

# Amendment

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**Protocol Title:** Phase 2 Trial of Alemtuzumab and Dose-Adjusted EPOCH In Chemotherapy Naive Aggressive T and NK-Cell Lymphomas

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\* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

\*\* I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

**IRB Meeting Date:** Expedited

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*Abbreviated Title: EPOCH-Campath in T Lymphomas*  
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**Abbreviated Title:** EPOCH-Campath in T Lymphomas

**CC Protocol #:** 03C0304 G

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

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- C. Obtaining the voluntary informed consent of individuals to be subjects
- D. Makes decisions about subject eligibility
- E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
- F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
- G. Some/all research activities performed outside NIH

**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  $\geq 17$  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.

**Abbreviated Title:** EPOCH-Campath in T Lymphomas  
**Version Date:** 05/22/2017

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## **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 phosphatidylinositolglycan 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  $5 \times 10^5$  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<sup>1</sup>. 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<sup>2</sup>. 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<sup>3</sup>. 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<sup>3</sup>. 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<sup>4-6</sup>. 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<sup>7</sup> 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 desisipeptide 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. Desisipeptide 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

<u>Consensus Diagnosis</u>	<u>No. of Cases % of total cases</u>	
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
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 lymphocytic (CLL)	76	38	35	13
Diffuse large B-	73	22	63	19

cell				
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  $\geq 17$  years.
- 2.1.4 Laboratory tests: Creatinine  $\leq 1.5$  mg/dL or creatinine clearance  $\geq 60$  ml/min; bilirubin  $< 2.0$  mg/dl unless due to Gilbert's, AST and ALT  $\leq 3x$  ULN (AST and ALT  $\leq 6x$  ULN for patients on hyperalimentation for whom these abnormalities are felt to be due to the hyperalimentation) and; ANC  $\geq 1000/mm^3$ , platelet  $\geq 75,000/mm^3$ ; 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 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 (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

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

**Next Cycle**

Day 21

<sup>1</sup>Begin the infusional agents immediately after Alemtuzumab is administered.

<sup>1</sup>Infusional agents should be administered through a central venous access device.

<sup>2</sup>Administer cyclophosphamide immediately after infusions are completed.

<sup>3</sup>Begin Prednisone the evening before start of infusional chemotherapy and Alemtuzumab with second dose given on the morning of alemtuzumab

<sup>4</sup> The last dose of prednisone is given on the morning of Day 5 (10 total doses of 60 mg/m<sup>2</sup> 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 <sup>2</sup> /day)	10	10	10	12	14.4	17.3	20.7	24.8
Etoposide (mg/m <sup>2</sup> /day)	50	50	50	60	72	86.4	103.7	124.4
Cyclophosphamide (mg/m <sup>2</sup> /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/m<sup>2</sup> PO. This would be the second dose of the 60 mg/m<sup>2</sup> 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 infusion-related 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 infusion-related dose-limiting toxicity

Reduce Alemtuzumab one dose level for:

- Grade 3 non-hematologic toxicity that does not resolve to  $\leq$  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 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  $\geq 500/\mu\text{l}$  on all measurements:  $\uparrow$  1 dose level above last cycle
    - If Nadir ANC  $< 500/\mu\text{l}$  on 1 or 2 measurements: Same dose level as last cycle
    - If Nadir ANC  $< 500/\mu\text{l}$   $\geq 3$  measurements:  $\downarrow$  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

<u>Grade</u>	<u>% Dose of Vincristine</u>
2	100
3	50

b. Motor neuropathy

<u>Grade</u>	<u>% Dose of Vincristine</u>
1	100
2	75
3	25
4	0

c. Hepatic dysfunction

<u>Bilirubin on Day 1</u>	<u>% Dose of Vincristine</u>
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-1@mail.nih.gov](mailto:ncicentralregistration-1@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  $< 10,000/\text{mm}^3$ . 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  $> 50,000/\text{mm}^3$ .

#### **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.

**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):  $\geq 50\%$  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  $\geq 50\%$  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  $\geq 50\%$  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:  $\geq 50\%$  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  $\geq$  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 for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 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.

### **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 re-consent 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

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

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.

