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Phase I Trial of Siplizumab and Dose-Adjusted EPOCH-Rituximab (DA-EPOCH-R) in T and NK-Cell Lymphomas

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Investigational Agent:

Drug Name:	Siplizumab
IND Number:	103970 – IND withdrawn 01-22-2013
Sponsor:	Dr. Thomas Waldmann
Manufacturer:	MedImmune

Commercial Agents:
Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, Rituximab

PRÉCIS

Background:

- 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.
- The combination of alemtuzumab and EPOCH chemotherapy was evaluated in patients with chemotherapy naïve aggressive T and NK cell lymphoid malignancy. Dose-limiting bone marrow toxicity prevented escalation of the alemtuzumab dose.
- Siplizumab is a humanized monoclonal antibody directed at CD2 that demonstrated activity in the treatment of relapsed/refractory T cell lymphoma, suggesting further development by combining with chemotherapy for untreated patients. Siplizumab caused EBV lymphoproliferative disease in patients treated with a weekly schedule of administration.
- Rituximab prevents the development of EBV lymphoproliferative disease in the allogeneic transplant setting and may be active in preventing EBV-related B cell lymphoma in other settings

Objective:

- Determine the toxicity and maximum tolerated dose of siplizumab and dose-adjusted EPOCH rituximab chemotherapy in chemotherapy naïve CD2-expressing T and NK lymphoid malignancies.

Eligibility:

- CD2-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.

Design:

- Four dose levels of siplizumab will be evaluated to determine the toxicity profile in a preliminary fashion and its activity in combination with dose-adjusted EPOCH with rituximab.
- Four dose levels of siplizumab will be explored in cohorts of three to six patients each. Patients will receive 3.4, 4.8, 8.5, or 15 mg/kg of siplizumab on day 1 of therapy, followed by dose-adjusted EPOCH-rituximab chemotherapy days 1-5 every 3 weeks for a total of 6 cycles.

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1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- Determine the toxicity and maximum tolerated dose of siplizumab and DA-EPOCH-R chemotherapy in untreated CD2-expressing T and NK lymphoid malignancies

1.1.2 Secondary Objectives

- Determine in a preliminary fashion the anti-tumor activity of the combination of siplizumab and DA-EPOCH-R chemotherapy
- Determine the time course of B, T, and NK cell depletion
- Determine the time course of B, T and NK cell recovery
- Monitor EBV reactivation and its association with the development of EBV lymphoproliferative disease

1.2 BACKGROUND

1.2.1 Siplizumab Background

Siplizumab (MEDI-507) is a humanized IgG1κ class monoclonal antibody that binds to the CD2 receptor found on human T-lymphocytes (T-cells), natural killer (NK) cells, and thymocytes. The functional protein is composed of two approximately 50 kDa heavy chains (γ1) and two approximately 25 kDa light chains (κ) for a combined molecular weight of approximately 150 kDa. Siplizumab was constructed using molecular techniques to insert the CD2 binding region (complementary determining regions: CDRs) from a characterized CD2 specific rat monoclonal antibody, BTI-322, developed by Bazin et al [1]. In an effort to reduce the potential for immunogenicity in humans, changes to the human framework of siplizumab have been kept at a minimum consistent with preservation of activity. Siplizumab has a binding coefficient determined by Scatchard analysis of 1-1.1 x 10-9 M. The number of CD2 binding sites varies; Jurkat cells have about 25,000 sites/cell and peripheral blood cells have about 7,500 sites/cell.

In vitro studies have shown that siplizumab induces alloantigen hyporesponsiveness and causes deletion of T- and NK-cells in mixed lymphocyte reaction (MLR). These properties have led siplizumab to be considered as an immuno-modulator in clinical settings where the suppression of T-cell reactivity may have clinical benefits such as psoriasis and other autoimmune diseases, graft-versus-host disease (GvHD), T-cell lymphoproliferative disorders, and in solid organ transplantation.

1.2.2 Phase 1 Clinical Trial Experience

The main therapeutic area of investigation in the siplizumab clinical program is cancer. Siplizumab has also been investigated in graft-versus-host disease (GvHD), renal transplantation, and psoriasis. In the GvHD and renal transplantation programs, high-dose, short duration regimens (1-2 weeks) of siplizumab were evaluated in four Phase 1 studies for treatment of T-cell mediated pathophysiology in GvHD following hematopoietic stem cell transplantation and graft rejection in renal transplantation. In the autoimmune disease program, extended dosing regimens (1-4 months) of siplizumab have been evaluated in four Phase 1 studies and in three Phase 2 studies for immune modulation of chronic inflammatory diseases, such as psoriasis; a follow-up observational study (MI-CP085) in psoriasis patients is ongoing. Results of Phase 1/2

studies in patients with GvHD and psoriasis did not warrant further development of siplizumab for these diseases.

In the cancer program, siplizumab has been investigated in two Phase 1 studies of similar design (MI-CP099 [NCI study] and MI-CP107 [multi-institutional study]) in patients with CD2-positive lymphoproliferative disorders. In these studies, patients have been treated with IV siplizumab at doses ranging from 0.4 to 8.5 mg/kg per treatment week using a variety of treatment schedules.

In MI-CP099 22 patients received siplizumab at doses ranging from 0.4 to 4.8 mg/kg/week administered on an every other week schedule and 7 patients received siplizumab at doses ranging from 0.8 to 4.8 mg/kg/week on a weekly schedule of administration (O'Mahony et al., manuscript submitted). The majority of the patients treated on the study had ATLL (15 pts) and LGL leukemia (7 pts). Responses were observed in nine patients with two complete responses and seven partial remissions. This change to a weekly schedule was made in order to increase the dose intensity because of evidence of tumor growth during the week off therapy. In addition, toxicity was minimal consisting of grade 1/2 infusion reactions, primarily manifested as fever and chills, usually confined to the first dose of treatment and CMV reactivation without clinically apparent organ involvement. With the switch to the weekly schedule of siplizumab three of six patients treated with multiple doses of siplizumab developed Epstein-Barr virus (EBV) lymphproliferative disease (LPD), including two cases of EBV related lymphoma. The initial 22 patient cases were reviewed and one case of EBV LPD was noted. This case occurred nine months after completion of siplizumab therapy and was attributed to the agent that the patient was being treated with at that time, depsipeptide, which has also been associated with other cases of EBV LPD (Bates S, personal communication).

MI-CP107 had an identical trial design to MI-CP099 and 22 patients were treated primarily with the biweekly schedule. The majority of the patients treated on this study had PTCL and CTCL and again responses were observed. The predominant toxicity has been Grade 1/2 infusion reactions. One case of EBV LPD was observed on that study. This occurred several months after discontinuation of siplizumab for progressive disease and at the time of development of EBV LPD the patient was receiving treatment for his underlying lymphoma. Of these five patients who developed EBV related complications, three had EBV lymphoma; one responded to EPOCH-rituximab therapy but two died of complications related to lymphoma although both also had progressive T cell lymphoma. Two patients had polymorphous EBV LPD; one responded to withdrawal of the siplizumab therapy and one responded to rituximab. The risk of EBV LPD in MI-CP099 was increased with the weekly schedule of siplizumab administration with only one case among the 22 patients treated every other week whereas three of seven patients treated with the weekly schedule developed EBV LPD. Although T cell depletion was similar with both schedules, two features differentiated the patients who developed EBV LPD from those that did not. First, CD2 is downregulated by exposure to siplizumab and recovery of its expression requires about 7-10 days. With chronic CD2 downregulation T cells may not be as reactive to EBV positive B cells that are reactivated. Lymphocytes from mice deficient in CD2 expression exhibit a profound defect in interferon gamma production and T cell proliferation in response to antigen stimulation although cytolytic T cell and NK cell function is not affected [2]. Second, a more severe depletion of NK cells was observed in patients who developed EBV LPD. Based on these findings, the trials of siplizumab alone in T cell lymphoproliferative disease were discontinued because of safety concerns.

1.2.3 Use of rituximab to control EBV LPD

The development of EBV LPD is a known complication of congenital or acquired immunodeficiency. Patients undergoing solid organ or stem cell transplants, individuals with HIV infection and patients treated with immunosuppressive chemotherapies particularly patients with rheumatoid arthritis following treatment with methotrexate or patients with lymphoma treated with fludarabine, deoxycoformycin and cladrabine are candidates to develop this complication[3-6]. Interestingly although alemtuzumab severely depletes T cells it is not generally associated with EBV LPD presumably because it simultaneously depletes B cells although a case of EBV LPD has recently been reported [7]. Transient EBV reactivation can be detected at early times after alemtuzumab administration but the level of EBV DNA detected in the serum is relatively low and can be detected for about two weeks in most patients [8]. This observation suggests that a strategy to eliminate B cells in conjunction with T cell depletion may prevent the emergence of EBV LPD. Rituximab has demonstrated activity in the treatment of EBV LPD particularly in patients whose disease is of recent onset where overall response rates of 44–75% and complete response rates of 35–69% are observed.[9,10] In addition rituximab has been tested in a preemptive fashion in patients undergoing T cell depleted stem cell transplantation. In this study patients who exhibited evidence of EBV reactivation as detected by monitoring plasma for EBV DNA at levels of greater than 1000 genome equivalents per milliliter of blood were treated with one infusion of rituximab[11]. In this study of 49 patients, 17 developed EBV reactivation as described including two patients who had EBV LPD at the time the blood EBV DNA level reached the treatment threshold. Treatment was effective in all but one patient who required additional rituximab and donor lymphocyte infusions to control the EBV LPD. These observations suggest that EBV LPD can be prevented by early administration of rituximab and that its use prior to T cell depletion may improve this outcome.

