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Treatment and Natural History Study of Lymphomatoid Granulomatosis

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Investigational Agents: None

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

PRECIS

Background:

- Lymphomatoid granulomatosis (LYG) is an angiocentric destructive proliferation of lymphoid cells predominantly involving the lungs, skin, kidneys, and central nervous system.
- It is divided into three grades, depending on the degree of necrosis and cellular atypia. The grades of disease are histologically-based and do not necessarily correlate with clinical outcome. However, like other EBV related LPD's, LYG can transform into an aggressive large B-cell lymphoma, which would be included within the grade 3 category. It is important to note that not all grade 3 lesions are a large B-cell lymphoma.
- Current evidence shows that LYG is a disease of B cells.

Objectives:

- To determine the response and long-term efficacy of alpha-Interferon in patients with lymphomatoid granulomatosis (LYG).
- To determine the response and long-term efficacy of dose-adjusted (DA)-EPOCH-R chemotherapy in patients with grade 3 LYG or in patients who have failed interferon

Eligibility:

- Patients must have a tissue diagnosis of grade 1, 2 and/or 3 LYG (or a diagnosis consistent with LYG) confirmed by the Laboratory of Pathology, NCI.
- Patients with any stage of disease will be eligible.
- Previously untreated and treated patients are eligible.
- Patients age 12 or older will be eligible.

Design:

- Interferon is used as initial treatment in patients with grades 1 and 2 LYG. Patients will receive interferon for one year past CR.
- Patients who progress after or during interferon, and patients with grade 3 LYG will receive aggressive combination chemotherapy with DA-EPOCH-R (rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide and prednisone).
- Patients who fail one treatment approach may be crossed over to the other.
- A total of 105 patients will be enrolled at this single institution.

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STATEMENT OF COMPLIANCE

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

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

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

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

1 INTRODUCTION

1.1 OBJECTIVES

1.1.1 Primary Objective

- To determine the response and long-term efficacy of alpha-interferon in patients with lymphomatoid granulomatosis (LYG)
- To determine the response and long-term efficacy of DA-EPOCH-R chemotherapy in patients with grade 3 LYG or in patients who have failed interferon

1.1.2 Secondary Objective

- To obtain tissue and blood to examine the immunologic phenotype, EBV viral loads and molecular markers of clonality in patients with LYG
- To assess overall survival (OS)

1.2 BACKGROUND AND RATIONALE

Lymphomatoid granulomatosis (LYG) is an angiocentric destructive proliferation of lymphoid cells predominantly involving the lungs, skin, kidneys, and central nervous system (1). Although the disease has been considered to be a reactive or vasculitic disease and not a neoplastic process, the 5-year survival of the initial series of patients was less than 50% with the use of corticosteroids and other conservative treatment approaches. Lethal midline granuloma (LMG) or midline malignant reticulosis is another angiocentric destructive lymphoproliferative process usually involving the sinuses or upper respiratory tract (2). Some 10 years ago DeRemee, et al. noted similarities between LYG and LMG and hypothesized that they were the same disease (3). Jaffe proposed a common pathological description for both lesions, and called them angiocentric immunoproliferative lesions (AIL) (4).

Clinical experience with AIL has identified a spectrum of natural histories for the disease and recently, histopathological correlations have emerged (5,6). Cytologic and architectural features, based on the degree of cell atypia, extent of the inflammatory background and cellular necrosis,

have been used to divide AIL into three histological grades (6). Grade I lesions are composed of angiocentric infiltrates of lymphocytes, plasma cells, and histiocytes with or without eosinophils. Large lymphoid cells are rare and when present show no cellular atypia. Necrosis is uncommon and the lymphocytes are nearly normal in appearance. In grade II lesions, cytologic atypia of the small infiltrating lymphocytes is more prominent, large lymphoid cells without atypia are common, and necrosis is frequently present. Grade III lesions are actual angiocentric lymphomas based on the monomorphism of the infiltrate, cytologic atypia in both the small and large lymphocytes, appreciable necrosis, and significantly less apparent background polymorphous inflammatory infiltrate.

Immunophenotypic examination of AIL shows the predominant cell to be a mature, post-thymic T cell with CD4 expressed on the cell surface. In grade I and II lesions, clonal rearrangement of the T-cell receptor gene is essentially never seen, and has only rarely been reported in grade III lesions (6,7). The lack of clonal T-cell gene rearrangements in grade III lesions is paradoxical because cytologically, they are malignant T-cell lymphomas. A number of explanations have been proposed for this, including hypotheses that the malignant T-cells may have rearrangements of some other, as yet unidentified, T-cell receptor, or that the truly malignant cells comprise a small percentage of the total cellular infiltrate. However, analyses of EBV in biopsies suggest that it may play a role in the progression of grade I and II to grade III AIL (malignant lymphoma) (8). In biopsies from 7 patients with grade I and II AIL, EBV-positive cells were rare or absent, while all 5 patients with grade III AIL had large numbers of cells containing EBV RNA. Furthermore, EBV was clonally integrated in two patients in whom it was checked (7).

More recently, there is evidence that LMG and LYG are patho-physiologically distinct diseases which involve different cell types. In LMG, immunohistochemical analysis shows expression of peripheral T cell antigens with occasionally coexpression of the natural killer (NK) cell marker, CD56 in the malignant cells (9). This disease is now felt to be a T-cell lymphoma derived from peripheral T cells expressing gamma-delta chains or from NK cells. In contrast, there is evidence that LYG is a disease of B cells. Immunohistochemical and PCR analysis of biopsies from 3 patients with LYG demonstrated that EBV was integrated into B-cells but not the T-cells, suggesting that LYG is an EBV-positive B cell lymphoproliferative disorder (Jaffe, unpublished observation).

Jaffe, et al. examined the clinical course of patients presenting to the National Institutes of Health with AIL of various histologic grades (6). Patients with grade I/II lesions were usually managed with cyclophosphamide/ prednisone, and patients with grade III lesions were treated with aggressive combination chemotherapy. Twenty-three patients were included in this report, nine with grade I, six with grade II, and eight with grade III lesions. The eight patients with grade III lesions were further categorized according to the Working Formulation for lymphomas: six diffuse mixed (DML), one diffuse large cell (DL), and one diffuse large cell immunoblastic (IBL). Lung was the most common site of involvement (13 of 23 patients) and there were no differences in anatomical distribution among the three histologic grades. Seven of nine grade I patients achieved CR with cyclophosphamide/ prednisone and 5/7 required no further therapy. The two patients who failed to achieve CR rapidly progressed and died of their disease, while 2/7 responders progressed to lymphoma from 2-4 years after diagnosis and died. Thus, cyclophosphamide/prednisone was curative in only 55% of patients with grade I AIL. Of the six patients with grade II AIL, 3 achieved an initial CR with cyclophosphamide/prednisone, but 4 of the 6 developed malignant lymphoma within a median of 12 months from diagnosis; only one of

the four lymphomas responded to combination chemotherapy. In contrast, 7 of 8 patients with grade III patients are in CR after combination chemotherapy ± radiation therapy at a median of 7 years. Thus, this study suggests that patients with grade III AIL (lymphoma) benefit from aggressive combination chemotherapy, while patients with grade I or II do not benefit from less aggressive chemotherapy.