#### 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 *greater 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<sup>2</sup>, 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<sup>2</sup> 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  $\geq$  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<sup>2</sup> 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, tachyarrhythmia 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.

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## 11 Appendix 1: EPOCH CHEMOTHERAPY

Drug	Total dose* (mg/m <sup>2</sup> /d)	Route	Day						22
			1	2	3	4	5	6	
Alemtuzumab	fixed total dose 30, 60 or 90 mg	IV	x						
Etoposide	50 mg/m <sup>2</sup> /day	CIV	x	x	x	x			
Vincristine	0.4 mg/m <sup>2</sup> /day	CIV	x	x	x	x			
Doxorubicin	10 mg/m <sup>2</sup> /day	CIV	x	x	x	x			
Cyclophosphamide	750 mg/m <sup>2</sup>	IV						x	
Prednisone	60 mg/m <sup>2</sup> /day BID	PO	x	x	x	x	x		
Filgrastim	480 mcg QD	SC						x until ANC recovery ≥ 5000/mm <sup>3</sup>	
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.

<b>Etoposide Dose</b>	<b>Volume of Fluid Containing a Daily Dose</b>	<b>Volume of Overfill (fluid + drug)</b>	<b>Total Volume in the Product (including overfill)</b>
< 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).

<b>Etoposide Dose</b>	<b>Total Volume to Infuse per 24 hours</b>	<b>Volume of Overfill (drug-containing fluid)*</b>	<b>Administration Rate</b>
< 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.

**Abbreviated Title:** EPOCH-Campath in T Lymphomas  
**Version Date:** 05/22/2017

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).



INSTITUTE: National Cancer Institute

STUDY NUMBER: 03-C-0304 PRINCIPAL INVESTIGATOR: Wyndham H. Wilson, M.D., Ph.D.

STUDY TITLE: Pilot Trial of Alemtuzumab and Dose-Adjusted Epoch in Chemotherapy Naïve Aggressive T and NK-Cell Lymphomas

Continuing Review Approved by the IRB 07/21/16

Amendment Approved by the IRB on 07/03/17 (G)

Date posted to web: 07/15/17

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Standard

### INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

### Description of Research Study

Lymphoma and its treatment: You/your child have a disease called T-cell or NK cell non-Hodgkin's lymphoma which your/your child's doctors think would be better treated with chemotherapy than surgery or radiation. For your/your child's particular kind of non-Hodgkin's

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lymphoma, previous studies have shown that combinations of drugs are much more likely to make the disease go away for appreciable periods of time than single drugs, which have only very limited effectiveness against this group of lymphomas. Studies have also shown that more intensive (i.e. higher dose) treatments have a greater chance of success than more gentle approaches. In general, mature T-cell and NK cell lymphomas are less responsive to standard therapies than B-cell lymphomas. This protocol is specifically for people with T-cell and NK cell lymphomas, as we are trying to find better treatments for these types of lymphoma. Studies conducted at the National Cancer Institute suggest that certain chemotherapy drugs may be more effective if given by continuous infusion into the vein rather than by the standard method of rapid intravenous injection. One such combination, which we call EPOCH (each letter stands for one of the drugs used in the combination), seems to have a high degree of effectiveness in patients whose tumors have stopped responding to standard regimens. We therefore plan to test this combination in patients who have never received chemotherapy previously. Recent evidence also indicates that the effects of chemotherapy may be improved by combination with monoclonal antibodies. Monoclonal antibodies are purified proteins that are specially made to attach to pieces of foreign substances (such as cancer cells) with the goal of inactivating them. A monoclonal antibody, a drug called Alemtuzumab (the trade name is Campath-1H), has been manufactured to attach to a protein called CD52 that your/your child's type of tumor could contain. We will attempt to determine if your/your child's tumor "expresses" CD52, but you/your child will be eligible for treatment even if the results are unknown. Up to 30 patients will be treated on this study.