1.2.4 Therapy of T cell lymphoma

The REAL classification has had a significant impact on the management of patients with lymphocytic neoplasms[12]. 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[13]. 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. 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 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 [14-16]. 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 also emphasized the importance of the IPI score in outcome for patients with peripheral T cell lymphoma [17]. 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 within 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. In contrast to anaplastic large cell lymphoma, a relatively newly described entity that was frequently included as a T cell neoplasm, which has a good prognosis, patients with other T cell neoplasms usually do not have durable disease control. These patients frequently respond to chemotherapy but as with low grade B cell neoplasms do not achieve durable complete remissions. A total of 13 patients with T cell neoplasms (2 gamma-delta hepatosplenic, 6

peripheral T cell not otherwise specified, 1 subcutaneous panniculitis-like T cell, 4 angioimmunoblastic lymphadenopathy) have been treated with EPOCH at the NCI. Eight of the 13 patients have died due to progressive disease. Five patients are alive (two patients with angioimmunoblastic lymphadenopathy and one patient with peripheral T cell not otherwise specified). Two additional patients are alive but both had disease progression on EPOCH chemotherapy; one achieved a complete remission with depsipeptide and the other is undergoing allogeneic transplantation. We also treated six patients with adult T cell lymphoma/leukemia with EPOCH chemotherapy in combination with Zenapax but all six patients were induction failures. All but one patient showed a transient response to treatment. Thus, in contrast to the good outcome in B cell lymphoma treated with EPOCH chemotherapy alone and the apparent improvement in outcome achieved with rituximab and EPOCH chemotherapy due to an improvement in outcome for patients with activated B cell phenotypes, progress is desperately needed in the treatment of T cell neoplasms.

Our first study to combine monoclonal antibodies with chemotherapy for T cell lymphoma used alemtuzumab and dose-adjusted EPOCH (DA-EPOCH) infusional chemotherapy to assess the maximum tolerated dose and safety in patients with CD52-positive aggressive NHL. A single infusion of alemtuzumab-1H (30, 60, or 90 mg) was given over 12 hours before each cycle of chemotherapy; patients were premedicated with prednisone 12 hours before the alemtuzumab infusion was initiated. DA-EPOCH was initiated immediately following completion of the alemtuzumab infusion. Toxicity during the first cycle of treatment was used to determine alemtuzumab dose escalation. Most patients experienced grade 1–2 allergic and infusional reactions manifested as fever, chills, and urticaria. Although not originally incorporated into the definition of dose-limiting toxicity, bone marrow suppression with reversible bone marrow aplasia prevented the administration of further treatment in 2 patients at the 60 mg dose level (cycle 3 and 5) and 2 pts at the 90 mg dose level (cycle 4 and 5) of alemtuzumab. Three of these four patients were CMV antigen positive and were treated with oral or intravenous gangcyclovir. Myelosuppression was common with this regimen but with the 30 mg dose of alemtuzumab myelosuppression was equivalent to that observed with EPOCH alone or in combination with rituximab. We evaluated the ability to dose escalate EPOCH chemotherapy in patients treated with alemtuzumab and found that there was no significant difference in dose escalation or reduction with the regimen. All but one patient developed grade 4 lymphopenia. Documented infections were common and included bacterial, fungal and viral pathogens. CMV antigen positivity during treatment was common and when detected inevitably required treatment. Another viral pathogen not commonly seen with EPOCH alone or with rituximab was hemorrhagic cystitis associated with BK virus infection in the urine that resolved despite continued treatment. In addition, there was one death due to disseminated toxoplasmosis in a patient who developed an allergy to trimethoprim sulfamethoxazole and a second sudden death during EPOCH infusion that was thought to be related to a cardiac arrthymia. The 30 mg dose level of alemtuzumab appears safe to administer in combination with DA-EPOCH and there has been no bone marrow suppression that prevented completion of therapy in any patient treated at the 30 mg dose of alemtuzumab. Our preliminary results do not appear to be significantly better than chemotherapy alone and the inability to escalate the dose of alemtuzumab suggests that other antibodies that target T cells should be tested. Siplizumab is of interest because of its limited infusional toxicity and its single agent activity in T cell malignancies. Two recent studies have been published combining alemtuzumab with CHOP chemotherapy for the treatment of newly diagnosed T cell lymphoma.[18,19] In the study conducted by Gallimini et al.[20] 24 patients

(21 with PTCL-U, 6 angioimmunoblastic T cell lymphoma, 3 Alk negative anaplastic large cell lymphoma and 1 enteropathy-associated T cell lymphoma) were entered in a phase I study. The initial four patients received four 30 mg doses of alemtuzumab with cycles 1-4 of therapy and the remaining patients received eight doses of alemtuzumab with each cycle of CHOP chemotherapy. Complete remission was obtained in 17 patients (71%) and one had a partial remission. The most frequent side effects were grade 4 neutropenia and cytomegalovirus reactivation. Major infections included Jacob-Creutzfeldt reactivation, aspergillosis, and bacterial infections. In the second study conducted by Kim et al.[21], 20 patients were treated with alemtuzumab (30 mg per cycle) and CHOP chemotherapy for six cycles. This study was terminated early due to two treatment-related deaths and a high incidence of adverse infectious and hematologic toxicities. Similar to the Gallimini study, a high response rate was observed (80% overall response rate, 65% complete remission and 15% partial response). Grade 4 neutropenia occurred in 90% of patients and febrile neutropenia in over half of the subjects. CMV reactivation occurred in 5 patients and was associated with retinitis and pneumonia.

In this study, we plan to use the lymphocyte specific monoclonal antibody siplizumab in combination with DA-EPOCH-rituximab chemotherapy in patients with peripheral T cell and NK cell lymphoma and no prior therapy. Four dose levels of siplizumab will be explored, in cohorts of three to six patients each. Patients will receive doses of 3.4, 4.8, 8.5 or 15 mg/kg of siplizumab on day 1 of therapy, followed by DA-EPOCH-R chemotherapy days 1-5.

Table 1: Distribution of NHL cases by the Consensus Diagnosis

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

Consensus Diagnosis	No. of Cases	% of total cases
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 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 lymphocyctic (CLL)	76	38	35	13
Diffuse large B-cell	73	22	63	19
Primary mediastinal large B-cell	77	0	69	0
High grade B-cell, Burkitt-like	71	0	71	0
Precursor T-lymphoblastic	29	40	29	40
Peripheral T-cell, all types	36	15	27	10
Anaplastic large T/null cell	81	83	49	83

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

1.3 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. Our phase I/II trial of dose-adjusted EPOCH chemotherapy with alemtuzumab showed that we were unable to increase the dose of alemtuzumab beyond 30 mg as a single infusion with

each cycle of EPOCH and there were significant infectious complications. This limited dose of alemtuzumab administered may be inadequate to penetrate lymph nodes whereas siplizumab which will be given at higher doses may permit administration of higher doses of antibody. The major safety concern associated with administration of siplizumab is the development of EBV LPD. We postulate that administration of rituximab in combination with siplizumab will prevent the development of EBV LPD and there will be a conservative stopping rule. We will place the trial on hold if there is more than one case of EBV LPD in patients treated with this combination. This is a phase I study to determine the toxicity of siplizumab in combination with DA-EPOCH-R infusional chemotherapy. Four dose levels of siplizumab 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 siplizumab will be significantly reduced by the administration of steroids with dose-adjusted EPOCH. The plan for siplizumab 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 siplizumab is to be given. It is our intent to administer a maximum dose of 15 mg/kg of siplizumab in combination with dose-adjusted EPOCH-R at the highest dose level.

2. ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 CD2-expressing lymphoid malignancy, confirmed by pathology or flow cytometry staff of the Hematopathology Section, Laboratory of Pathology, NCI. At least 30% of the malignant cells must be CD2 positive for inclusion in this study.

2.1.2 Patients with chemotherapy naïve 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 ≥18 years.

2.1.4 Laboratory tests: Creatinine ≤1.5 mg/dL or creatinine clearance ≥ 60 ml/min; bilirubin < 2.0 mg/dl unless due to Gilbert's (unconjugated hyperbilirubinemia without other known cause), AST and ALT ≤ 3x ULN (AST and ALT ≤ 6x ULN for patients on hyperalimentation for whom these abnormalities are felt to be due to the hyperalimentation) and; ANC ≥ 1000/mm^3, platelet ≥ 75,000/mm^3; unless impairment due to respective organ impairment by tumor.

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

2.1.6 Patients must not have a marked baseline prolongation of QT/QTc interval (e.g., demonstration of a QTc interval >500 milliseconds (ms)).

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

2.1.8 Signed informed consent by the patient or patient's representative.

2.1.9 Willing to use contraception

2.1.10 Not pregnant or nursing, because of the unknown effects of DA-EPOCH-R or siplizumab on the developing fetus and infant.

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

2.2 SCREENING EVALUATION

Tests to be done within 4 weeks before study entry (prior to receiving any intervention); the laboratory tests in Sections **2.2.2**, **2.2.7**and **2.2.8** 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 CD2 staining if accessible tissue is available. Where possible, tumor biopsies will be obtained by core needle biopsy or surgery pre-treatment. Laparotomy, thoracotomy, or biopsy of relatively inaccessible lymph nodes (i.e. high axillary nodes) will only be performed if needed for definitive diagnosis and not for research purposes alone.

