnormal prior to study will be repeated to document the degree of maximal response.

5.3 TOXICITY CRITERIA

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting. All

appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section **9** (Pharmaceutical Information). A copy of the CTCAE version 3.0 can be downloaded from the CTEP *web site (http://ctep.cancer.gov/reporting/ctc.html).*

6 STATISTICAL CONSIDERATIONS

Determination of sample size: This is pilot study to evaluate the feasibility of administration of Alemtuzumab in combination with EPOCH infusional chemotherapy. The primary objective of this study is to evaluate the overall and hematologic toxicities of this combination. Previous administration of steroids and/ or other biologic therapy is unlikely to affect these parameters. There will be a maximum of 24 patients in this trial, with three to six patients treated in each cohort examining different doses of Alemtuzumab with treatment of an additional 6 patients at the maximum tolerated dose. Thus, a total of 12 patients will be treated at the maximum tolerated dose. It is assumed that 10 patients per year will be accrued to this trial, and that all accrual can be achieved within 2.5 years. As it is a secondary objective, the small number of patients treated at the MTD will have clinical responses reported based on criteria stated in section **5.2**.

To date, the patients enrolled on the study have been from three principal histologies: AITL (4), PTCL (6) and HTLV-1 ATLL (7). We are interested in obtaining a limited amount of additional data on the progression free survival and response durations in patients in each of the three most prominent types of histologies enrolled to date. To do so, the study will be amended to allow up to 15 additional patients to be enrolled at the 30 mg alemtuzumab dose level, with the goal of obtaining approximately 5 more patients from each of the three main categories and thereby obtaining an improved estimate of the outcome parameters. These estimates will be useful in planning the subsequent study and the additional patients will also allow better information on toxicity to be obtained, and to allow patients to continue to be enrolled on a study with these agents pending the opening of a subsequent trial. Thus, the new accrual ceiling is 39 patients.

At this point there have been no patients among the 18 treated who developed bone marrow aplasia at the 30 mg dose level of alemtuzumab. If two or more cases of bone marrow aplasia occur in the remaining cohort of patients treated at this dose level, the study will be placed on hold to accrual and future plans discussed with the IRB.

7 HUMAN SUBJECTS PROTECTION

7.1 RATIONALE FOR SUBJECT SELECTION

All subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in Section **2.1**. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to gender or to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

7.2 PARTICIPATION OF CHILDREN

Patients of at least 17 years of age will be eligible. T-cell lymphomas are infrequently curable with standard treatment. This study may provide increased clinical benefit compared to standard approaches and would be appropriate for a patient of 17 years. However, younger patients have not been included at this time because of the rarity of these diseases in this age group. Where deemed appropriate by the clinician and the child's parent(s) 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. 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 was obtained as appropriate for children age 17 and the parent or guardian signed the designated line on the informed consent attesting to the fact that the child gave assent. We request waiver of the two patient signatures for consent because both parents may not be able to accompany the patient.

7.3 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 from research participation (Section **7.4**), 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 as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 and NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

7.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The potential benefits to the subject are that the patient may achieve a partial or complete remission. The benefits of combinations of chemotherapy and monoclonal antibodies may produce remissions that cannot be achieved with either approach alone. Chemotherapy may produce bleeding or infectious complications as a result of chemotherapy-induced myelosuppression. Alemtuzumab causes immunosuppression which may be made more severe as a result of combining it with chemotherapy.

7.5 RISKS/BENEFITS

Patients eligible for this protocol will be subject to the toxicity associated with EPOCH infusional chemotherapy, which include myelosuppression, stomatitis, numbness or tingling in the extremities, motor weakness, and the need for transfusion or hospitalization due to complications of treatment noted. There may be adverse effects due to the combination of agents

that is not seen when either is given alone. The long-term outcome for T cell lymphoma is particularly poor with about 25% of low risk patient surviving at 5 years and virtually all patients with advanced disease dying in this interval. Combining EPOCH with Alemtuzumab may produce increased immune suppression and myelosuppression. The risk/benefit analysis for adults with the capacity to consent, as well as for adults who may become unable to provide consent, and for children is greater than minimal risk with the prospect of direct benefit based on the risks and potential benefits described in Section **7.4**.