Because the treatment of grade I/II AIL with cyclophosphamide/ prednisone has been disappointing, some investigators have advocated the use of aggressive combination chemotherapy. However, there are several concerns with this approach. First, there are no controlled studies of the use of aggressive combination chemotherapy in grade I/II AIL. Furthermore, patients with grade II AIL who progressed to grade III disease had a poor response to aggressive chemotherapy. Second, grade I/II AIL is not a clonal disease and is associated with immuno-suppression (low CD-4 counts), which may be exacerbated by aggressive chemotherapy.

A major shortcoming of these studies is that they did not distinguish LMG from LYG. Pathologically, LMG is a malignant lymphoma of T cell or NK cell origin and should be treated with combination chemotherapy. In contrast, preliminary evidence suggests that LYG is an EBV positive B cell lymphoproliferative disorder which occurs in a partially immunocompromised host. Interferon offers a rational treatment approach for LYG because it has both anti-proliferative and anti-viral activity. Recently, we have had anecdotal experience with the treatment of grades I/II LYG with alpha-interferon. Eighteen months ago, a 21-year-old man with grade II LYG developed progressive pulmonary nodules 2 months after completing CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy. The patient entered a complete remission after 6 months of interferon therapy (10×10^6 units 3 x week) and continues in remission on interferon. Three additional patients with grade II LYG are receiving interferon for 7, 6 and 1 months and all show continuing disease resolution.

In this protocol, we plan to treat all patients with Grade 1 and 2 LYG with interferon. Patients will receive interferon for one year past CR. Patients who progress after or during interferon, and patients with grade 3 LYG will receive aggressive combination chemotherapy with DA-EPOCH-R (rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide and prednisone). Extensive experience with EPOCH in relapsed and refractory non-Hodgkin's lymphoma has shown it to be very well tolerated and effective (10). Patients who relapse after DA-EPOCH-R may be treated with interferon providing they do not relapse with an aggressive large B-cell lymphoma.

The recent approval of rituximab (humanized monoclonal antibody for treatment of CD20 positive B-cell malignancies) provides a potential new treatment for LYG. Early experience with this agent in post-transplant LPD has shown anecdotal responses (11-13). For patients who fail interferon, rituximab may provide an important new treatment. Furthermore, it has been shown in vitro, that rituximab may increase the efficacy of chemotherapy, and clinical data suggests high activity and reversal of clinical drug resistance with the addition of rituximab to EPOCH (14-15). We currently have a protocol of DA-EPOCH, as administered in the present trial, with rituximab administered on the first day of each cycle, prior to beginning the infusions. Preliminary data in relapsed patients has shown this to be an effective regimen (14-15). For patients who fail to achieve a durable remission with interferon and chemotherapy, there are no clearly effective treatments. Thus, we wish to be able to treat such patients with rituximab alone or with interferon, as clinically appropriate. In some of these cases, the patients will have

relapsed following EPOCH-R or interferon and may benefit from additional intervention with rituximab. Furthermore, in patients who fail to achieve a remission with EPOCH-R, rituximab alone may provide disease control. This has been seen in unpublished experience in indolent lymphomas. Because these patients have a rare disorder, we believe that we may obtain important pilot information through the treatment of these relapsed patients with these standard agents.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Patients must have a tissue diagnosis of grade 1, 2 and/or 3 LYG (or a diagnosis consistent with LYG) confirmed by the Laboratory of Pathology, NCI. Final histopathologic classification and pathologic grade will be determined by Stefania Pittaluga, M.D. or her designee.

2.1.2 Patients with any stage of disease will be eligible.

2.1.3 Previously untreated and treated patients are eligible.

2.1.4 Patients age 12 or older will be eligible.

2.1.5 Patients with a history of coronary artery disease with angina pectoris, or a history of congestive heart failure will not be eligible to receive DA-EPOCH-R chemotherapy.

2.1.6 Patients with significant renal (Cr. > 1.5 mg/dl or creatinine clearance< 40 cc/min) or hepatic (bilirubin > 2.5 u) dysfunction not due to tumor involvement will not be eligible to receive DA-EPOCH-R chemotherapy.

2.1.7 Informed consent must be obtained.

2.1.8 Patients who in the opinion of the principal investigator are poor psychiatric or medical risks are not eligible.

2.1.9 Patients who received > 450 mg/m^2 doxorubicin and have a cardiac ejection fraction on echocardiogram ≤ 40% on protocol entry are not eligible to received DA-EPOCH-R.

2.1.10 Patients with prior hepatitis B exposure may be included in the study provided that they have HBV DNA levels below the World Health Organization's cutoff of 100 IU/mL prior to starting therapy.

2.2 RECRUITMENT STRATEGIES

This study will be posted on NIH websites and NIH Social Media forums.

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

2.3 SCREENING EVALUATION

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

The following activities will be performed only after the subject has signed the consent for study

01C0129, on which screening activities will be performed.

NOTE: Results from outside NIH or on another NIH protocol are accepted. Other body areas may be imaged if clinically indicated.

NOTE: Assessments and procedures to confirm study eligibility should be completed within 28 days prior to registration (unless otherwise noted).

2.3.2 Clinical Evaluations

- Complete history and physical examination with measurement of all palpable peripheral lymph nodes, skin, liver, spleen and other measurable lesions.
- Biopsy of tumor may be performed when possible by needle or peripheral biopsy to confirm the diagnosis. Biopsies requiring laparotomy or thoracotomy will only be performed if necessary for patient care and not for research purposes alone

2.3.3 Laboratory Evaluations

- Chemistry Studies: Acute Care Panel (sodium, potassium, chloride, CO_2, glucose, BUN, creatinine); Hepatic panel (alkaline phosphatase, ALT, AST, total and direct bilirubin), and 24-hour creatinine clearance if creatinine $\geq$ 1.5 mg/dl and beta-HCG. HBV DNA Levels (for participants with prior exposure to Hepatitis B).
- Serum or urine pregnancy test in women of childbearing potential.