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

2.2.5 CMV, EBV and toxoplasmosis serologies

2.2.6 CMV antigen by PCR, serum BK virus by PCR, EBV viral load

2.2.7 Urinalysis and urine for BK virus by PCR

2.2.8 Serum pregnancy test in women of childbearing potential.

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

2.2.10 Electrocardiogram

2.2.11 Radionuclide bone and PET scans as clinically indicated.

2.2.12 Unilateral bone marrow aspiration and biopsy.

2.2.13 Lumbar puncture for cell count, chemistry, cytology, 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 sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. 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 phase I trial of siplizumab in combination with DA-EPOCH-R given every 21 days for a total of 6 cycles of treatment. Four cohorts of three to six patients will be treated. Patients in cohort 1 will receive 3.4 mg/kg of siplizumab. Subsequent cohorts will receive 4.8, 8.5 and 15 mg/kg of siplizumab. Six 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. The toxicity observed during the first cycle of treatment will

be used to determine the dose escalation of siplizumab. 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 lowest dose level that has been successfully completed without dose limiting toxicity in three or six patients. If three patients have been entered and dose limiting toxicity occurs in this patient, two additional patients will be added to bring the total number of patients evaluated at the dose level to six, and accrual to the current dose level will be suspended. If six patients have been entered and dose limiting toxicity occurs in this patient, accrual to the currently accruing dose level will be allowed to continue. A delay in protocol accrual will thus be necessary only following the first dose level. Toxicities observed during subsequent cycles will be used to determine the dose of siplizumab that will be used in phase II trials.

3.2 DRUG ADMINISTRATION (VIA CENTRAL CATHETER)

3.2.1 Siplizumab DA-EPOCH-R Chemotherapy (Appendix 1):
Siplizumab will be given on day 1 of each treatment cycle. The volume of siplizumab to be infused and the minimum duration of infusion are given in Section **11.9.3**.

Cohort 1 – Siplizumab 3.4 mg/kg

Cohort 2 – Siplizumab 4.8 mg/kg

Cohort 3 – Siplizumab 8.5 mg/kg

Cohort 4 – Siplizumab 15 mg/kg

The patients' baseline weight will be used to determine all doses of siplizumab. Dosing will be adjusted if there is a change in weight greater than or equal to 10% during one cycle. Patients will receive each treatment cycle until unacceptable toxicity, documentation of disease progression, completion of six cycles of therapy or other reasons for patient withdrawal, whichever comes first.

Patients will be treated with an escalating dose schedule of siplizumab as detailed above. Patients should be premedicated as described in Section **3.2.4**. Siplizumab will be administered as described in Section **11.9.3**. an IV infusion..

If anaphylaxis (Grade 4) hypersensitivity reactions occur, further treatment with siplizumab will be discontinued. Infusional reactions should be managed according to procedures outlined in **Table 3**. Meperidine 25 mg IV should be administered for treatment of patients with rigors. It is recommended that infusions should not exceed 24 hours in duration and administration should be controlled by a volumetric pump.

Table 3: Treatment Guidelines for Management of Siplizumab Infusion Reactions

	Treatment Guidelines
Severity of Symptoms	**Siplizumab**
Mild Localized cutaneous reactions such as mild pruritus, flushing, rash and chills	• Stop siplizumab infusion until the patient is evaluated. • Following evaluation, the infusion may be restarted under observation and monitor subject; complete siplizumab infusion at the initial planned rate. • Additional diphenhydramine 25-50 mg oral may be administered at the discretion of the treating physician. Chills without rigors can be managed with warm blankets.
Moderate	• Stop siplizumab infusion

	Treatment Guidelines
Severity of Symptoms Generalized pruritus, flushing, rash, dyspnea, fever, chills, rigors, and hypotension with systolic blood pressure >80 mmHg	**Siplizumab** • Administer diphenhydramine 50 mg IV and monitor patient until symptoms resolve. Resume siplizumab at one-half the initial infusion rate after recovery of symptoms; if symptoms develop after restarting the infusion, the infusion should be stopped and no additional siplizumab should be administered at that time. • Additional oral or IV antihistamine may be administered. A maximum dose of diphenhydramine of 100 mg in a 6 hour period should not be exceeded. Rigors should be managed with IV meperidine 25 mg every 5-10 minutes to a maximum of 100 mg. • Give oral diphenhydramine, 50 mg and acetaminophen 650 mg 30 minutes prior to the next scheduled dose of siplizumab.
Severe Any reaction such as bronchospasm, generalized urticaria, angioedema, or systolic BP ≤80 mmHg)	• Immediately stop siplizumab infusion • Bronchospasm, hypotension unresponsive to intravenous fluids, or angioedema may require administration of epinephrine 1 mg subcutaneously and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV or dexamethasone 20 mg IV, as needed, as well as supplemental oxygen. • Hypotension should be managed with intravenous fluids but if unresponsive may require more aggressive intervention such as phenylephrine infusion. • Monitor patient until resolution of symptoms. • Give oral diphenhydramine, 50 mg and acetaminophen 650 mg 30 minutes prior to the next scheduled dose of siplizumab
Anaphylaxis Defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion	• Manage as described above for severe reaction and discontinue further treatment with siplizumab

3.2.2 Dose-Adjusted EPOCH-R regimen

All patients initiate therapy at Dose Level 1 of DA-EPOCH-R shown below. Subsequent treatment doses are determined by hematological toxicity experienced on the previous cycle according to the dose-adjustment paradigm in Section **3.3.2**. **Dose adjustment is based on measurements of twice weekly CBC only (e.g., Monday and Thursday, or Tuesday and Friday), even if additional CBCs are obtained.**

Cycle 1 Doses

Drug	**Dose**	**Route**	**Treatment Days**
Infused Agents[1]			
Siplizumab	3.4, 4.8, 8.5 or 15 mg/kg	IV	day 1
Rituximab[5]	375 mg/m^2	IV	day 5
Etoposide	50 mg/m^2/day	CIV	1,2,3,4 (96 hours)
Doxorubicin	10 mg/ m^2/day	CIV	1,2,3,4 (96 hours)
Vincristine	0.4 mg/ m^2/day	CIV	1,2,3,4 (96 hours)
Bolus Agents			
Cyclophosphamide[2]	750 mg/ m^2/day	IV	day 5
Prednisone[3]	60 mg/ m^2 /bid	PO	day 0-5[4]
Filgrastim	480 mcg	SC	days 6 to ANC recovery ≥ 5000/mm^3

[1] *Begin the rituximab immediately after EPOCH infusion has completed. For the first cycle of treatment, the EPOCH infusion may be infused on days 2-6 if the Siplizumab infusion is prolonged due to infusion reaction. Begin the infusional agents immediately after siplizumab infusion has completed. Infusional agents should be administered through a central venous access device.*
[2] *Administer cyclophosphamide immediately after infusions are completed over 30 minutes.*
[3] *Begin Prednisone the 8-12 hours before start of siplizumab with second dose given just prior to siplizumab.*
[4] *The last dose of prednisone is given on the morning of Day 5 (10 total doses of 60 mg/m2 would be administered over 5 days).*
[5] *Rituximab is given as outlined in Section **11.7.4**.*

3.2.3 Table of doses per level for adjusted agents:

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

3.2.4 Premedication for Monoclonal Antibody Infusions

Premedicate 30-90 minutes before Siplizumab infusion with

- 650 mg acetaminophen PO
- 25 mg diphenhydramine PO
- 25 mg IV meperidine IV– first cycle required, subsequent cycles at PI discretion
- Prednisone 60 mg/ m^2 PO. This would be the second dose of the 60 mg/ m^2 bid prednisone regimen that is part of the EPOCH therapy. The first dose is given 8-12 hours before siplizumab.

For prevention of rigors, patients will receive 25 mg IV meperidine at the start of the first siplizumab infusion and thereafter only if medically necessary, unless the patient is allergic to meperidine. If the patient tolerated the first dose of siplizumab with grade 2 or less adverse events associated with the infusion, siplizumab can be given 1 hour after initiating the prednisone on subsequent cycles.

Prophylaxis for tumor lysis syndrome will be administered at the discretion of the Principal Investigator according to institutional practice. Hydration and urine alkalinization will be administered according to the discretion of the Principal Investigator.

Premedicate 30-60 minutes before rituximab infusion with

- 650 mg acetaminophen PO
- 25 mg diphenhydramine PO

Rituximab infusion should begin immediately after the EPOCH infusion has completed and infuse over 4-5 hours as per Section **11.7.4**. There will be no dose adjustments for rituximab.

3.2.5 CNS Prophylaxis and Treatment

3.2.5.1 CNS Prophylaxis

Patients with (1) ≥ 2 extranodal sites and elevated LDH, or (2) bone marrow involvement by lymphoma will receive CNS prophylaxis consisting of intrathecal methotrexate 12 mg on day 1 (or day 2) of Cycles 3, 4, 5, and 6.

3.2.5.2 Treatment of CNS Disease

- **Treatment of CNS Disease**
  If the CSF is positive at the time of enrollment the patient should receive active treatment of the CSF with methotrexate (see below). If this treatment either is not tolerated or found to be not effective, then cytarabine alone or in combination with methotrexate may be used. Additionally, a brain MRI should be obtained and radiation consolidation administered at the end of chemotherapy if there are parenchymal lesions.
- **CNS Induction Treatment**
  CNS induction treatment will be administered twice per week for two weeks beyond negative cytology with a minimum of 4 weeks of treatment. CNS induction may consist of one of the following:
  - Intrathecal methotrexate 12 mg or intraventricular (via Ommaya) methotrexate 6 mg

    OR
  - Intrathecal or intraventricular (via Ommaya) cytarabine 70 mg

    OR
  - Intrathecal methotrexate 12 mg + cytarabine 30 mg **or** intraventricular (via Ommaya) methotrexate 6 mg + cytarabine 30 mg
- **CNS Consolidation Treatment**
  CNS consolidation will consist of the same treatment as induction, but administered weekly x 6.
- **CNS Maintenance Treatment**
  CNS maintenance will consist of the same treatment as induction, but administered monthly x 4.