**Objectives and design of this study:**

The general purpose of this study is to develop treatments for lymphoma that are more effective than existing therapies. The experimental part of this treatment program is to test whether giving alemtuzumab in combination with continuous infusion EPOCH chemotherapy with filgrastim is safe and if it improves the outcome of therapy of your/your child's lymphoma. In this study five chemotherapy drugs are given together in an intensive combination called EPOCH. Each series of treatments is called a cycle; a cycle is repeated every three weeks and drugs are administered during the first five days of every cycle. EPOCH consists of prednisone by mouth on days 1-5, and etoposide, doxorubicin, and vincristine as a continuous infusion on days 1 through 5 (total of 96 hours). In addition, cyclophosphamide is given by intravenous injection over about 15 minutes on day 5. You/your child will also receive a dose of alemtuzumab on day 1, immediately before the chemotherapy begins. Each cycle lasts 3 weeks: 5 days of chemotherapy followed by 16 days of no chemotherapy. You/your child will receive repeated cycles of Alemtuzumab and EPOCH until remission (disappearance of tumor) is achieved or until the tumor shows no further evidence of shrinkage. Between cycles of treatment we give another drug, filgrastim, whose purpose is to help your/your child's normal bone marrow cells recover from the chemotherapy and produce normal white cells. The use of filgrastim in this way may help us increase the total amount of chemotherapy you/your child can receive.

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**Treatment consists of the following drugs:**

1. Doxorubicin, etoposide, and vincristine - These three drugs are given by continuous IV infusion over four days, beginning on day 1 and ending on day 5 of each cycle. We deliver these drugs with the aid of one lightweight, portable infusion pump, each about the size of a portable tape recorder; this permits treatment on an outpatient basis. The pumps deliver the therapy through an intravenous catheter, which is placed in your/your child's vein beforehand. You/your child will be taught about the use and care of the pump and what to do if it stops working.
2. Cyclophosphamide - This is given over about 15 minutes on day 5 of each treatment cycle.
3. Prednisone - These are pills given by mouth twice a day for the first 5 days of every cycle.
4. Alemtuzumab – Administered by vein over approximately twelve hours on the first day of therapy, immediately before the chemotherapy infusion begins.
5. Filgrastim - This is given by injection under the skin once a day starting on day 6 of each cycle and continuing until recovery of the white blood cell count or until day 19 of each cycle. If your/your child's white blood cell count is still very low on the day treatment is due to begin again, the chemotherapy may be deferred and the filgrastim will be given until you/your child have a fuller recovery of the white count. This drug is given to stimulate your/your child's bone marrow to produce neutrophils, one of your/your child's white blood cells. You/your child will be taught how to administer the filgrastim to yourself/your child during the first treatment cycle.

We expect that treatment will be given for 6 cycles (18 weeks), depending on how you/your child's respond to the therapy. In general you/your child will receive two cycles past the point of maximum response. Since several of these drugs can lower your/your child's resistance to infection, we also require that you/your child take a combination antibiotic, trimethoprim/sulfamethoxazole (SeptraR or BactrimR) for three days each week while you/your child are on chemotherapy, acyclovir (or an alternative drug) daily and fluconazole in an attempt to prevent infections. If allergic to these preparations, you/your child will be given other drugs with similar activities in their place.

**What happens after treatment is completed:**

This depends on how you/your child have responded to the therapy. If all evidence of disease has disappeared, we will schedule periodic visits to the Clinical Center for follow-up examination and tests. If the disease gets worse while receiving therapy, does not disappear entirely or if it should recur after having disappeared for a period of time, then you/your child may need further therapy. At that time you/your child will be given the opportunity of

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participating in additional research protocols that may be appropriate for you/your child. If no such protocols are available, you/your child will be returned to the care of your/your child's local physician. It is important to stress that participation in this protocol does not constitute a promise of long-term medical care here at the Clinical Center. It is conceivable that participation in this study may make you/your child ineligible to participate in certain other research protocols because the requirements for entry onto these protocols may not allow patients who have already been treated with certain drugs or who have had certain side effects from previous treatment. You/your child may decide now not to receive treatment on this protocol, or you/your child may choose at any point in time to stop the treatment and withdraw from the protocol; in either case you/your child will be returned to the care of your/your child's referring physician.