2.3.4 Imaging Studies:

- CT Scan (Site varies on disease).
- Head CT scan or brain MRI.

2.3.5 Other Procedures

- Echocardiogram for patients receiving > 450 mg/m^2 doxorubicin.

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.4.1 Treatment Assignment and Randomization/Stratification Procedures

2.4.1.1 Cohorts

Number	Name	Description
1	Patients with lymphomatoid granulomatosis (LYG)	Patients with grades 1, 2 or 3 LYG

2.4.1.2 Arms

Number	Name	Description
1	Interferon	Interferon starting at 7.5 million Units subQ 3 times a week and increasing on the designated schedule, as tolerated. Patients continue taking interferon for 1 year beyond CR. Patients who progress may crossover to receive EPOCH-R.
2	EPOCH-R	EPOCH-R every 3 weeks for up to 6 cycles, based on response.

2.4.1.3 Arm Assignment

Subjects in Cohort 1 directly assigned to Arm 1 or Arm 2 based upon grade and stage of disease, at investigator's discretion (treatment is non-randomized and open-label). Subjects initially assigned to Arm 1, and who progress, may crossover to Arm 2.

2.5 BASELINE EVALUATION

2.5.1 Hematology Studies: CBC with differential, ESR, PT, PTT, fibrinogen, Coomb's test.

2.5.2 Serology Studies: Anti-EBV Antibody Panel, HIV 1/2 Antibody/Antigen Combo, Hepatitis B Core Antibody, Hepatitis B Surface Antibody, Hepatitis B Surface Antigen, and Hepatitis C Antibody.

2.5.3 Acute care panel (Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR, Anion Gap), Hepatic panel (Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin), Total protein, Mineral panel (serum calcium, phosphate, magnesium and albumin), LDH, CK, uric acid, serum protein electrophoresis, quantitative immunoglobulin levels, TSH and free thyroxine if TSH is abnormal, and urinalysis.

2.5.4 FACS analysis for lymphocyte subsets including Total T and B cells, CD4, CD8, CD19 or CD56 (NK).

2.5.5 CMV/EBV PCR

2.5.6 Pregnancy test (Female patients only)

2.5.7 Lumbar puncture with CSF for cytology, flow cytometry, cell count and chemistry in all patients.

2.5.8 FDG-PET Scan

2.5.9 Bone marrow biopsy and aspirate to determine if bone marrow has disease involvement.

2.5.10 Optional biopsy of tumor may be performed when possible by needle or peripheral biopsy for research purposes. Biopsies requiring laparotomy or thoracotomy will only be performed if necessary for patient care and not for research purposes alone. These biopsies may be done by CT guidance.

2.5.11 Analysis of fresh tissue and/or paraffin blocks for in-situ hybridization for EBV; immunohistochemistry for B and T cell antigens; and isolate DNA for T-cell receptor and immunoglobulin gene rearrangements by PCR if available.

2.5.12 Obtain up to 50 cc blood for storage and analysis of EBV viral loads and T-cell responses to EBV.

Note: Biopsies for experimental purposes will not be done on children.

3 STUDY IMPLEMENTATION

Please note that this protocol was on Administrative Hold from October 17, 2016 through February 8, 2017. Amendment AA serves as the formal notification to the IRB of the Administrative Hold. During the time the protocol was on Administrative Hold, no new patients were enrolled; however, patients who were on-study were followed per protocol.

3.1 TREATMENT WITH ALPHA INTERFERON

Grade 1 and 2 LYG will be initially treated with interferon-∝2b. However, in rare circumstances, patients with advanced and symptomatic grade 2 LYG may be treated with DA-EPOCH-R, at the discretion of the PI, if they require a rapid clinical response. Interferon will be started at 7.5 x 10^6 Units subcutaneously (sc) three times per week (TIW). Interferon dose can be escalated every 1-2 weeks, if no grade 3 or 4 toxicity (excluding fever) is observed and it is clinically tolerated (i.e. fatigue), on the following schedule: 10 x 10^6 U; 15 x 10^6 U; 20 x 10^6 U; 25 x 10^6; and increased in 5 x 10^6 U increments as clinically indicated, thereafter. If a patient develops grade 3 toxicity (except hematological and fever) or has intolerable fatigue, the dose will be reduced one to two dose levels. If a patient develops grade 4 toxicity (except hematological), interferon will be stopped until toxicity recovers to < grade 2 and then interferon may be restarted at 50% of the last dose. If patient develops grade 4 neutropenia, standard treatment with filgrastim (e.g. 300 ug TIW) may be used to increase neutrophil count. Patients with thrombocytopenia or anemia may be supported as clinically indicated with transfusions. If the toxicity does not resolve to < grade 2 (except hematological) within 4 weeks, interferon will be permanently discontinued.

Interferon treatment duration: Patients who enter a complete remission/stable residual abnormalities will receive interferon for 12 months beyond reaching this state. Patients with progressive disease will cross-over to receive DA-EPOCH-R chemotherapy as outlined in Section **3.2**.

3.2 TREATMENT WITH DA-EPOCH-R

Patients with grade 3 LYG and patients who progress on interferon will be treated with: DA-EPOCH-R chemotherapy. However, in rare circumstances, patients with advanced and symptomatic grade 2 LYG may be treated with DA-EPOCH-R at the discretion of the PI as initial therapy if they require a rapid clinical response. Patients who achieve a CR/stable residual abnormalities will be followed. However, patients who achieve a PR (clear disease present) with DA-EPOCH-R will receive interferon beginning 4 weeks after the last dose of chemotherapy according to the algorithm in Section **3.1**.

3.2.1 DA-EPOCH-R treatment duration

Patients will receive DA-EPOCH-R for 2 cycles beyond CR, for a maximum of 6 cycles.

3.2.2 DA-EPOCH-R Starting Dose Level (Level 1)

Drug	Dose	Route	Treatment Days
Infused Agents			
Etoposide	50 mg/m2/day	CIV	1,2,3,4 (96 hours)
Doxorubicin	10 mg/m2/day	CIV	1,2,3,4 (96 hours)

Drug	Dose	Route	Treatment Days
Vincristine	0.4 mg/m2/day	CIV	1,2,3,4 (96 hours)
Bolus Agents			
Cyclophosphamide	750 mg/m2/day	IV	day 5
Prednisone	60 mg/m2/bid	PO	day 1-5
Rituximab	375 mg/m2/day	IV	day 1
Neupogen®	300 mcg/day (if < 75 kg) or 480 mcg/day (if ≥ 75 kg)	SC	day 6 until ANC>5000

3.2.3 Administration

- Begin the infusional agents immediately after rituximab is completed.
- Administer cyclophosphamide immediately after infusion is completed on day 5.
- Repeat cycles every 3 weeks (21 days).
- NOTE: DA-EPOCH-R infusional drugs should be administered through a central venous access device.