3.2.6 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.

3.2.7 Definition of Dose-Limiting Toxicity

Expected toxicities due to the DA-EPOCH-R chemotherapy regimen or support medication administration (as listed in the protocol or in the package inserts for commercial agents) will not be considered DLTs. Infusional toxicities such as fever, chills, hypotension, shortness of breath, throat-tightness, or abdominal pain are common with monoclonal antibodies and will not be considered DLTs unless the criteria below is met. Grade 3 laboratory events will not be

considered a DLT. Dose-limiting toxicity will be defined as at least possibly related to siplizumab and as:

- any grade 3 non-hematologic toxicity lasting longer than 6 hours after infusion is completed
- any grade 4 non-hematologic toxicity (except grade 3 or 4 dyspnea (unless intubation is required) and grade 4 uric acid).
- development of an EBV LPD.

Patients with rising EBV DNA levels should be evaluated for evidence of EBV LPD (CT and PET scan) but rising EBV DNA levels alone will not be considered a dose limiting toxicity.

If any grade 5 toxicity related to siplizumab administration occurs the trial will be placed on hold to further patient accrual until the toxicity and plan for management for all patients is clarified. If more than one patient develops EBV-LPD the trial will be placed on hold until discussed with the FDA and IRB and a plan to permit additional accrual is formulated.

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 excluding neurologic toxicity attributed to vincristine which will be handled as described in Section **3.3.2.2**. If the siplizumab toxicity does not resolve to grade 1 or less within 28 days from day 1 of treatment, the siplizumab will be removed from protocol treatment. Patients who experience infusional DLT may be retreated at the next cycle at the next lower dose level. If a patient experiences DLT at the reduced dose of siplizumab from Section **3.3.1**, siplizumab will be discontinued on future cycles, but treatment with EPOCH-R will continue.

3.3 TREATMENT MODIFICATIONS

3.3.1 Siplizumab Dose Adjustments

3.3.1.1 DLT

If a patient experiences a DLT (defined in Section **3.2.7**) while on treatment, subsequent doses will be modified as shown below.

Siplizumab Dose Modifications

	Siplizumab Doses (mg/kg)[a,b]	
	Original Doses	**Modified Doses**
Cohort 1	3.4	2.6
Cohort 2	4.8	3.4
Cohort 3	8.5	4.8
Cohort 4	15	8.5

a. Patients in Cohorts 1 through 4 will receive siplizumab 1 day of each cycle until unacceptable toxicity, documentation of disease progression, or other reasons for patient withdrawal, whichever comes first.
b. See Section **11.9** for calculated volume of siplizumab.

3.3.1.2 QTc Prolongation

If the QTc value is ≥ 500 msec or there is an increase in the QTc of ≥ 100 msec from baseline, siplizumab must be discontinued. ECGs and electrolytes should be followed 3 times per week post QTc prolongation until QTc falls below 460 msec.

If the QTc value is ≥ 500 msec (and < 550 msec), or there is an increase from baseline of ≥ 60 msec (but < 100 msec), to a QTc value ≥ 460 msec, then a repeat ECG should be performed within 48 hours to confirm the QTc prolongation. If the repeat ECG meets the criteria again, then siplizumab must be discontinued. ECGs and electrolytes should be followed 3 times per week post QTc prolongation until QTc falls below 460 msec.

3.3.2 EPOCH Dose Adjustments

3.3.2.1 Hematological Toxicity

No dose adjustments at cycle 1 will be made for patients that have low neutrophil count or platelet count due to bone marrow involvement of disease. Drug doses may be modified from the following algorithm at the discretion of the investigator for severe life-threatening toxicity such as ICU admissions for sepsis. When two different rules give different answers for a particular dose decision, use the lower of the two dose options.

Dose-Adjustment Paradigm

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

    Or
  - If Nadir platelet < 25,000/μl on 1 measurement: ↓ 1 dose level below last cycle
- If ANC ≥ 1000/μl and platelets ≥ 75,000/μl on day 21, and filgrastim was stopped 24 hours before begin treatment.
- If ANC < 1000/μl or platelets < 75,000/μl on day 21, delay up to 1 week. Filgrastim 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 <u>twice weekly CBC only (3 days apart).</u> Only use twice weekly CBC for dose-adjustment, even if additional CBC's are obtained.**

3.3.2.2 Non-Hematological Toxicity

a. <u>Sensory neuropathy</u>

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

b. <u>Motor neuropathy</u>

<u>Grade</u>	<u>% Dose of Vincristine</u>

1	100
2	75
3	25
4	0

c. Bilirubin
Vincristine dose will be decreased for elevated bilirubin **only** secondary to lymphoma as follows:

Bilirubin (mg/dL)	Vincristine Dose
> 1.5- < 3	decrease by 25%*
≥ 3	decrease by 50%*

Vincristine dose will be re-escalated as hyperbilirubinemia improves.

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%.

e. Dose Modifications Based on Creatinine Clearance Secondary to Lymphoma
No etoposide dose modifications will be made for decreased creatinine clearance or increase creatinine. It is anticipated that decreased clearance or increased creatinine will improve after the first treatment cycle.

3.3.3 Dose Modification for Obese Patients
All dosing is based on the patient's BSA as calculated from actual weight. There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.

3.4 PHARMACOKINETICS AND IMMUNOGENICITY
Venous blood samples will be collected and stored for future pharmacokinetic analysis at the following timepoints during the first treatment cycle:

Cycle 1 Day 1:

- Pretreatment
- End of siplizumab infusion (prior to starting EPOCH infusion)
- 2 hours post siplizumab infusion
- 6 hours post siplizumab infusion

Cycle 1 Day 2:

- 24 hours post siplizumab infusion

Cycle 1 Day 3:

- 48 hours post siplizumab infusion

Cycle 1 Day 4:

- 72 hours post siplizumab infusion

Cycle 1 Day 5:

- End of EPOCH infusion but before start of rituximab
- End of Rituximab infusion but before start of cyclophosphamide
- End of cyclophosphamide infusion

Three additional samples of blood will be drawn in all subsequent cycles:

- Prior to starting the siplizumab infusion
- End of siplizumab infusion
- End of EPOCH infusion

In the event of unexpected toxicity occurring, suggestive of a drug-drug interaction, samples will be analyzed for pharmacokinetics of the combination agents, using validated LC-MS-MS or ELISA assays.

An additional sample will be collected pre-treatment each cycle, for evaluation of immunogenicity with a human anti-humanized antibody (HAHA) assay.

Samples cannot be drawn from the same site as study drug administration. They must be obtained from a separate peripheral IV site or central line. Venous blood samples should be collected in a 8.5-ml Serum Separator Tube (SST). Immediately invert 5 times, keep specimens at room temperature for 30 minutes (to allow for clotting) and then refrigerate. The date and **exact** time of each blood draw should be recorded on the sample tube and the PK sheet. Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred). Page 102-11964 for sample pick-up. For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

A PK sheet with specific instructions will be provided to the nurses caring for each patient. Please record infusion start and end times for all infusions.

Upon arrival in the CPP, blood samples will be centrifuged for 10 minutes at 1000-1300 x *g*. The serum will be transferred into two cryovials and immediately frozen. All samples will be stored at -80°C until the time of analysis.

3.5 On Study Evaluation

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

3.5.2 At the beginning of each cycle, and near Day 21 of the last cycle: CMV PCR, BK antigenemia, EBV viral load, urine BK, CD4, CD8, B and NK cell counts.

3.5.3 Electrocardiograms (ECGs) will be conducted for a formal assessment of QTc. During cycle 1 only, 2 ECGs will be performed at each of the following time points: 1) prior to siplizumab dose 1 and 2) within 1 hour following of the completion of the siplizumab

infusion. Data regarding the effect of siplizumab on QTc interval in humans is required during evaluation of new drugs by the FDA. Guidance for management of prolonged QTc interval is provided in Section **3.3.1.2**.

3.5.4 Each cycle: Samples for pharmacokinetics and immunogenicity (HAHA) will be obtained as per Section **3.4**.

3.5.5 During cycles: CBC/differential BIW.

3.5.6 Restaging: Day 21, cycles 4 and 6. Repeat all initially positive staging tests, including peripheral blood flow cytometry.

3.5.7 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.)

3.5.8 9cc of blood in light blue sodium citrate tube for polymerase chain reaction to define T cell receptor gene rearrangement at baseline, post cycle 4, and post cycle 6.

3.5.9 A fresh tissue biopsy of accessible lymph node or a core needle biopsy will be obtained if possible without major surgery or requirement for general anesthesia. Lymphapheresis may be performed pre-treatment in patients with leukemic PTCL. The pretreatment lymph node biopsy or apheresis (in the case of leukemic disease) will be used to perform all standard diagnostic tests. In addition we will extract RNA and protein for research studies such as microarray, proteomic analysis, and identification of mutations in target genes in tumor tissues. Analysis of mutations in germline tissue will not be performed without patient consent. If patient consent is obtained, tumor tissue may be stored for future research assays which are related to this study and do not pose an increase in patient risk.