7.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

All patients are thoroughly screened for eligibility prior to admission onto this study. During this time the patient, along with family members, will be presented with a detailed description of the treatment. The specific requirements, objectives, and potential risks and benefits will be discussed. The informed consent document is given to the patient, who is asked to review the document, discuss it with his/her family and write down questions to discuss with the principal investigator or treating physician. The patient is informed that participation is voluntary and that he/she may withdraw at any time without loss of benefits without consequence. The patient or their legal representative must sign the consent document prior to receiving any protocol related treatment.

7.6.1 Telephone consent for reconsent only

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

8 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

8.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable

possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

8.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

8.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

8.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

8.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

8.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

8.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

8.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

9 PHARMACEUTICAL INFORMATION

EPOCH/Filgrastim

9.1 ETOPOSIDE/DOXORUBICIN/VINCRISTINE ADMINISTRATION

These drugs are commercially available. Stability studies conducted by the Pharmaceutical Development Service, Pharmacy Department, NIH Clinical Center, have demonstrated that admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, USP 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 and 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 degrees C. Etoposide, doxorubicin, and vincristine will be combined in a single ('3-in-1') admixture, diluted in a volume of 0.9% Sodium Chloride (NS), Injection, USP, that is based on the amount of etoposide needed to complete 24 hours of treatment. If etoposide $\leq$ 150 mg per 24 hours, then dilute drugs in 500 mL 0.9% sodium chloride; if etoposide > 150 mg per 24 hours, then dilute drugs in 1000 mL 0.9% sodium chloride. Etoposide, doxorubicin and vincristine will be administered as a 96 hour continuous IV infusion. The chemotherapy will be administered with a suitable infusion pump via a central venous access device. Temporary PICC lines or permanent lines may be used. Extravasation of these diluted agents has not caused local tissue damage due to their low concentrations in the solution. Interruption of the infusions should be avoided expect during the time it takes to change the daily cassette.

Doxorubicin causes myelosuppression. Other toxicities include; cardiac toxicity which may occur at low doses, but significantly increases at total doses > 550 mg/m^2, nausea, vomiting, stomatitis , diarrhea and alopecia. Skin infiltration causes tissue necrosis. **Etoposide** toxicities include nausea, vomiting, stomatitis, diarrhea, neutropenia, thrombocytopenia and alopecia. Secondary AML has been associated with this drug. **Vincristine** causes neurological toxicities with paresthesias, jaw pain, ataxia, foot-drop, cranial nerve palsies, paralytic ileus, constipation, abdominal pain, and loss of deep tendon reflexes. It is also a vesicant, and occasionally causes alopecia and myelosuppression.

9.2 CYCLOPHOSPHAMIDE ADMINISTRATION

Commercially available as a lyophilized powder in 2 gram vials. Reconstitution with 100 ml of sterile water for injection in final concentration of 20 mg/ml. Cyclophosphamide will be diluted in 100 ml of D5W or NS and infused over 15 minutes. Patients will be instructed to drink an adequate amount of fluids and empty their bladders frequently during cyclophosphamide administration. **Cyclophosphamide** causes myelosuppression, nausea, vomiting, gastrointestinal toxicity and hemorrhagic cystitis. Maintaining good hydration and urinary output during the use of this drug may prevent this latter toxicity. Secondary AML has been associated with this drug.

9.3 PREDNISONE

Commercially available in a variety of solid and liquid dosage forms. Tablet strengths include: 1, 2.5, 5, 20, and 50 mg and the oral solution contained 1 mg/ml. Prednisone 60 mg/m^2 will be administered orally on days 0 to 5. The prednisone starts on the evening of Day 0, with two

doses being consumed before the first alemtuzumab dose. In patients unable to tolerate oral medication, methylprednisolone can be substituted at an equivalent dose, diluted in 25 ml of NS, and infused over 15 minutes. **Prednisone** frequently causes gastritis, immunosuppression, muscle wasting, fluid retention and hyperglycemia. To reduce gastrointestinal side effects, prednisone should be taken with food