3.3 PROGRESSION WHILE ON TREATMENT

Patients who progress on the protocol treatment with interferon and/or DA-EPOCH-R or another doxorubicin-based regimen may be treated with standard therapy to include rituximab. Patients who receive rituximab will be treated with a standard dose of 375 mg/m2 IV. When given without chemotherapy, 4 doses are given over 1- 4 weeks for each treatment cycle. The treatment of such patients will depend on their prior treatment history. Consent for treatment with these standard agents will be individually obtained because the treatment is using standard agents and is not systematically studied on this protocol. However, patients will remain enrolled on this study as the vehicle for this treatment so that we can obtain pilot information on these treatment approaches.

3.4 DOSE ADJUSTMENTS

Goals and General Strategy: The aim is to maximize DA-EPOCH-R dose-intensity while minimizing toxicity. Drug doses may be modified for severe toxicity either manifests on day 1 or occurring during the previous cycle and resolved by day 1 of the next cycle. The rules for either eventuality are described separately below. When two different rules give different answers for a particular dose decision, use the lower of the two dose options. The rules are for events that occur during the preceding cycle.

3.5 HEMATOLOGIC 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 ≥ 100,000/μl on day 21, begin treatment.
- If ANC < 1000/μl or platelets ≤ 100,000/μl on day 21, delay up to 1 week. G-CSF may be started for ANC < 1000/μl and stopped 24 hours before treatment. If counts still low after 1 week delay, ↓ 1 dose level below last cycle.

Important: Measurement of ANC nadir is 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.

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

3.6 NEUROLOGIC AND HEPATIC DOSE ADJUSTMENT PARADIGM

3.6.1 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 not necessary to stop the vincristine altogether. Furthermore, because the therapy administered in this study is potentially curative, every effort should be made to avoid unnecessarily reducing vincristine doses. The following guidelines for symptomatic ileus on a previous cycle should be followed:

Clinical ileus < 8 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting >2 days: Reduce vincristine dose 25%.

Clinical ileus 8-12 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting > 2 days: Reduce vincristine dose 50%.

Clinical ileus > 12 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting > 2 days: Hold vincristine on next cycle. May restart at 50% reduction on subsequent cycle.

3.6.2 Sensory neuropathy

Grade	% Dose of Vincristine
2	100
3	50

3.6.3 Motor neuropathy

Grade	% Dose of Vincristine
1	100
2	75
3	25

4	0

3.6.4 Hepatic dysfunction

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

3.6.5 Rituximab toxicity (skin)

Side effects of rituximab may be infusion rate related and may be reduced by slower administration or premedication. Thus, dose reductions of rituximab will not be made for rate related reactions. Rituximab will be discontinued in patients with grade 4 allergic reactions. Patients who develop significant skin toxicity including mucositis and/or diffuse rash felt secondary to rituximab and at risk of toxic epidermal necrolysis will have rituximab discontinued and will only receive EPOCH alone for the remainder of cycles. Patients will be given a rituximab toxicity reporting sheet for presentation to their local physicians if they develop any skin, mouth or bleeding symptoms or signs.

3.7 STUDIES DURING AND AFTER THERAPY

3.7.1 Patients receiving interferon

- CBC/differential and liver panel weekly until stable dose of interferon and then every other week while on interferon.
- TSH and free thyroxine if TSH is abnormal q3 months while receiving interferon.
- Clinic visit q4 weeks and appropriate imaging (i.e. CT Scan and MRI in patients with CNS disease) until on stable dose of interferon or a maximum of 6 monthly scans. Thereafter q3 months while receiving interferon.
- On completion of interferon, approximately 30 days after last dose (by phone or in clinic) a toxicity assessment only will be done, followed by clinic visits, CT Scans (type of scan depended on site of disease) and brain MRI if there is CNS involvement for restaging, and labs as follows: q3 months x 1 year, q4 months x 1 year, q6 months x 1 year and yearly thereafter for 2 years. FDG-PET will be done at the completion of interferon therapy or as clinically indicated. After 5 years of follow-up, we will continue to see you in clinic (or contact you by phone) at least yearly; restaging and labs will be done as clinically indicated. Restaging of involved sites with appropriate scans/x-rays will be done at each scheduled visit. Labs to be collected at each clinic visit during follow-up: CBC w/differential, PT, PTT, acute care, mineral and hepatic panels, total protein, LDH, TSH and free thyroxine if TSH is abnormal.
- FACS analysis for CD-4/CD-8 cells are to be drawn at the following times: Pre-treatment; then Q4 weeks until stable interferon dose and then q 3 months during treatment and with each surveillance follow-up visit. FACS analysis will also be performed at each restaging visit during follow-up.The FACS analysis for CD4/CD8 cells will be performed in the Clinical Center Laboratory.
- EBV Viral Loads: EBV viral loads are to be drawn at the following times: Pre-treatment; then Q4 weeks until stable interferon dose and then q 3 months during treatment and at each surveillance follow-up visit . EBV viral loads will be performed in the Clinical

Center Laboratory.

3.7.2 Patients receiving DA-EPOCH-R

- Patients will be seen in clinic q3 weeks for DA-EPOCH-R chemotherapy. Labs to be collected: CBC w/differential, PT, PTT, acute care, mineral, hepatic panels, total protein, and LDH q3 weeks. Restaging of all involved sites will be performed after cycles 4 and 6. CBC w/differential 2 x week, three days apart, will be performed while receiving DA-EPOCH-R therapy.
- When DA-EPOCH-R is completed, approximately 30 days after last dose (by phone or in clinic) a toxicity assessment only will be done, followed by clinic visits, restaging, and labs as follows: q3 months x 1 year, q4 months x 1 year, q6 months x 1 year and yearly thereafter for 2 years. After 5 years of follow-up, we will continue to see you in clinic (or contact you by phone) at least yearly; restaging and labs will be done as clinically indicated. Restaging of involved sites with appropriate CT scans will be done at each scheduled visit (type of scan depended on site of disease) and brain MRI if there is CNS involvement as well as PET Scans (at the completion of therapy). Labs to be collected at each clinic visit during follow-up: CBC w/differential, PT, PTT, acute care, mineral and hepatic panels, total protein, and LDH.
- FACS analysis for CD4/CD8 cells performed at the following time-points: 1. Pre-treatment; 2. Patients on DA-EPOCH-R: prior to each cycle of therapy, and at the end of treatment. When patients have completed therapy, obtain FACS analysis at each restaging visit during follow-up. The FACS analysis will be performed in the Clinical Center Laboratory.
- EBV Viral Loads: EBV viral loads are to be drawn at the following times: 1. Pre-treatment; 2. Patients on DA-EPOCH-R: prior to each cycle of therapy, and at the end of treatment. When patients have completed therapy, obtain EBV viral loads at each restaging visit during follow-up. EBV viral loads will be performed in the Clinical Center Laboratory.