Studies	Pre-therapy[A]	Day -1 or day 1 of each cycle	Bi-weekly during therapy	Post cycles 4 & 6	Follow-up[B]
Hx; PE; VS; PS	x	x			x
Tumor Measurement	x			x	x
CBC/diff	x[F]	x	x		x
Electrolytes, Creatinine/BUN, ALT, AST, Bilirubin, LDH, Ca^{++}, Phos, Mg	x[F]	x			x
CMV PCR, BK antigenemia, EBV Viral load, urine BK, T-cell subsets	x	x			
Pharmacokinetics		x			
HAHA assay		x			
T cell gene rearrangement	x			x	
Clinical PET scan [D]	x				
ECG	x				
CT chest/abdomen/pelvis [C]	x			x	x
Bone marrow biopsy & aspirate [E] and	x			x[E]	

peripheral blood for flow cytometry where indicated					
Lumbar puncture	x				
Tumor biopsy and/or apheresis [G]	x				

A. Initial assessment performed within 1-4 weeks prior to starting treatment as per Section **2.2**.
B. Follow-up to occur as per Section **3.8**.
C. Extent of CT scans may be limited to assess sites of prior disease.
D. PET scans will be performed pre-therapy if clinically indicated. PET may be obtained at the first post-treatment restaging in patients in CRu.
E. Obtain pre-treatment and after patients achieve CR by other staging.
F. These laboratory tests must be obtained within one week of initial treatment.
G. Where possible, tumor biopsies will be obtained by core needle biopsy or surgery pre-treatment. Snap freeze and store tissue biopsies at -80°C. Lymphapheresis may be performed pre-treatment in patients with leukemic PTCL.

3.6 CONCURRENT THERAPIES

(continue until CD4 count greater to/equal to 200)

3.6.1 **Pneumocystis jiroveci 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 or atovaquone. Patients with positive serologies for toxoplasmosis should receive atovaquone.

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

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

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

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

3.7.1 Criteria for Removal from Protocol Therapy

- Excessive toxicity (as defined in Section **3.2.6**)
- Progressive disease
- Intercurrent illness that prevents further administration of treatment
- General or specific changes in a patient's condition that render the patient unacceptable for further treatment as determined by that principal investigator

3.7.2 Off Study Criteria

- Death
- Patient non-compliance
- Patient voluntary withdrawal
- Patient becomes decisionally impaired

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 Update Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

3.8 Post-Treatment Evaluation

3.8.1 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, T/B/NK cell quantitation, mineral panel, electrolytes, AST, ALT, Bilirubin, and LDH. The timing for these visits may be adjusted $\pm$ 2 months.

3.8.2 All patients will be followed at restaging visits with CMV antigen levels until the CD4 count is greater than 200.

3.8.3 All patients will have a monthly CBC with differential every month for six months post treatment.

4. CONCOMITANT/SUPPORTIVE CARE

4.1 Pneumocystis Jiroveci 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/mm3. 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/mm3.

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. CORRELATIVE STUDIES FOR RESEARCH

5.1 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

5.1.1 Procedures for PK and HAHA samples

All samples will be barcoded, with data entered and stored in Labrador, the Patient Sample Data Management (PSDM) System utilized by the CPP. This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. The program creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in a locked freezer at or below -20°C. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the PSDM System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the PSDMS. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.1.2 Procedures for Collecting, Processing, and Storing of Tumor Biopsies and/or Peripheral Blood Cells

- Orders for tumor biopsies, research blood samples and lymphapheresis collections should be placed in CRIS (Clinical Research Information System, Clinical Research Center, NIH, Bethesda, MD)

- Lymphapheresis is performed in the Department of Transfusion Medicine, and blood will be collected in the phlebotomy suite, on a clinical ward, or in an outpatient clinic of the CRC, NIH. Samples will be transferred to the NCI research laboratory at room temperature. Cells will be separated by Ficoll density gradient centrifugation and only mononuclear cells will be harvested, processed, analyzed, and stored.
- Tumor and normal blood cells may be viably frozen, typically at concentrations of 20-100x10^6/mL in FCS with 10% DMSO using a temperature controlled freezing process to optimize sample viability. Samples will be transferred to Nitrogen tanks for long term storage.
- Tumor and normal blood cells can be further processed. Additional purification may be carried out by selection with magnetic beads binding to appropriate surface molecules, typically CD19. For analysis cells may be lysed to obtain RNA (using Qiagen manufactured kits are similar) or proteins (salt and/or triton containing buffers with addition of protease and phosphatase inhibitors). Integrity of RNA is monitored by gel electrophoresis and concentration of RNA or protein is measured spectrophotometrically.
- Research sample inventory and storage. All research samples are assigned a unique number and cataloged. Viably frozen cells are stored in a temperature controlled, alarm secured Nitrogen tank in the NCI Department of Hematopathology. Tumor biopsies and processed biologic material (RNA, protein) is stored at -80°C in a temperature controlled, alarm secured -80°C freezer.
- If patient consent is obtained, tumor tissue may be stored by the Department of Hematopathology for future research assays which are related to this study and do not pose an increase in patient risk. Tissue that is given to the technician will be assigned an accession number (HP#) in the HP Case Log book. A Patient background sheet will be filled out and filed with any accompanying paperwork in the black notebook. Final reports and any supplemental reports that follow will be added to these notebooks which are located in Room 2N110.
- Frozen Specimens: Tissue snap frozen or embedded in OCT is wrapped in aluminum foil labeled with the patient's name and accession number (HP#), put into a zip-lock bag, and stored in liquid nitrogen freezer. The liquid nitrogen freezers are monitored daily for temperature variations. A FileMaker Pro data base called HP Patient Information and Specimen Inventory is used for tracking the samples.

5.1.3 Protocol Completion/Sample Destruction

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

6. DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist

with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 30 days after removal from study treatment or until off-study, whichever comes first.

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

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

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.

6.1.1 Exceptions for data collection/recording on case report forms, include:

- The results of physical exams do not need to be recorded in the database.
- Since the patient is receiving multiple agents which include commercially available agents (EPOCH-R and supportive medications) in combination with the investigational agent, all grade 1 adverse events do not require reporting/ recording in the database.
- Only concomitant medications used for treatment of or prophylaxis for infections will be recorded in the database. Other concomitant medications will not be recorded in the database.
- As patients will potentially remain on protocol until the time they die, subsequent regimens received after completing treatment on this protocol will be recorded in the database.

6.2 RESPONSE CRITERIA

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

Complete Remission (CR): Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease related symptoms if present before therapy and normalization of those biochemical abnormalities (for example LDH) definitely assignable

to the lymphoma. All lymph nodes must have regressed to normal size (less than or equal to 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in greatest diameter must have decreased to less than or equal to 1 cm or by more than 75 percent in the sum of the products of the greatest diameters. The spleen, if considered to be enlarged before therapy, must have regressed in size and not be palpable on physical examination. The bone marrow must show no evidence of disease by histology. Flow cytometry, molecular or cytogenetic studies will not be used to determine response. Response must persist for 1 month.

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

Partial Response (PR): ≥ 50% decreased in SPD of 6 largest dominant nodes or nodal masses. No increase in size of nodes, liver or spleen and no new sites of disease. Splenic and hepatic nodules must regress by ≥ 50% in the SPD. Bone marrow is irrelevant for determination of a PR.

Relapsed disease (CR, CRu) requires the following: Appearance of any new lesion or increase by ≥ 50% in the size of the previously involved sites. Greater than or equal to 50% increase in greatest diameter of any previously identified node > 1 cm in its shortest axis or in the SPD of more than one node.

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

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

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

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7. SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally

associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.1.2 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.

7.1.3 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.

7.1.4 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.

7.1.5 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.

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events:
If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue drug.

7.1.6 Disability

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

7.1.7 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.

7.1.8 Protocol Deviation (NIH Definition)
Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 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.

7.1.10 Unanticipated Problem
Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NIH INTRAMURAL IRB IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NIH Intramural IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths
The Protocol PI will report in the NIH Problem Form to the NIH Intramural IRB and NCI Clinical Director (NCI CD):

- 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.

7.2.2 NIH Intramural IRB Requirements for PI Reporting at Continuing Review
The protocol PI will report to the NIH Intramural 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.

7.3 EXPEDITED ADVERSE EVENT REPORTING CRITERIA TO THE IND MANUFACTURER

All serious adverse events that are reported to the IRB will also be faxed to MedImmune Product Safety at: 301.398.4205.

7.4 DATA AND SAFETY MONITORING PLAN

All data will be collected in a timely manner and reviewed by the PI and/or lead associate investigator for toxicity. In the event that unacceptable toxicity occurs, the IRB will be informed and appropriate measures as outlined in the protocol will be taken

This trial will be monitored by a CCR Contractor to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients' will be randomly selected and monitored at least quarterly, based on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

NOTE: It may be noted that this trial is no longer monitored as all subjects are off treatment and the IND is withdrawn.

7.4.1 Principal Investigator/Research Team

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

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8. STATISTICAL CONSIDERATIONS

Determination of sample size: This is a phase I study to evaluate the feasibility of administration of siplizumab in combination with dose adjusted EPOCH-rituximab 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 30 patients in this trial, with three to six patients treated in each cohort examining different doses of siplizumab 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 3 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 **6.2**. Since there will be only 12 patients at the MTD, this information will be considered as an early estimate of the response rate to the combination. Responses at the MTD will be identified and reported with a 95% confidence interval; since the number of patients will be limited, this will be considered preliminary and may be useful information to guide parameter estimation for a subsequent trial. The more definitive estimate will be obtained in a subsequent trial enrolling a greater number of patients at a single dose level.

B, T, and NK cell depletion and recovery will primarily be evaluated in a descriptive manner, but also by comparing the results after each cycle to those obtained at baseline. The differences will be tested for potential statistical significance using a Wilcoxon signed rank test, focusing on the findings in patients treated in a consistent manner at the MTD. As an illustration, for a given parameter and a particular time point, with 12 patients, a difference equal to one standard deviation of the difference can be detected with a two-tailed 0.05 alpha level test and >80 % power. The fact that multiple parameters and multiple time point comparisons may be undertaken will be used when the findings are being interpreted.