9.4 FILGRASTIM (G-CSF)

is a commercially available recombinant human protein produced by Amgen Corp., Thousand Oaks, CA, and marketed under the brand name **Neupogen**. It is provided in either 1 ml vials (300 mcg) or 1.6 ml vials (480 mcg). Intact vials should be stored in the refrigerator (2-8 degrees C); do not freeze. Do not dilute with sodium chloride solutions. Filgrastim is stable for at least 1 year when refrigerated. The product is suitable for SC or direct IV injection. Filgrastim will be administered at doses of 300 mcg/day (Pediatric dose 5 mcg/kg/day to a maximum of 300 mcg/day) as a subcutaneous injection starting on day 6 and continuing until the AGC ≥ 5000. Dose adjustments will be allowed as clinically indicated.

9.5 ALEMTUZUMAB (CAMPATH®)

Alemtuzumab will be supplied by the clinical center pharmacy. Alemtuzumab causes the lysis of lymphocytes by fixing to CD52, a highly expressed, non-modulating antigen on the surface of lymphocytes. It mediates the lysis of lymphocytes via complement and antibody-dependent cell-mediated cytotoxicity mechanisms. Alemtuzumab is supplied as a clear, colorless, isotonic solution free from visible particulate matter. Alemtuzumab is available for intravenous or subcutaneous use in ampoules containing 30 mg of antibody in 3 ml of sterile phosphate buffered saline

Storage and preparation for injection of Alemtuzumab: Alemtuzumab should be stored at a temperature of 2-8°C and protected from light. Prepare Alemtuzumab for IV infusion within four hours of administration. The required dose should be drawn up into a syringe from the ampoule and further diluted in 100 ml of 0.9% sodium chloride or 5% dextrose, USP. The resulting solution should be within the concentration range of 20-4800 μg/ml. Alemtuzumab must be filtered prior to administration. **Note:** Alemtuzumab must be filtered with a sterile, low-protein binding, non-fiber releasing 5 micron filter when removing the dose from the ample.

Stability: Alemtuzumab was physically and chemically stable at room temperature for up to 24 hours after dilutions at concentrations between 20 and 4800 μg/ml in 0.9% sodium chloride and 5% dextrose infusion bags. However, since the product does not contain any preservative it must be used within 8 hours of preparation. In static conditions (no flow) and low concentrations (20 μg/ml) of Alemtuzumab in 0.9% sodium chloride, IV administration sets caused a detectable reduction in Alemtuzumab concentration that was not demonstrated in the higher concentration (4800 μg/ml) in either sodium chloride or 5% dextrose.

Method of administration: The Alemtuzumab solution should be given IV over approximately 12 hours. Patients should be premedicated with 50 mg of diphenhydramine, 650 mg of acetaminophen and two 60 mg/m^2 doses of prednisone as indicated in section **3.2.4** before the infusion. During the alemtuzumab infusion, the patient's vital signs (blood pressure, pulse, respirations, temperature) should be monitored every 15 minutes times 4 or until stable and then hourly until the infusion is discontinued.

Special handling: No special precautions are warranted. Empty and partial ampoules should be disposed of as biological waste.

Alemtuzumab The majority of adverse events seen in trial have been administration related and of short duration. Serious adverse events, some of which fatal, have been observed in association with treatment of Alemtuzumab.

Main Adverse Events:

- **Infusional reactions** occur in most patients. They commonly consist of rigors, fever, headache, nausea, vomiting and diarrhea, rash, pruritis, dyspnea and hypotension. Acute infusional reaction may also include chills, abdominal and back pain, Bronchospasm, angioedema, tachyarrythmia etc. These reactions are most prominent during the first week of alemtuzumab administration and improve with subsequent treatments. To reduce the frequency and severity of the first dose reaction, a step-up dose escalation schedule and proper premedication should be used (see "method of administration" above)
- **Hematologic:** Anemia, neutropenia, thrombocytopenia, prolonged and profound lymphopenia
- **Infections**: common bacterial (pneumonia and sepsis) or opportunistic infections (e.g. Pneumocystis carinii pneumonia, oral candidiasis, herpes zoster, CMV reactivation, cryptococcosis).