**Treatment of disease in the nervous system:**

It occasionally happens that lymphomas spread to the coverings of the brain (the meninges) at some point during the illness. We will test to see whether there is any evidence of lymphoma in your brain or spinal fluid before you receive any treatment. If this should happen, the treatment usually includes the instillation of one of two chemotherapy drugs (methotrexate and cytarabine) directly into the fluid (the cerebrospinal fluid, or CSF) surrounding the brain. This is usually done by first placing a small reservoir (an Ommaya reservoir) under the skin of the scalp; this reservoir is connected to a catheter that is placed through the brain itself into the fluid. This procedure is performed by a neurosurgeon under general anesthesia. These drugs may also be administered through a spinal tap (also called a lumbar puncture). Depending on how you/your child responds to this therapy, it may be necessary to modify it and to also administer radiation to your/your child's brain and spinal cord. Each of these therapies will be discussed with you/your child if they are needed. Patients who have lymphoma in their bone marrow are at higher risk of developing lymphoma in the brain areas. To reduce this risk, patients at higher risk will receive methotrexate by a spinal tap on days 1 and 5 of cycles 3-6 of their EPOCH chemotherapy. Your/your child's treating physicians will discuss this with you/your child.

**Risks or Discomforts of Participation**

In order to determine whether this study is suitable for you/your child, a number of tests will have to be done. This period of evaluation may take up to two weeks and is usually done on an outpatient basis. Depending on the tests you/your child have already had before coming here, these may include blood and urine tests, studies of lung function, CAT or MRI scans, radioisotope scans, and biopsies of tumor tissue, bone marrow, liver, or other sites. As reviewed in the section above, you will undergo a lumbar puncture to remove a small amount of spinal fluid (about 1-2 teaspoons) that will be tested for the presence of lymphoma cells. A lumbar puncture is done by inserting a small sterile needle through the skin and muscle, going between the bones of the spine in the lower back until the needle punctures the spinal canal covering. The spinal fluid will then drain out through the needle on its own.

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Biopsies will, when possible, be done under local anesthesia. The risks associated with blood draws include pain, blood clots, bruises, infection and nerve damage. The risks associated with bone marrow biopsies include pain, bleeding, and infection. Risks of biopsies include pain, bleeding, infection, and the risks to the particular area undergoing surgery. General anesthesia itself is generally very safe but has a very small risk of major complications such as heart attack or stroke. The surgical and anesthetic risks will be explained to you/your child in more detail at the time of surgery, if this is needed.

In order to receive this therapy you/your child will need to have an intravenous catheter placed. This catheter is usually placed in the arm, chest or neck area into a major vein inside your/your child's chest. We usually remove the catheter after each cycle but on occasion it can be left in for several cycles. The catheter is necessary for infusion of chemotherapy and for the drawing of blood. It is usually inserted under local anesthesia. The risks associated with the procedure include pain, bleeding, infection, and puncture of the underlying lung. Lung puncture can result in lung collapse, which might require that a chest tube be placed into the chest cavity (usually for a day or two) to help the lung reinflate. The long-term risks of the catheter include infection and clotting of the vein in which the catheter sits. If these occur, it may be necessary to remove the catheter. These risks will be explained to you/your child in more detail at the time of the insertion.

**Side effects that have been observed with the drugs in this program when they are used individually include the following:**

- a. Doxorubicin may cause sore mouth, loss of hair, a fall in blood counts with increased risk of serious infection or bleeding, tissue damage if the drug contacts the skin, heart damage and, rarely, death due to heart failure. However, the infusion method used in this study has been shown to reduce the risk of heart damage compared to the standard rapid infusion method.
- b. Cyclophosphamide may cause a fall in blood counts with increased risk of serious infection or bleeding, loss of hair, damage to the lining of the urinary bladder with painful and bloody urination, loss of function of the ovaries or testes, and nausea and vomiting. The bladder irritation can be minimized by drinking at least two quarts of fluid each day. Fluid retention with lowering of blood salt levels (known as SIADH) can rarely occur.
- c. Vincristine often causes numbness of the hands and feet after several cycles. Patients also may have constipation and medications will be given to reduce this. In most instances, these symptoms resolve when the drug is stopped, but resolution of the numbness in the hands and feet may sometimes take months or even years. The drug can also cause tissue damage if it contacts the skin, low or high blood pressure, frequent or burning on urination, weight loss, rash, fever, headache, jaw pain and eye problems. Fluid retention with lowering of blood salt levels (known as SIADH) can rarely occur.