EBV reactivation and development of EBV lymphoproliferative disease are expected to occur rarely, but the presence and absence of the two conditions will be described by a 2 x 2 table and evaluated with appropriate epidemiologic measures if either occurs in more than a single patient.

9. COLLABORATIVE AGREEMENTS

9.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

The agent(s) supplied by MedImmune used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Lymphoid Malignancies Branch. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http:// ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

9.1.1 Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

9.1.2 For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements ,

the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

9.1.3 Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

9.1.4 When a Collaborator wishes to initiate a data request, the request should be sent to the Sponsor of the protocol, Dr. Thomas Waldmann.

10. HUMAN SUBJECTS PROTECTIONS

10.1 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 2.0. 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.

10.2 Participation of Children

Patients less than 18 years of age will be excluded because siplizumab has not been given to minors in combination with chemotherapy.

10.3 For Adults who may be become Unable to Consent

Adults unable to give consent were excluded from enrolling in the protocol. Re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. Because all patients are in follow-up, there is no longer a prospect of direct benefit. Therefore, if a patient becomes decisionally impaired, he/she will be removed from the study.

10.4 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. Siplizumab causes immunosuppression which may be made more severe as a result of combining it with chemotherapy.

10.5 Risks/Benefits Analysis

Patients eligible for this protocol will be subject to the toxicity associated with EPOCH-rituximab 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-R with siplizumab may produce increased immune suppression and myelosuppression. The development of EBV LPD is a risk in patients treated on this study and will result in discontinuation of accrual to the protocol if more than one patient develops this complication.

10.6 Consent 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 or friends, 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. The patient will receive a copy of the signed consent.

10.6.1 Telephone Re-consent

Re-consent on this study may be obtained via telephone according to the following procedure: 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 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.

11. PHARMACEUTICAL INFORMATION

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal

of chemotherapeutic agents in a self-contained, protective environment. Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination. The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose. The weight at Cycle 1 should be used for dose calculations for all cycles unless there is a ≥10% change over a period of one cycle. If a weight change ≥ 10% occurs within one cycle, then doses should be recalculated and the new dose used from that time forward.

11.1 DOXORUBICIN HCL (ADRIAMYCIN PFS™, ADRIAMYCIN RFS™, RUBEX®)

11.1.1 Availability

Doxorubicin is commercially available as a lyophilized powder for reconstitution in 10, 20, 50, and 100 mg vials. Also available are 2 mg/mL solutions for injection in 10, 20, 50, and 200 mg vials. Please refer to the FDA-approved package insert for doxorubicin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

11.1.2 Storage & Stability

Intact vials of doxorubicin solution should be stored in the refrigerator. Intact vials of powder for reconstitution should be stored at room temperature. Reconstituted solutions are stable for 7 days at room temperature and 15 days under refrigeration when protected from light. Commercially available solutions labeled as such are intended to be multidose vials.

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, 350 mcg/mL are stable for at least 36 hours at room temperature when protected from light. Also, admixtures containing vincristine, doxorubicin, etoposide concentrations of 1.6, 40, and 200 mcg/mL are stable for at least 30 hours at 32°C.

11.1.3 Preparation

Reconstitute the vials of doxorubicin powder with 5, 10, 25, or 50 mL, respectively, of sodium chloride for injection, USP, resulting in a concentration of 2 mg/mL.

The daily dose (i.e., 24-hour supply) of doxorubicin will be admixed in 0.9% sodium chloride, along with vincristine and etoposide. Infusion solutions should be changed every 24 hours. The volume of the infusion solution will be determined by the 24 hour etoposide dose. If etoposide ≤ 150 mg per 24 hours, then dilute drugs in 500 mL; if etoposide > 150 mg per 24 hours, then dilute drugs in 1000 mL 0.9% sodium chloride. Infusion solutions should be protected from light.

11.1.4 Administration

Doxorubicin will be administered as a 96-hour continuous IV infusion, along with vincristine and etoposide in the same infusion solution (see “Storage and Stability” above). 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.

11.1.5 Toxicities

- Hematologic: Leukopenia (dose-limiting), thrombocytopenia, anemia. Nadir in 10-14 days with recovery usually in 21 days.
- Dermatologic: alopecia (usually complete; reversible) radiation recall reactions; increased sensitivity to sunlight.
- Gastrointestinal: nausea and vomiting (doxorubicin is generally considered moderately to highly emetogenic), anorexia, diarrhea, mucositis (stomatitis, esophagitis).
- Cardiovascular: cardiomyopathy may occur and is related to total cumulative lifetime dose. The risk for cardiomyopathy increases with total doses > 450 mg/m^2. ECG changes and less often, arrhythmias, are seen. Rarely, sudden death has occurred.
- Other: Red discoloration of urine for 24-48 hours after drug administration. Doxorubicin is a vesicant and can cause tissue necrosis if extravasated, especially at the concentration usually employed for bolus injections (i.e., 2 mg/mL).
- Fluconazole should not be given during EPOCH infusional chemotherapy because of pharmacologic interactions

11.2 ETOPOSIDE (VEPESID®, EPIDOPHYLLOTOXIN, VP-16)

11.2.1 Availability

Etoposide is commercially available as a solution for injection in 5 mL, 7.5 mL, 25 mL, and 50 mL vials containing 20 mg/mL. Please refer to the FDA-approved package insert for etoposide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

11.2.2 Storage & Stability

Intact vials of etoposide for injection should be stored at room temperature and protected from light.

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, 350 mcg/mL are stable for at least 36 hours at room temperature when protected from light. Also, admixtures containing vincristine, doxorubicin, etoposide concentrations of 1.6, 40, and 200 mcg/mL are stable for at least 30 hours at 32°.

11.2.3 Preparation

The daily dose (i.e., 24-hour supply) of etoposide will be admixed in 0.9% sodium chloride, along with vincristine and doxorubicin. Infusion solutions should be changed every 24 hours. The volume of the infusion solution will be determined by the 24 hour etoposide dose. If etoposide ≤ 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.

11.2.4 Administration

Etoposide will be administered as a 96-hour continuous IV infusion, along with vincristine and doxorubicin in the same infusion solution (see "Storage & Stability" above). 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.

11.2.5 Toxicity
Myelosuppression, predominantly neutropenia and thrombocytopenia, is the most common toxicity associated with etoposide. Nausea and vomiting range from mild to severe in severity, depending on the dose. Mucositis is also more common at the dose used in this study. Alopecia is likely. Hypotension is associated with too rapid administration of etoposide. This would be unlikely to occur in this trial.

Fluconazole should not be given during EPOCH infusional chemotherapy because of pharmacologic interactions

11.3 ETOPOSIDE PHOSPHATE

11.3.1 Source
ETOPOPHOS® (etoposide phosphate) for Injection will be purchased by the NIH Clinical Center Pharmacy Dept. from commercial vendors.

11.3.2 Formulation
ETOPOPHOS® is commercially marketed as a sterile lyophilized product in individually cartoned, single-dose vials with white flip-off seals containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate, USP, and 300 mg dextran 40.

Etoposide phosphate is a water soluble ester of etoposide, with an advantage over the latter drug of a decreased potential for precipitation following dilution and during intravenous administration.

11.3.3 Preparation
The contents of each vial of ETOPOPHOS® must be reconstituted prior to use with one of the following solutions:

- Sterile Water for Injection, USP (SWFI);
- 5% Dextrose Injection, USP (D5W);
- 0.9% Sodium Chloride Injection, USP (0.9%NS);
- Bacteriostatic Water for Injection with Benzyl Alcohol (BWFI); or
- Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol (B0.9%NS)

Use the quantity of diluent shown below to reconstitute each vial of ETOPOPHOS® containing 100 mg etoposide equivalents

Volume of Diluent	Resulting Concentrations	
	Etoposide Equivalents	Etoposide phosphate
5 mL	20 mg/mL	22.7 mg/mL
10 mL	10 mg/mL	11.4 mg/mL

Following reconstitution, etoposide phosphate may be further diluted to concentrations as low as 0.1 mg/mL etoposide with either 0.9%NS or D5W.

11.3.4 Dosage and Administration
Etoposide and etoposide phosphate (ETOPOPHOS®) may be used interchangeably. Etoposide phosphate dosages and calculated doses are expressed as etoposide equivalents. Administration routes, rates, durations, intervals, and schedules are the same for either etoposide or etoposide phosphate.

11.3.5 Storage
Store unopened vials under refrigeration 2°–8°C (35.6°–46.4°F) in the original packaging to protect the drug product from light.

11.3.6 Stability
Unopened vials of ETOPOPHOS® for Injection are stable until the date indicated on the package when stored in the original packaging under refrigeration 2°–8°C (35.6°–46.4°F).

After reconstitution, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration for up to 7 days; at controlled room temperature 20°–25°C (68°–77°F) for 24 hours following reconstitution with SWFI, D5W, or 0.9%NS; or at controlled room temperature for 48 hours following reconstitution with BWFI or B0.9%NS.

After further dilution, etoposide phosphate solutions may be stored under refrigeration or at controlled room temperature for up to 24 hours.

Etoposide phosphate is not less stable than etoposide base when prepared as an admixture with doxorubicin and vincristine in the proportions used in the EPOCH chemotherapy regimen; i.e., 5 parts etoposide to 1 part doxorubicin to 0.04 parts vincristine (initial dose level). [reference: Yuan P, et al. Am J Health Syst Pharm 2001;58:594-8]. Consequently, the same strategies and procedures for preparation, stability, and expiration dating that apply to admixtures containing etoposide + doxorubicin + vincristine will apply to admixtures in which etoposide is replaced by etoposide phosphate.