Reported adverse events by organ systems:

- **Body as a whole:** Allergic reaction, rigors, fever, chills, headache, back and abdominal pain, infection, fatigue
- **Cardiovascular**: Hypertension, hypotension, tachycardia, Atrial arrhythmia, ventricular tachycardia, angina and myocardial infarction, peripheral vasoconstriction
- **Digestive**: anorexia, nausea, vomiting, diarrhea, constipation, dyspepsia, liver function abnormality
- **Hematological**: Neutropenia, lymphopenia, thrombocytopenia, anemia, DIC, hemolysis, eosinophil disorder, bleeding (GI, gum, ecchymosis)
- **Muscular Skeletal:** Myalgia, Arthritis, bone pain, hypotonia, tremor
- **Metabolic and nutritional**: Tumor lysis syndrome, acidosis
- **Nervous system**: Dizziness, confusion, somnolence, peripheral neuropathy, Cerebral hemorrhage, speech disorder, mental status changes, paresthesia, syncope, depression, aphasia
- **Pulmonary**: Bronchospasm, cough, Pleural effusion, pulmonary edema, interstitial pneumonitis
- **Skin/subcutaneous**: Angioedema, facial flushing, diaphoresis, pruritis, rash, urticaria, injection site reaction (subcutaneous route)
- **Urogenital**: Hematuria, oliguria, polyuria, urinary retention, urinary tract infection, impotence

- **Tinnitus**

9.6 DIPHENHYDRAMINE

Diphenhydramine will be supplied from commercial sources by the clinical center pharmacy. Diphenhydramine hydrochloride, is an antihistamine drug having the chemical name 2-(Diphenylmethoxy)-N,N-dimethylethylamine hydrochloride and has the empirical formula $C_{17}H_{21}NO \cdot HCl$. It occurs as a white, crystalline powder and is freely soluble in water and alcohol and has a molecular weight of 291.82. Each diphenhydramine HCl capsule contains 25 mg or 50 mg diphenhydramine hydrochloride for oral administration. The most frequent adverse reactions are underscored. General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat. Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles. Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis. Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, neuritis, convulsions. GI System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation. GU System: Urinary frequency, difficult urination, urinary retention, and early menses. Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness. The dose of diphenhydramine is 50 mg, administered orally before each infusion of alemtuzumab to help prevent allergic reactions.

9.7 ACETAMINOPHEN

Acetaminophen will be supplied from commercial sources by the clinical center pharmacy. Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. It has the following molecular formula $C_8H_9NO_2$ with a molecular weight of 151.16. No significant adverse reactions are expected but patients will be monitored for hepatic toxicity. The dose of acetaminophen is 650 mg, administered orally before each infusion of alemtuzumab to help prevent inflammatory responses.

9.8 TRIMETHOPRIM/SULFAMETHOXAZOLE

Trimethoprim/sulfamethoxazole will be supplied from commercial sources by the clinical center pharmacy. More common side effects may include: Hives, lack or loss of appetite, nausea, skin rash, vomiting. Less common or rare side effects may include: Abdominal pain, allergic reactions, anemia, chills, convulsions, depression, diarrhea, eye irritation, fatigue, fever, hallucinations, headache, hepatitis, inability to fall or stay asleep, inability to urinate, increased urination, inflammation of heart muscle, inflammation of the mouth and/or tongue, itching, joint pain, kidney failure, lack of feeling or concern, lack of muscle coordination, loss of appetite, low blood sugar, meningitis (inflammation of the brain or spinal cord), muscle pain, nausea, nervousness, red, raised rash, redness and swelling of the tongue, ringing in the ears, scaling of dead skin due to inflammation, sensitivity to light, severe skin welts or swelling, skin eruptions, skin peeling, vertigo, weakness, yellowing of eyes and skin. The dose of trimethoprim/sulfamethoxazole is one tablet twice daily for three days each week.