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- d. Etoposide may cause nausea and vomiting, diarrhea, loss of hair, lowering of blood pressure during administration, rash, itching, liver abnormalities, allergic reactions, mouth ulcers, and lowering of blood counts.
- e. Alemtuzumab has a spectrum of side effects that can be divided into infusional reactions, immune suppression, bone marrow toxicity, and other side effects. These reactions are detailed below.

Acute infusion reactions

Some patients have reactions during the first few treatments that do not occur with later infusions of Alemtuzumab. The administration of Alemtuzumab can cause allergic reactions which may appear as shortness of breath or wheezing. If the shortness of breath becomes severe, you/your child may be required to have a tube placed in your/your child's throat to help you/your child breathe. Other types of allergic-like possibilities include severe lowering of blood pressure, fever, chills, rash, hives, itching, or abdominal pain and throat swelling. Lowering of the blood pressure may cause damage to the heart or brain and this damage may be permanent. These reactions can be severe and some patients have died as a result of such reactions. You/your child will be given acetaminophen and diphenhydramine to reduce the severity of these side effects. Your/your child's doctors or nurses will closely monitor you/your child closely throughout the treatment for these side effects.

Immune suppression

The normal cells that fight infection in your/your child's body are killed by this treatment. Without these cells you/your child may develop infections that occur in patients whose immune system does not function. Patients treated with this drug can develop infection with viruses, fungi, parasites and bacteria. You/your child will be treated with oral medications to prevent certain infections and they will be continued until your/your child's doctors have determined that it is safe to discontinue them.

Bone marrow toxicities

Many patients have had low blood counts when Alemtuzumab is given at the doses used in this trial. These effects are even more severe when Alemtuzumab is given to patients with bone marrow abnormalities. Anemia or a low red blood cell count, which causes weakness or fatigue has occurred and may require blood transfusion. Low platelet counts, which may cause a tendency to bleed, may require platelet transfusions and low white blood cell counts may make you/your child susceptible to infection. If the infection fighting white blood cells fall to low levels we may give you/your child G-CSF to stimulate the production of these cells. Occasional patients have had severe depression of all of the normal blood elements, a condition called aplasia.

Miscellaneous toxicities

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Other common side effects include loss of appetite, nausea, vomiting, fatigue, headache, diarrhea, muscle or joint pain, ringing in the ears, difficulty with thinking, and damage to the liver. Blood pressure has been seen to increase following administration of Alemtuzumab and may require treatment. Your/your child body may react to the Alemtuzumab by making antibodies to it. These antibodies may rapidly inactivate the injected Alemtuzumab making it ineffective. Infections caused by organisms that normally inhabit your/your child body and cause no disease may become evident as a result of the treatment with Alemtuzumab. You/your child may also be more susceptible to viral and bacterial infection. In addition the combination of Alemtuzumab and EPOCH chemotherapy may produce toxicities that are unknown.

- f. Prednisone may cause ulceration in the stomach or bowel, increased blood pressure, high blood sugar (diabetes), increased risk of infection, a round appearance of your/your child's face, weight gain, change in mood, thinning of your/your child's bones with increase in the risk of fracture, increased pressure in the eye (known as glaucoma) and clouding of the eye (called cataracts). It can also cause or worsen acne.
- g. Filgrastim can occasionally cause bone pain by stimulating normal bone marrow. This stops when drug administration stops. It has also been reported sometimes to cause skin rash, skin reddening around the injection site, muscle cramps, decreased platelets (not clinically significant), pain or numbness and tingling around the chin, worsening of certain pre-existing inflammatory conditions (such as psoriasis eczema, or vasculitis), fever, body aches, and alterations in certain laboratory tests. With prolonged administration filgrastim has been associated with hair thinning and enlargement of the spleen. These side effects do not necessarily stop when drug treatment stops.
- h. Trimethoprim/sulfamethoxazole can cause a skin rash that goes away when the drug is stopped. It is possible that the rash may not resolve and could indicate a severe reaction (i.e. Stevens-Johnson syndrome). If you/your child are allergic to this drug, you/your child will receive inhaled pentamidine instead. Inhaled pentamidine can cause coughing, wheezing, and burning pain in the throat. All of these symptoms usually go away shortly after the inhalation treatment is finished
- i. Acyclovir can cause nausea/vomiting, diarrhea, headache, vertigo, insomnia, irritability, depression, skin rash, acne, accelerated hair loss, arthralgia, fever, palpitations, sore throat, muscle cramps, menstrual abnormalities, and lymphadenopathy.
- j. Fluconazole can cause nausea. Less common side effects may include: Abdominal pain, diarrhea, headache, skin rash, vomiting and elevated liver enzymes.
- k. Methotrexate, when administered into the spinal fluid, may cause low blood counts and ulcerations in the mouth, stomach, and intestines. It can cause acute headache, back pain, stiff neck, and /or fever; it can also cause weakness or paralysis of certain muscles. It can cause seizures and coma. Other side effects it can cause are usually associated with intravenous administration rather than intrathecal (lumbar puncture administration), but