3.7.3 Research Samples

Note: See Section **5** for additional information

3.8 COST AND COMPENSATION

3.8.1 Costs

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

3.8.2 Compensation

Participants will not be compensated on this study.

3.8.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of

these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

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

3.9.1 Criteria for removal from protocol therapy

- A patient will no longer receive study agents (DA-EPOCH-R or interferon) if he/she develops a serious medical condition (irreversible > grade 3 or 4 non-hematologic toxicity) which makes their administration life-threatening. However, the patient may continue to be followed on study.
- If a woman becomes pregnant while on this study, treatment will be stopped.
- Patient voluntary withdrawal: Patient may withdraw from treatment and continue to be followed on-study.
- Investigator discretion.

3.9.2 Criteria for removal from study

- Participant requests to be withdrawn from study.
- Patient non-compliance; that is, the patient does not follow the instructions provided by the research team.
- Pregnancy
- Death.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 PROPHYLAXIS OF PNEUMOCYSTIS JIROVECI (FORMERLY PNEUMOCYSTIS CARINII)

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

4.2 CNS TREATMENT GUIDELINES

Patients with Grade 1, 2 or 3 leptomeningeal LYG without transformation to a large B-cell lymphoma who are receiving interferon will be monitored every 2-4 weeks after the start of interferon by CSF analysis and/or brain scan until evidence of resolving disease. If there are no progressive neurological signs or symptoms and evidence of resolving CNS disease, patients may be followed without intrathecal chemotherapy or radiation as appropriate. Intrathecal chemotherapy and/or radiation will be used in patients receiving interferon with evidence of disease progression in the CNS, patients receiving interferon who at the investigators discretion are felt to have neurological symptoms (based on severity and duration of symptoms) warranting cytotoxic/radiation treatment, patients with evidence of aggressive lymphoma in the CNS and

patients receiving DA-EPOCH-R chemotherapy.

4.2.1 Guidelines for intrathecal treatment: Patients will initially receive monotherapy with methotrexate and/or cytarabine.

- Doses for IT therapy are methotrexate 12 mg or cytarabine 70 mg.
- Doses for Ommaya therapy are methotrexate 6 mg or cytarabine 70 mg.

4.2.2 Due to unforeseeable events, the above therapy may be modified as clinically indicated. All decisions should be discussed with the PI or protocol chairperson.

4.2.3 Treatment Schedule: Induction: Twice weekly for 2 weeks beyond negative cytology or FACS, for a minimum of 4 weeks (obtain CSF for cytology and flow cytometry weekly); Consolidation- Weekly for 6 weeks (obtain CSF for cytology weekly); Maintenance- Monthly for 6 months (obtain CSF for cytology and flow cytometry monthly).

4.2.4 Radiation treatment: Patients who have progressive disease on intrathecal chemotherapy and/or have parenchymal lesions may receive radiation treatment.

4.3 MONITORING AND TREATMENT TO PREVENTHEPATITIS B REACTIVATION

Patients who are positive for either Hepatitis B core antibody (anti-HBc) or Hepatitis B surface antigen (HBsAg) and not acutely infected are at varying risk for reactivation of Hepatitis B when treated with DA-EPOCH-R. Patients with prior hepatitis B exposure may be included in the study provided that they have HBV DNA levels below the World Health Organization's cutoff of 100 IU/mL prior to starting therapy. These patients will be treated with entecavir (or equivalent) to prevent hepatitis B reactivation and should have HBV DNA levels obtained monthly for at least 12 months after the last cycle of therapy by means of real-time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL.

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

If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving antiviral

medication, study treatment must be permanently discontinued.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 SUMMARY

Sample	Collection Details	Time Points	Laboratory
Blood Samples			
EBV Analysis	• 4 x 8.5 mL yellow top	• Pre-treatment • Each Clinic Visit • First 4 follow-up visits after treatment ends	CSL (Leidos)
Serum Storage	• 1 x 10 mL red top	• Pre-treatment • Every 3-6 months during treatment • Each re-staging visit during follow-up	CSL (Leidos)
Tissue Samples			
Archival Tissue	• FFPE or other, as available	• Baseline	NCI LP
Tumor Biopsy (optional)	• Excision (single or multiple nodes) or core (4-6 passes); placed in media per routine practice	• Baseline	
NOTE: • Tubes/media may be adjusted at the time of collection based upon materials available and/or to ensure the best viable samples are collected for planned routine and/or research analysis at the time of procedure. • All blood/ tubes should remain at ambient temperature after collection and until processing, do not place samples on ice. Processing windows; SST/red top tubes should be processed same day, whenever possible.			

5.2 BLOOD SAMPLE COLLECTION AND PROCESSING

5.2.1 EBV Analyses

For patients receiving Interferon or EPOCH-R, 4 yellow top tubes should be drawn at the time points outlined in Section **5**.

These yellow top tube samples should be sent via courier to the Clinical Support Laboratory, Leidos Biomedical Research Inc. in Frederick, MD. The storage for these samples is described in Section **5.3.1**.

Studies to be performed on these bloods includes analysis of EBV specific T cells by tetramer staining, markers for senescence, clonal exhaustion by flow, and functional activity of virus specific T-cells. EBV-transformed B cell lines from select patients may be created which will be used as antigen-presenting cells to be used for other studies in the future. Additional studies may be done on these samples that are related to understanding the pathogenesis of LYG and its treatment providing those studies are of minimal risk to the patients. If the studies are not of

minimal risk, IRB approval and patient consent will be obtained.

5.2.2 Serum Storage

For patients receiving Interferon or EPOCH-R, one red top tube for serum storage should be drawn at the time points outlined in Section **5**.

These serum samples should be sent to the laboratory of Clinical Support Laboratory, Leidos Biomedical Research Inc. in Frederick, MD. Processing and storage procedures are described in Section **5.3.1**.