9.9 FLUCONAZOLE

Fluconazole will be supplied from commercial sources by the clinical center pharmacy. The most common side effect is nausea. Less common side effects may include: Abdominal pain,

diarrhea, headache, skin rash, vomiting. The dose of fluconazole is 200 mg orally daily. Fluconazole should not be given during EPOCH infusional chemotherapy because of pharmacologic interactions

9.10 METHOTREXATE

Commercially available folic acid antagonist, and only the preservative-free preparation may be used for intrathecal injection. It should be stored at 15-30°C and protected from light. Prior to intrathecal or intraventricular injection, the prescribed dose of methotrexate should be reconstituted/diluted with preservative-free 0.9% sodium chloride to a total volume of 3 to 5 mL. Prepared methotrexate doses should be utilized within 4 hours of preparation. **Toxicities:** It can cause leukopenia, and as such leucovorin may be administered 24 hours after each dose. It can cause headaches, drowsiness, and blurred vision. It can also cause a transient acute neurologic syndrome manifested by confusion, hemiparesis, seizures, and coma.

9.11 CYTARABINE

A commercially available pyrimidine nucleoside antimetabolite, and should be stored at –15-30°C, and used within 2 years of the date of manufacture. Prior to intrathecal injection it is reconstituted with preservative free 0.9% sodium chloride, and should utilized within 4 hours of preparation. Prior to intrathecal or intraventricular injection, the prescribed dose of cytarabine should be reconstituted/diluted with preservative-free 0.9% sodium chloride to a total volume of 3 to 5 mL **Toxicities:** It can cause myelosuppression, fever, dizziness, somnolence, and arachnoiditis.

10 REFERENCES

1. Wing MG, Moreau T, Greenwood J, Smith RM, Hale G, Isaacs J, Waldmann H, Lachmann PJ, Compston A: Mechanism of first-dose cytokine-release syndrome by CAMPATH 1-H: involvement of CD16 (FcgammaRIII) and CD11a/CD18 (LFA-1) on NK cells. J Clin.Invest 98: 2819-2826, 1996

2. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, Wolf-Peeters C, Falini B, Gatter KC: A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group [see comments]. Blood 84: 1361-1392, 1994

3. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 89: 3909-3918, 1997

4. Gisselbrecht C, Gaulard P, Lepage E, Coiffier B, Briere J, Haioun C, Cazals-Hatem D, Bosly A, Xerri L, Tilly H, Berger F, Bouhabdallah R, Diebold J: Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 92: 76-82, 1998

5. Lopez-Guillermo A, Cid J, Salar A, Lopez A, Montalban C, Castrillo JM, Gonzalez M, Ribera JM, Brunet S, Garcia-Conde J, Fernandez dS, Bosch F, Montserrat E: Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann.Oncol. 9: 849-855, 1998

6. Melnyk A, Rodriguez A, Pugh WC, Cabannillas F: Evaluation of the Revised European-American Lymphoma classification confirms the clinical relevance of immunophenotype in 560 cases of aggressive non-Hodgkin's lymphoma. Blood 89: 4514-4520, 1997

7. Ansell SM, Habermann TM, Kurtin PJ, Witzig TE, Chen MG, Li CY, Inwards DJ, Colgan JP: Predictive capacity of the International Prognostic Factor Index in patients with peripheral T-cell lymphoma. J.Clin.Oncol. 15: 2296-2301, 1997

11 Appendix 1: EPOCH CHEMOTHERAPY

Drug	Total dose* ($mg/m^2/d$)	Route	Day 1 2 3 4 5 6	22
Alemtuzumab	fixed total dose 30, 60 or 90 mg	IV	x	
Etoposide	50 mg/m2/day	CIV	x-x-x-x-	
Vincristine	0.4 mg/m2/day	CIV	x-x-x-x-	
Doxorubicin	10 mg/m2/day	CIV	x-x-x-x-	
Cyclophosphamide	750 mg/m2	IV	x	
Prednisone	60 mg/m2/day BID	PO	x-x-x-x-x	
Filgrastim	480 mcg QD	SC	x until ANC recovery $\geq$ 5000/mm3	
New cycle begins				x

*First cycle doses, refer to 3.2 for dose escalations and 3.3.2 for dose modifications

12 Appendix 2: 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).