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these include liver function abnormalities, inflammation and scarring of the lungs, inflammation of the tissue covering the heart, and severe skin reactions.

- I. Cytarabine given by lumbar puncture can cause nausea, vomiting, fever, and headaches. Rarely, it can cause weakness and seizures. When given into the spinal fluid, it does not usually cause systemic toxicity, but we will monitor you/your child for low blood counts, and liver function abnormalities, which can occur with cytarabine when given by vein.

It is important to emphasize that when you/your child have a decreased white blood cell count, you/your child are at risk of infection. Such infections can be very serious and can even cause death if not quickly and properly treated. Therefore, if you/your child have a temperature greater than 38.3° C (101° F), you/your child must call your doctor immediately. Chemotherapy may also cause your platelets to fall; since platelets are the blood elements that permit blood to clot, this may place you/your child at increased risk of serious bleeding. It may be necessary to give you/your child transfusions of platelets if your/your child's platelet counts reach very low levels. You/your child may also need red blood cell transfusions if your/your child's hemoglobin level drops very low. There is a small chance that damage to the normal bone marrow may eventually result in bone marrow failure, leading to a serious shortage of one or more kinds of cells in the blood, or to leukemia. Because this is a relatively new combination of drugs, it is always possible that unanticipated side effects may occur.

Many of the drugs used in this treatment program are toxic to the cells in the ovary and testicle and may produce sterility. Recovery of normal fertility is not well studied although we know that some patients treated with this combination have remained fertile after the therapy has been completed. For this reason, men who are about to receive this treatment should, if they wish to have children in the future, consider sperm banking before start of the treatment. These drugs may also be very toxic to an unborn child. Therefore, adequate birth control measures (such as the contraceptive pill, condoms, diaphragm with contraceptive foam or ointment, contraceptive sponge, etc.) should be used by participants or their sexual partners while receiving treatment on this study. Women of childbearing age will have a pregnancy test, which must be negative at the time of study entry. This test requires that blood be drawn from a vein one or two days prior to the study. The results of the pregnancy test will be made available to you/your child prior to the initiation of the study. Your/your child's physicians will watch you/your child closely for side effects and will stop treatment if any side effects become a serious threat to your/your child's life or well-being. Your/your child's physicians will also stop the treatments if it becomes clear that the treatment is not successfully controlling your/your child's disease. Complications of Ommaya insertion are uncommon when done by an experienced group but could include infection and bleeding at the operative site or in the brain itself. Complications of lumbar puncture may include pain or bleeding at the site of needle insertion (the low back), infection, and headache. Most patients tolerate this treatment without serious side effects, although drugs placed into the brain fluid (CSF) may cause headache, stiff neck, and confusion that resolve when they are stopped. With long-term treatment, confusion and a slowing of thought processes may occur. If this treatment becomes necessary for you/your child, the complications of the

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lumbar puncture or Ommaya insertion and methotrexate instillation will be discussed in more detail.

### Potential Benefits of Participation

It is likely that most patients will have at least a temporary improvement from treatment with Alemtuzumab and EPOCH chemotherapy. However, we cannot be certain if you/your child will be cured of your/your child's lymphoma and it is possible that you/your child may not respond to treatment.