11.4 VINCRISTINE SULFATE (VCR, LEUROCRISTINE SULFATE, ONCOVIN®, VINCASAR PFS)

11.4.1 Availability
Vincristine is commercially available in 1 mL, 2 mL, and 5 mL vials in a concentration of 1 mg/mL. Please refer to the FDA-approved package insert for vincristine sulfate for product information, extensive preparation instructions, and a comprehensive list of adverse events.

11.4.2 Storage & Stability
Unopened vials should be stored under refrigeration and protected from light. Commercially available solutions labeled as such are intended to be multidose vials.

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, 350 mcg/mL are stable for at least 36 hours at room temperature when protected from light. Also, admixtures containing vincristine, doxorubicin, etoposide concentrations of 1.6, 40, and 200 mcg/mL are stable for at least 30 hours at 32°.

11.4.3 Preparation
The daily dose (i.e., 24-hour supply) of vincristine will be admixed in 0.9% sodium chloride. Infusion solutions should be changed every 24 hours. The volume of the infusion solution will be

determined by the 24 hour etoposide dose. If etoposide ≤ 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. Infusion solutions should be protected from light.

11.4.4 Administration
Vincristine will be administered as a 96-hour continuous IV infusion, along with etoposide and doxorubicin. These three agents should be admixed in the same infusion solution (see "Storage & Stability" above). The chemotherapy will then 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.

11.4.5 Toxicity
The most common toxicity associated with vincristine is neurotoxicity. Peripheral manifestations of neurotoxicity include: numbness of extremities, paresthesias, loss of deep tendon reflexes, neuropathic pain and muscle weakness. GI manifestations of neurotoxicity include constipation, and adynamic ileus. Cranial nerve manifestations include: diplopia, hoarseness, tinnitus, jaw pain (the latter usually occurring with the first dose of vincristine). Orthostatic hypotension & SIADH may also be seen. Vincristine is a vesicant and may cause tissue necrosis upon extravasation. This is more likely with bolus injections as opposed to dilute infusions.

Fluconazole should not be given during EPOCH infusional chemotherapy because of pharmacologic interactions

11.5 CYCLOPHOSPHAMIDE (CYTOXAN®; NEOSAR®)

11.5.1 Availability
Commercially available as a powder for reconstitution in 100 mg, 200 mg, 500 mg, 1 gram, and 2 gram vials. Please refer to the FDA-approved package insert for cyclophosphamide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

11.5.2 Preparation
Reconstitute 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials with 5, 10, 25, 50, or 100 mL of sterile water for injection or 0.9% sodium chloride to give a final concentration of 20 mg/mL. The appropriate dose should be added to 100 mL of 0.9% sodium chloride for infusion. Vigorous shaking and/or gentle warming may be necessary for non–lyophilized preparations. Bacteriostatic water for injection (paraben preserved only) may be used; benzyl alcohol derivatives may NOT be used.

11.5.3 Storage & Stability
Intact vials should be stored at room temperature. Reconstituted and diluted solutions are stable for 24 hours at room temperature and 6 days if refrigerated.

11.5.4 Administration
The total dose of cyclophosphamide will be administered by IV bolus injection over 30 minutes.

All patients should receive hydration with 0.9% sodium chloride at the following volumes (based on cyclophosphamide dose levels) and rates with half administered before and half administered after cyclophosphamide.

DA-EPOCH-R Levels 1-2:	1 liter NS @ 300-500 cc/hr
DA-EPOCH-R Levels 3-5:	2 liter NS @ 300-500 cc/hr

DA-EPOCH-R Level 6 :	2.5 liter NS @ 300-500 cc/hr

11.5.5 Toxicity
Myelosuppression, hemorrhagic cystitis (patients must be well-hydrated before, during, and after treatment and have adequate renal function). Syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, alopecia, anorexia, nausea, vomiting, hyperuricemia, azospermia, amenorrhea, cardiotoxicity (myocardial necrosis) usually at doses higher than those used in this study.

11.5.6 Drug Interactions
Cyclophosphamide undergoes metabolic activation via cytochrome P450 3A4 in the liver and may potentially interact with any drug affecting the same isoenzyme. Inhibitors of 3A4 (e.g., itraconazole) could theoretically inhibit activation and inducers of 3A4 (e.g., phenytoin) could theoretically enhance activation of cyclophosphamide to active akylating species. For the most part, such interactions have not yet been documented clinically.

11.6 PREDNISONE (DELTASONE, MISCELLANEOUS)

11.6.1 Availability
Commercially available in 1, 2.5, 5, 10, 20, 25, and 50 mg tablets, or as an oral solution or syrup - 5 mg/5 ml (in 5% alcohol); solution concentrate - 5 mg/ml (with 30% alcohol). Please refer to the FDA-approved package insert for prednisone for product information, and a comprehensive list of adverse events.

11.6.2 Storage & Stability
Store tablets, solutions and syrup in tightly closed containers at room temperature.

11.6.3 Administration
Oral.

11.6.4 Toxicity
Side effects likely to be encountered with intermittent high doses include: GI (dyspepsia, ulceration), insomnia, and hyperglycemia. Occasionally a “withdrawal syndrome” after short-term high doses, such as in this study, manifest muscle aches and pains. Immunosuppression with risk of infection is also seen.

11.7 RITUXIMAB

11.7.1 Availability
Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL. Please refer to the FDA-approved package insert for rituximab for product information, extensive preparation instructions, and a comprehensive list of adverse events.

11.7.2 Storage & Stability
Intact vials should be stored under refrigeration. Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

11.7.3 Preparation
The desired dose of rituximab should be diluted in 0.9% NaCl or D_5W to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

11.7.4 Administration
Oral pre-medication 650 mg of acetaminophen and 25 mg diphenhydramine hydrochloride will

be administered 30 to 60 minutes prior to starting each infusion of rituximab. Rituximab will be administered as an intravenous infusion at 375 mg/m^2 on day 5 of each cycle of DA-EPOCH-R, just after the EPOCH infusion has completed. The first rituximab infusion should be started at 50 mg/hr, and increased in 50-mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. If this rate of escalation is well tolerated the second and subsequent infusions can begin at a rate of 100 mg/hr and increase in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

11.7.5 Toxicity
The most severe serious adverse events associated with rituximab include severe infusion reactions, tumor lysis syndrome, and severe mucocutaneous reactions. Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab.

Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells ($\geq$ 25,000/μL).

Severe mucocutaneous reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills, and dyspnea. The mechanism of rituximab infusion reactions is thought to be secondary to release of cytokines. If a reaction occurs, then the infusion should be stopped until the symptoms resolve, and then restarted at a 50% slower rate.

Recent reports describe hepatitis B reactivation with fulminant hepatitis, hepatic failure and death in some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately 1 month after the last dose.

11.8 FILGRASTIM

(G-CSF; r-met HuG-CSF; Granulocyte Colony Stimulating Factor; Neupogen®)

11.8.1 Availability
Commercial filgrastim is available in 1 mL and 1.6 mL vials containing 300 mcg and 480 mcg filgrastim, and in prefilled syringes containing 300 mcg/0.5 mL or 480mcg/0.8 mL. Please refer to the FDA-approved package insert for filgrastim for product information, extensive preparation instructions, and a comprehensive list of adverse events.

11.8.2 Storage & Stability
Intact vials and prefilled syringes should be stored in the refrigerator at 2-8° Centigrade (36-46° Fahrenheit). Do not freeze.

11.8.3 Administration
Filgrastim will be administered as a subcutaneous injection. The daily dose will be 480 mcg administered daily starting day 6 and continued until ANC is >5000 post nadir.

11.8.4 Toxicity
The most common side effect associated with filgrastim is medullary bone pain. Bone pain is

usually reported as mild or moderate and, if necessary, may be treated with non-opioid or opioid analgesics.

11.9 SIPLIZUMAB (IND #103970 – WITHDRAWN 1/22/13)

Supplies of siplizumab will be requested from MedImmune as specified in the Clinical Trial Material Manual provided to investigators. Shipments are sent out via FedEx and are performed Monday thru Wednesday. Thursday shipment for Friday delivery is available if there is an urgent need.

Accountability of the supplies received may be done through NIH Clinical Center standard procedures with pre-approval by a staff member of MedImmune Clinical Research Pharmacy Services. Otherwise, accountability must be maintained utilizing a MedImmune accountability record.

11.9.1 Formulation

Siplizumab is a humanized IgG1k class monoclonal antibody and will be supplied by MedImmune. The functional protein is composed of two approximately 50 kDa heavy chains (g1) and two approximately 25 kDa light chains (k) for a combined molecular weight of approximately 150 kDa. Siplizumab was constructed using molecular techniques to insert the CD2 binding region (complementary determining regions: CDRs) from a characterized CD2 specific rat monoclonal antibody, BTI-322, developed by Bazin et al. This antibody binds to the human CD2 receptor that is involved in the T-cell costimulatory signal. In an effort to reduce the potential for immunogenicity in humans, changes to the human framework of siplizumab have been kept at a minimum consistent with preservation of activity.

Siplizumab is supplied as a clear colorless solution. The bulk solution was sterilized by filtration and aseptically filled into prewashed, presterilized, depyrogenized vials. Siplizumab is available in one of two formulations, 5 mg/mL or 10 mg/mL. These formulations are described in Table below.