5.3 TUMOR BIOPSY SAMPLES

5.3.1 Overview

Excision or core needle biopsy will be performed per routine standard of care, by Surgery Consultants or Interventional Radiology, as appropriate. A procedure-specific consent form will be signed by the patient prior to the procedure. Every attempt will be made to perform excisional biopsies to obtain the best quality tissue for translational investigation. Consideration of alternative biopsy methods (e.g., core needle biopsy) will only be made if follow-up excisional biopsy is not possible/safe or patient is unwilling to undergo repeat excisional biopsy. These biopies may be done by CT guidance.

In the event that a surgical biopsy procedure is performed, more than one lesion and at more than one anatomic site may be collected, provided the additional procedures are not unacceptable risk to the patient. In the event of core needle biopsy, these are obtained typically by using a 16-18G needle at the discretion of the provider performing the procedure. Conscious sedation may be used, if warranted, and the use and risks are acceptable to the patient.

Potential site(s) of biopsy include, but are not limited to: bone marrow lesions, bony lesions, extramedullary disease/masses, and lymph nodes. The type of procedure to be done and manner in which it will proceed (e.g., excision/core, single vs. multiple sites of biopsy) will be discussed with the patient prior to the biopsy procedure. The patient will be reminded that all sampling for research is voluntary.

If the patient agrees to the optional biopsy, he/she will sign a procedure consent at the time of the procedure. If the patient refuses the optional biopsy, the refusal will be documented in the medical record and in the research record.

5.3.2 Processing and Handling

All samples will be handled/processed as per routine processes applicable to the type of sample (e.g., formalin fixation, snap frozen, and/or single-cell preparation). It is anticipated that all samples will go through NCI Laboratory of Pathology for review/processing prior to release for research analyses.

5.3.3 Analysis

Analysis of fresh tissue and/or paraffin blocks for in-situ hybridization for EBV; immunohistochemistry for B and T cell antigens; and isolate DNA for T-cell receptor and immunoglobulin gene rearrangements by PCR if available.

Immunohistochemical (IHC) analyses will take part in tumor tissue samples, including but not

necessarily limited to CD10, CD20, BCL6, and MUM1.

5.4 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 appropriate approvals and/or agreements, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below for an indefinite amount of time. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2.1**.

5.4.1 Procedures for stored blood specimens

- The Clinical Support Laboratory (CSL), Leidos Biomedical Research Inc.-Frederick, processes and cryopreserves samples in support of IRB-approved, NCI clinical trials. All laboratory personnel with access to patient information annually complete the NIH online course in Protection of Human Subjects. The laboratory is CLIA certified for CD4 immunophenotyping and all laboratory areas operate under a Quality Assurance Plan with documented Standard Operating Procedures that are reviewed annually. Laboratory personnel are assessed for competency prior to being permitted to work with patient samples. Efforts to ensure protection of patient information include:
- The laboratory is located in a controlled access building and laboratory doors are kept locked at all times. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.
- An electronic database is used to store information related to patient samples processed by the laboratory.
- The database resides on a dedicated program server that is kept in a central, locked computer facility.
- The facility is supported by two IT specialists who maintain up to date security features including virus and firewall protection.
- Program access is limited to specified computers as designated by the laboratory director. Each of these computers has a password restricted login screen.
- The database sample entry program itself is accessed through a password protected entry screen.
- The database program has different levels of access approval to limit unauthorized changes to specimen records and the program maintains a sample history.
- Upon specimen receipt each sample is assigned a unique, sequential laboratory accession ID number. All products generated by the laboratory that will be stored either in the laboratory freezers or at a central repository facility are identified by this accession ID.
- Inventory information will be stored at the vial level and each vial will be labeled with

both a sample ID and a vial sequence number.

- Vial labels do not contain any personal identifier information.
- Samples are stored inventoried in locked laboratory freezers and are routinely transferred to the NCI-Frederick repository facilities for long term storage.
- Access to stored clinical samples is restricted. Investigators establish sample collections under "Source Codes" and the investigator responsible for the collections, typically the protocol Principal Investigator, specifies who has access to the collection. Specific permissions will be required to view, input or withdraw samples from a collection.
- Sample withdrawal requests submitted to approved laboratory staff by anyone other than the repository source code owner are submitted to the source code owner for approval. The repository facility will also notify the Source Code holder of any submitted requests for sample withdrawal.
- It is the responsibility of the Source Code holder (generally the NCI Principal Investigator) to ensure that samples requested and approved for withdrawal are being used in a manner consistent with IRB approval.
- The Clinical Support Laboratory does perform testing services that may be requested by clinical investigators including, but not limited to, immunophenotyping by flow cytometry and cytokine testing using ELISA or multiplex platforms.
- When requests are submitted by the NCI investigator for shipment of samples outside of the NIH it is the policy of the laboratory to request documentation that a Material Transfer Agreement is in place that covers the specimen transfer. The laboratory does not provide patient identifier information as part of the transfer process but may, at the discretion of the NCI investigator, group samples from individual patients when that is critical to the testing process.
- The NCI investigator responsible for the sample collection is responsible for ensuring appropriate IRB approvals are in place and that a Material Transfer Agreement has been executed prior to requesting the laboratory to ship samples outside of the NIH.

5.4.2 Procedures for storage of tissue specimens

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

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

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 AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1, through 30 days after the last study intervention was administered. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will only be considered an AE if the laboratory abnormality is characterized by any of the following:

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

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

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

6.1.1 Special considerations for data collection/recording:

- As the toxicity profile of EPOCH-R is well defined and published, grade 1 clinical adverse events will not be recorded in the database.
- All hospitalizations, regardless of reason, will be recorded in the database with the reason of hospitalization and the duration of hospitalization noted.
- Only the highest grade of each event during a cycle of treatment during EPOCH-R will be recorded in the database.
- All grade 2 events and above that occur while the patient is treated with interferon will be recorded.
- In certain circumstances, patients may stay on study and receive non-protocol therapy for a diagnosis other than LYG. In these cases, adverse events that are attributed to the non-protocol therapy will not be collected.

6.2 RESPONSE CRITERIA

6.2.1 Complete Remission: No evidence of active disease on restaging for at least 2 months duration. Because LYG frequently involves the lungs, residual scar may be present. To be considered in CR, all lesions must have decreased by > 75%, be gallium or PET

negative (if obtained) and be stable for > 3 months without new lesions appearing. If lesions can be biopsied, such as the skin, or pleural, peritoneal or CSF fluid collected, these must be negative for disease.

6.2.2 Partial Remission: 50% or greater decrease in the sum of the products of the diameters of all measurable lesions for at least one month.