### Alternative Approaches or Treatments

It should be emphasized that we do not know at this point whether the combination of drugs we propose to give you/your child is superior, inferior, or equivalent to standard combination chemotherapy for your/your child's disease. Alternative procedures that could be used to treat your/your child's disease include:

1. Other combination drug regimens and other schedules of the same drugs used in this study. For example, a chemotherapy called CHOP given in the conventional manner would be suitable standard therapy for your/your child's condition.
2. Treatment with single drugs. This is known to produce brief responses of a few months' duration in many patients but to have little beneficial effect in long-term control of the disease.
3. Radiation (X-ray) treatments. This can stop tumor growth in particular locations, such as bone, abdomen, and other sites but is not successful in controlling the disease overall unless the disease is very localized at the start of therapy.
4. Surgery. As with radiation, surgery can be successful in removing tumor from particular locations but cannot be used successfully to remove all lymphoma cells from the body, since the disease is almost always present in multiple locations. Also, surgery cannot be used against tumor in some of the organs most commonly involved by lymphoma, such as the liver or the lungs.
5. Waiting, without active therapy. Although a period of watchful waiting is appropriate treatment for some kinds of tumors, in lymphomas similar to yours/your child's, the disease will often grow and spread rapidly if no treatment is administered.
6. No treatment. You/your child can choose not to receive any therapy for your/your child's lymphoma. In this case, your/your child's doctor can give you/your child's medications that will make you/your child feel comfortable.

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### Research Subject's Rights

Any complication arising from this treatment will receive full and prompt medical attention. However, the National Cancer Institute, federal government, and Clinical Center do not provide financial compensation for injury or long-term medical treatment for such injuries, except as may be provided by remedies available under law.

You/your child will not be paid for taking part in this study. Your/your child's medical care and the costs of the laboratory and radiographic studies done at the Clinical Center, NIH will be at no expense to you/your child. If the blood tests needed to monitor the effects of treatment are to be done by your/your child's local physician, you/your child can be reimbursed for the costs if your/your child's insurance does not cover this expense; permission for this must be obtained by your/your child's NIH physician in advance. The NIH cannot, however, reimburse you/your child for the costs of other types of medical care delivered outside the NIH, even if you/your child are seeking medical attention as a result of side effects from treatment given here, unless permission is granted in advance by the principal investigator of this study. Similarly, we do not ordinarily reimburse the costs of diagnostic radiology tests (such as CT scans, MRI, or chest X-rays) done outside the NIH, even if they are done for the purposes of this study.

### Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

A description of this clinical trial will be available on <http://www.Clinicaltrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

### Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to \$15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

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### Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

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**OTHER PERTINENT INFORMATION**

**1. Confidentiality.** When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

**2. Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

**3. Payments.** The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

**4. Problems or Questions.** If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Wyndham H. Wilson, M.D., Ph.D.; Building 10, Room 4N115, Telephone: 240-760-6092. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

**5. Consent Document.** Please keep a copy of this document in case you want to read it again.

<b>COMPLETE APPROPRIATE ITEM(S) BELOW:</b>			
<p><b>A. Adult Patient's Consent</b></p> <p>I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.</p> <hr/> <p>Signature of Adult Patient/ Legal Representative</p> <p style="text-align: right;">Date</p> <hr/> <p>Print Name</p>	<p><b>B. Parent's Permission for Minor Patient.</b></p> <p>I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.</p> <p>(Attach NIH 2514-2, Minor's Assent, if applicable.)</p> <hr/> <p>Signature of Parent(s)/ Guardian</p> <p style="text-align: right;">Date</p> <hr/> <p>Print Name</p>		
<p><b>C. Child's Verbal Assent (If Applicable)</b></p> <p>The information in the above consent was described to my child and my child agrees to participate in the study.</p> <hr/> <p>Signature of Parent(s)/Guardian      Date      Print Name</p>			
<p><b>THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 21, 2016 THROUGH JULY 20, 2017.</b></p>			
<hr/> <p>Signature of Investigator</p> <p style="text-align: right;">Date</p> <hr/> <p>Print Name</p>	<hr/> <p>Signature of Witness</p> <p style="text-align: right;">Date</p> <hr/> <p>Print Name</p>		