Table of Siplizumab Formulations

Formulation	**10 mg/mL**	**5 mg/mL**
Active Ingredient	siplizumab	siplizumab
Amount per mL	10 ± 1.0 mg	5 ± 0.5 mg
PH	6.0 ± 0.5	6.0 ± 0.5
Volume	1 mL	1 mL
Inactive Ingredients (per mL)	1.552 mg Histidine, USP 6.14 mg Sodium chloride, USP	1.552 mg Histidine, USP 6.14 mg Sodium chloride, USP

11.9.2 Storage & Stability

The appropriate amount of siplizumab should be mixed with 0.9% Sodium Chloride for Injection, USP and infused within 24 hours of preparation. The calculated volume of siplizumab should be mixed with 0.9% Sodium Chloride for Injection as follows:

Table of Calculated Volume of Siplizumab	
Dose Level	**Dilute with 0.9 % sodium chloride to total volume**
3.4 mg/kg	350 mL

4.8 mg/kg	450 mL
8.5 mg/kg	800 mL
15 mg/kg	1250 mL

Siplizumab drug product at 10 mg/mL has been placed on stability testing. It is stable at 2°C to 8°C. Stability testing of drug product is ongoing. As siplizumab contains no preservatives, the product should be used immediately after dilution for use and within 24 hours of preparation. If the prepared infusion is not used immediately it should be stored at 2 to 8°C. Opened vials must not be used after 6 hours.

11.9.3 Administration

Siplizumab will be administered as an IV infusion. Siplizumab must not be administered via IV push or bolus Siplizumab must not be administered via IV push or bolus. The prepared Siplizumab diluted solution must be used within 24 hours of preparation The initial infusion of antibody should be given over 2-24 hours. The infusion rate for the first 30 minutes should be 25 mL/hr and if well tolerated may be increased to 50 mL/hr. If this is well tolerated after 30 minutes the rate of infusion may be increased to 75 mL/hr. If this is well tolerated after 30 minutes the rate of infusion may be increased to 100 mL/hr. After the first course of siplizumab therapy, the rate of infusion may be increased to a maximum of 200 ml/hr at the discretion of the investigator. After the first two courses of siplizumab therapy, the rate and duration of siplizumab infusions will be adjusted by the treating physician, provided that previous infusions were well tolerated with no more than a Grade 1 toxicity. It is anticipated that the first infusion will be the longest due to infusional toxicity but that subsequent infusions should be better tolerated and the infusion duration will be shortened. The infusion should be held for hypotension requiring fluid resuscitation, hypoxia requiring oxygen supplementation, chills requiring meperidine or other untoward clinical events at the discretion of the investigator. The infusion should be restarted at the infusion rate that was tolerated prior to the development of toxicity.

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

11.9.4 Toxicity

Siplizumab is a foreign protein that binds to specific immune cells and therefore allergic reactions, including anaphylaxis, or cytokine release syndrome may be observed after administration of siplizumab.

Based upon the clinical experience to date, the most common clinical symptoms reported are chills, headache, myalgia, changes in vital signs, and (SC administration only) injection site reaction. These events generally have been temporally associated with dosing, brief in duration, and resolved without sequelae. Changes in hematological parameters, including decreased absolute lymphocyte count (ALC), have also been observed. Dose-level-dependent reductions in ALC occur after treatment with siplizumab administered SC or IV. Sustained reduction of ALC has been observed. Doses as high as 4.8 mg/kg have been administered. These events are not unexpected given the mechanism of action of the molecule.

11.10METHOTREXATE

11.10.1Availability

Methotrexate is commercially available in 2 mL (25 mg/mL) vials or 20 mg, 25, mg, 50 mg, or 100 mg vials for reconstitution. Only the preservative free methotrexate formulation should be used for intrathecal dosing. Read the manufacturer's package labeling carefully for solution concentrations. Please refer to the agent's package insert for additional information.

11.10.2Storage & Stability

Unopened vials of methotrexate should be stored at room temperature, and protected from light.

11.10.3Preparation

For intrathecal/intraventricular injection: reconstitute to a concentration of 1-5 mg/mL with an appropriate sterile, preservative free medium such as Sodium Chloride Injection, USP.

11.10.4Administration
In this study, methotrexate will be administered as an intrathecal injection of 12 mg or intraventricular injection of 6 mg. Methotrexate will be given to select patients as described in Section **3.2.5.2**.

11.10.5Toxicity
Toxicities associated with intrathecal administration: arachnoiditis, ataxia, coma, confusion, dementia, encephalopathy, headache, paresis, seizures.

11.10.6Drug interactions
The use of NSAIDs, probenecid, salicylates, sulfonamides may prolong methotrexate levels and enhance toxicity.

11.11Cytarabine

11.11.1Availability
A commercially available pyrimidine nucleoside antimetabolite. Read the manufacturer's package labeling carefully for solution concentrations. Please refer to the agent's package insert for additional information.

11.11.2Storage & Stability
Unopened vials 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.

11.11.3Preparation
For intrathecal/ intraventricular injection: reconstitute to a total volume of 3 to 5 mL with an appropriate sterile, preservative free medium such as Sodium Chloride Injection, USP.

11.11.4Administration
In this study, cytarabine will be administered as an intraventricular or intrathecal injection of 30 or 70 mg. Cytarabine will be given to select patients as described in Section **3.2.5.2**.

11.11.5Toxicity
Toxicities associated with intrathecal administration: myelosuppression, fever, dizziness, somnolence, and arachnoiditis

12. REFERENCES

(1) de la Parra B., van den Branden, Smyej I, Bazin H. Inhibition of T-cell activation by LO-CD2-1, a rat monoclonal antibody against the human CD2 glycoprotein. Belg J Zool. 1991;13.

(2) Teh SJ, Killeen N, Tarakhovsky A, Littman DR, Teh HS. CD2 regulates the positive selection and function of antigen-specific CD4- CD8+ T cells. Blood. 1997;89:1308-1318.

(3) Abruzzo LV, Rosales CM, Medeiros LJ et al. Epstein-Barr virus-positive B-cell lymphoproliferative disorders arising in immunodeficient patients previously treated with fludarabine for low-grade B-cell neoplasms. Am J Surg Pathol. 2002;26:630-636.

(4) Bird AG, McLachlan SM. Cyclosporin A and Epstein-Barr virus. Lancet. 1980;2:418.

(5) Bhargava R, Barbashina V, Filippa DA, Teruya-Feldstein J. Epstein-Barr virus positive large B-cell lymphoma arising in a patient previously treated with Cladribine for hairy cell leukemia. Leuk Lymphoma. 2004;45:1043-1048.

(6) Birkeland SA, Hamilton-Dutoit S. Is posttransplant lymphoproliferative disorder (PTLD) caused by any specific immunosuppressive drug or by the transplantation per se? Transplantation. 2003;76:984-988.

(7) Roch N, Salameire D, Gressin R et al. Fatal adenoviral and enteroviral infections and an Epstein-Barr virus positive large B-cell lymphoma after alemtuzumab treatment in a patient with refractory Sezary syndrome. Scand J Infect Dis. 2007;1-4.

(8) Scheinberg P, Fischer SH, Li L et al. Distinct EBV and CMV reactivation patterns following antibody-based immunosuppressive regimens in patients with severe aplastic anemia. Blood. 2007;109:3219-3224.

(9) Choquet S, Leblond V, Herbrecht R et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood. 2006;107:3053-3057.

(10) Milpied N, Vasseur B, Parquet N et al. Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. Ann Oncol. 2000;11 Suppl 1:113-116.

(11) van Esser JW, Niesters HG, van der HB et al. Prevention of Epstein-Barr virus-lymphoproliferative disease by molecular monitoring and preemptive rituximab in high-risk patients after allogeneic stem cell transplantation. Blood. 2002;99:4364-4369.

(12) Harris NL, Jaffe ES, Diebold J et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical

Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol. 1999;17:3835-3849.

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

(14) Gisselbrecht C, Gaulard P, Lepage E et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood. 1998;92:76-82.

(15) Lopez-Guillermo A, Cid J, Salar A et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann Oncol. 1998;9:849-855.

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

(17) Ansell SM, Habermann TM, Kurtin PJ et al. Predictive capacity of the International Prognostic Factor Index in patients with peripheral T-cell lymphoma. J Clin Oncol. 1997;15:2296-2301.

(18) Gallamini A, Zaja F, Patti C et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood. 2007;110:2316-2323.

(19) Kim JG, Sohn SK, Chae YS et al. Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas: a phase II study. Cancer Chemother Pharmacol. 2007;60:129-134.

(20) Gallamini A, Zaja F, Patti C et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood. 2007;110:2316-2323.

(21) Kim JG, Sohn SK, Chae YS et al. Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas: a phase II study. Cancer Chemother Pharmacol. 2007;60:129-134.

13. APPENDICES

13.1 APPENDIX 1: EPOCH-RS CHEMOTHERAPY

EPOCH-RS CHEMOTHERAPY

Drug	Total dose* ($mg/m^2/d$)	Route	Day 1 2 3 4 5 6	22
Siplizumab	fixed total dose	IV	x	
	3.4, 4.8, 8.5 or 15 mg/kg			
Rituximab	375 mg/m2	IV	x	
Etoposide	50 mg/m2/day	CIV	x-x-x-x-	
Vincristine	0.4 mg/m2/day	CIV	x-x-x-x-	
Doxorubicin	10 mg/m2/day	CIV	x-x-x-x-	
Cyclophosphamide	750 mg/m2	IV	x	
Prednisone	60 mg/m2/day BID	PO	x-x-x-x-x	
Filgrastim	480 mcg QD	SC	x until ANC recovery ≥ 5000/mm3	
New cycle begins				x

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

For the first cycle of treatment, the EPOCH infusion may be infused on days 2-6 if the Siplizumab infusion is prolonged due to infusion reactions.

13.2 APPENDIX 2: EPOCH ADMIXTURES

EPOCH ADMIXTURES: PREPARATION AND ADMINISTRATION

Preparation

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

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

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

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

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

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

Administration

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

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

* DO NOT attempt to infuse the overfill.

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

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

13.3 APPENDIX 3: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.