6.2.3 Disease Progression: 25% or greater progression in the sum of the products of the diameter of any measurable lesion over one month or the appearance or any new lesion consistent with metastatic disease.

6.2.4 Disease Stabilization: No change in the sum of the products of the diameters of all measurable lesions over two months and no new lesions consistent with disease.

6.3 TOXICITY CRITERIA

Adverse events will be documented according to the Common Toxicity Criteria v. 2.0, which can be found at http://ctep.cancer.gov/reporting/ctc.html. Serious (≥ grade 3) which are unexpected and reasonably ascribed to treatment drugs and all fatal reactions occurring on this study should be reported immediately by phone to Dr. Wyndham Wilson at 240-760-6092.

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

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

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

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

7.3 NCI CLINICAL DIRECTOR REPORTING

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

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

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

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

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

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

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

8 STATISTICAL CONSIDERATIONS

Initially, 15 patients each with Grade I/II and Grade III LYG may be enrolled in this study. The first 9 patients in each group entering a CR or stable PR will have their remission durations observed, and the proportions with durations exceeding 12 months will be noted. If 9 patients in any group of 9 progress with the same disease grade (i.e. grades I/II or III) within 12 months, no additional patients beyond 15 will be entered into that group (15 will probably have been enrolled by the time nine have had a minimum of 12 months potential follow-up). This will allow us to conclude with 95% confidence and power that the true proportion of patients with response durations exceeding 12 months is less than 30%.

If at least one of 9 patients in either group have response durations exceeding 12 months, then up to 30 patients will be enrolled in that group. If at least 10 of 29 patients with CR or stable PR have remission duration > 12 months, we can conclude that the true proportion with remission duration exceeding 12 months is at least 20%, with 95% power and confidence.

In order to have 60 evaluable patients enrolled on this protocol, the accrual ceiling will be 70 patients to account for 10 non-evaluable patients.

All patients will be followed for survival and disease-free survival (among appropriately responding patients), with appropriate life-table analyses performed at the conclusion of the study.

Due to the rarity of this disease and its now recognized multiple subtypes (grade I, II and III), we wish to increase the number of patients overall in the series to a total of 85 patients.

Effective with Amendment Y (Version Date: 09/16/2014), the accrual ceiling is being increased by 5 to a total of 90 patients. This will allow for continuation of our ongoing work with the very complex LYG patients until we complete the development of the new protocol, which is in the early stages of development.

Effective with Amendment CC (Version Date: 06/10/2019), the accrual ceiling is being increased by 15 to a total of 105 patients. LYG is a rare disease that does not have effective treatments. This increase in accrual for this natural history study allows for continued work on the biology and management of a very rare lymphoproliferative process. We have a new protocol testing novel agents that can be offered to these patients, but that protocol does not

allow us to perform baseline mutational testing or manage patients who do not active therapy.

9 COLLABORATIVE AGREEMENTS

None/Not applicable.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

LYG is a rare disorder which affects otherwise normal individuals. It may be seen in patients of all ages and sex, and may be associated with immunodeficiency states such as HIV infection and CID. Any patient with a diagnosis of LYG at least 12 years of age, regardless of gender, ethnicity, or race will be eligible for this study. Patients who in the opinion of the principal investigator are poor psychiatric or medical risks are not eligible. This study is addressing the natural history of LYG and testing the efficacy of interferon and/or DA-EPOCH-R treatment in a disease in which there is no standard treatment.

10.2 PARTICIPATION OF CHILDREN

We wish to include patients who are at least 12 years old because this disease does occasionally affect younger age patients and because there is no adequate treatment at this time. The age cutoff is based on the rarity of this disease in younger children.

10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally-impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **10.4**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR,as needed.

Please see section **10.5.1** for consent procedure.

10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS:

Patients may obtain direct benefit from treatment with interferon and/or DA-EPOCH-R chemotherapy. Preliminary results indicate that interferon may induce durable remissions in over 50% of patients. The risks of interferon and DA-EPOCH-R chemotherapy are well described and reasonable in anticipation of expected benefits.

10.4.1 Hepatitis B Reactivation

Because of the risk hepatitis B reactivation in patients receiving DA-EPOCH-R, patients will be closely monitored as per Section **4.3**. Patients who test positive for either hepatitis B surface antigen or hepatis B core antibody will receive prophylaxis. HBV PCR is also closely monitored

while patients are receiving treatment.

10.4.2 Risks related to CT and PET scans

CT and PET scans often use a contrast agent. There is a small risk of having a reaction to the contrast and most often include nausea, pain in the vein where the contrast is given, headache, metallic and/ or bitter taste in the mouth and a warm, flushing feeling. Rarely, some people have more severe allergic reactions to the contrast which may include skins rashes, shortness of breath, wheezing or low blood pressure.

10.4.3 Risks from Radiation Exposure

On this study, patients who are given EPOCH-R will receive up to two (2) PET Scans and four (4) CT Scans (type of scan varies by disease, max dose possible is from Neck/Chest/Abdomin/Pelvis scans) maximum in annual period. Patients who are given Interferon will receive up to two (2) PET Scans and eight (8) CT Scans (type of scan varies by disease, max dose possible is from Neck/Chest/Abdomin/Pelvis scans) maximum in annual period. Participants in both arms will undergo up to one (1) optional CT guided biopsy. The procedures for performing the CT and [^{18}F]-FDG PET scans will follow clinical policies, no special procedures will apply to these assessments for research purposes.

The total radiation dose for research purposes will be approximately 12.4 rem for patient who receive Interferon. The total radiation dose for research purposes will be approximately 7.2 rem for patient who receive EPOCH-R. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer.

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

10.4.5 Risks related to Gadolinium enhanced MRI

During part of the MRI patient will receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for research purposes.
The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling. There is also a risk of kidney damage from the use of gadolinium.

10.4.6 Blood Sampling

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

10.4.7 Lumbar Puncture

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

10.4.8 Biopsy Collection

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

guidance may be used in obtaining biopsies (see **10.4.3** for radiation risk).

10.4.9 Bone Marrow Aspiration/ Biopsy

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

10.5 Consent and Assent Process and Documentation

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

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

With regard to the optional biopsy for research in the protocol, the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

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

For participants addressed in section **10.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **10.5.**

10.5.2 Consent Process for Minors

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

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

record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable.

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

10.5.3 Consent for minors when they reach the age of majority

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

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

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.

(3) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 STUDY DISCONTINUATION AND CLOSURE

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

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

11.2 Quality Assurance and Quality Control

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

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

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

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

11.3 Conflict of Interest Policy

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

11.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

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

The study monitor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records

for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

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

12 PHARMACEUTICAL INFORMATION

12.1 INTERFERON ALPHA 2-B

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

12.1.1 Supply

Commercially manufactured by Schering Corporation. It is supplied as a sterile liquid in vials containing 5 MU (million units)/0.5 ml or 10 MU/ml. Vials should be stored at 2-8^{o}C.

12.1.2 Toxicities

Acute side effects include fever and flu-like symptoms of headache, myalgias, and chills. Chronic toxicities appear to be related to the weekly cumulative dose and are persistent as long as treatment is continuing. Other toxicities include depression, hypothyroidism, severe fatigue, hemophagocytic syndrome, gastrointestinal symptoms such as constipation, neurological side effects involving both the peripheral and central nervous system such as memory loss, rapidly reversible granulocytopenia, and transaminitis. Clinically significant cardiovascular side effects are infrequent.

12.2 CYCLOPHOSPHAMIDE

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

12.2.1 Supply

Commercially available in white crystalline formulation for intravenous injection, in vials containing 100 mg, 200 mg, 500 mg, 1gm, or 2 gm. Intact vials are stable at room temperature storage (not to exceed 30^{o}C). Reconstitute with appropriate amounts of Sodium Chloride

Injection (0.9%NS) to produce a solution with final concentration of 20 mg/ml. Discard solution after storage for 24 hours at room temperature. After reconstitution, cyclophosphamide is stable for up to 6 days if refrigerated (2-8^{o}C). Cyclophosphamide will be diluted in 100 mL of 5% Dextrose Injection or 0.9%NS and infused over 30-60 minutes.

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

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

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

12.3 DOXORUBICIN

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

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

12.3.2 Toxicities
Myelosuppression, stomatitis, alopecia, nausea and vomiting, and acute and chronic cardiac toxicity, manifested as arrhythmias or a congestive cardiomyopathy, the latter uncommon at total cumulative doses less than 500 mg/m^2. The drug causes local necrosis if infiltrated into subcutaneous tissue.

12.4 VINCRISTINE

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

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

12.4.2 Toxicities
Peripheral neuropathy, autonomic neuropathy, alopecia. Local necrosis if injected

subcutaneously.

12.5 ETOPOSIDE

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

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

12.5.2 Toxicities
Myelosuppression, nausea, vomiting, anaphylactoid reactions, alopecia, and hypotension if infusion is too rapid.

12.6 ADMINISTRATION OF VINCRISTINE/DOXORUBICIN/ETOPOSIDE

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

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

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

12.7 PREDNISONE

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

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

- **Doses**: Prednisone utilization will be simplified by using only 20- and 50-mg tablets to produce individual doses and by stratifying prednisone doses by a patient's body surface area

(BSA), according to the chart below. These are recommendations and not requirements.

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

12.7.2 Toxicities
Proximal muscle weakness, glucose intolerance, thinning of skin, redistribution of body fat, Cushingoid facies, immunosuppression, propensity to gastrointestinal ulceration.

12.8 FILGRASTIM

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

12.8.1 Supply
Commercially available as a clear sterile solution in single use vials containing 300 mcg (1 mL vial) and 480 mcg (1.6 mL vial). Filgrastim will be stored at 2-8°C and is stable for at least 1 year when maintained under refrigeration. DO NOT FREEZE and DO NOT SHAKE the drug product. Final concentration is 300 mcg/ml. Filgrastim will be given by subcutaneous injection; patient or other caregiver will be instructed on proper injection technique.

12.8.2 Toxicities
Rare anaphylactic reactions with the first dose; bone pain at sites of active marrow with continued administration. Local reactions at injection sites. Constitutional symptoms, increased alkaline phosphatase, LDH, uric acid; worsening of pre-existing inflammatory conditions.

12.9 METHOTREXATE

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

12.9.1 Supply
Commercially available folic acid antagonist, and only the preservative-free preparation may be used for intrathecal injection. It should be stored at 15-30°C and protected from light.

12.9.2 Toxicities
It can cause leukopenia, and as such leucovorin should be administered 24 hours after each dose. It can cause headaches, drowsiness, and blurred vision. It can also cause a transient acute neurologic syndrome manifested by confusion, hemiparesis, seizures, and coma.

12.10 CYTARABINE

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

12.10.1 Supply
A commercially available pyrimidine nucleoside antimetabolite, and should be stored at 20 - 25°C, and used within 2 years of the date of manufacture. Prior to intrathecal injection it is reconstituted with preservative free 5% dextrose or 0.9% sodium chloride, and should be used as

soon as possible.

12.10.2 Toxicities
It can cause myelosuppression, fever, dizziness, somnolence, and arachnoiditis.

12.11 RITUXIMAB

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

12.11.1 Supply
The NIH Clinical Center Pharmacy Dept. will purchase rituximab from commercial sources. Rituximab is provided in pharmaceutical grade glass vials containing 10 mL (100 mg) or 50 mL (500 mg) at a concentration of 10 mg of protein per milliliter. Please refer to the FDA-approved package insert for rituximab for product information, extensive preparation instructions, and a comprehensive list of adverse events.

12.11.2 Storage
Rituximab for clinical use should be stored in a secure refrigerator at 2 to 8^{o} C.

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

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

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

Prophylaxis against hypersensitivity and infusion-related reactions associated with rituximab will include acetaminophen 650 mg and diphenhydramine hydrochloride 50-100 mg administered 30 to 60 minutes prior to starting rituximab. Patients will also receive their first dose of prednisone 60 mg/m^2 (or a glucocorticoid equivalent dose of an alternative steroid) at least 60 minutes before rituximab treatment commences.

Rituximab will be administered as an intravenous infusion at 375 mg/m^2 on day 1 of each cycle of EPOCH, immediately prior to starting etoposide + doxorubicin + vincristine administration. Rituximab infusions will be administered to patients primarily in an outpatient clinic setting.

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

mg/hour (maximum rate = 200 mL/h).

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

90-minute Administration

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

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

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

Standard Administration for Second & Subsequent Infusions

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

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

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

12.11.6 Toxicities

Common toxicities include fever, chills, nausea, asthenia, headache, angioedema, pruritis and rash. Leukopenia occurs in approximately 10% but grade 3 or 4 neutropenia is uncommon. Hypotension occurred in 10% of patients during rituximab infusion, and serious bronchospasm and urticaria associated with rituximab infusion each occurred in fewer than 10% of patients. Less common toxicities include abdominal pain, vomiting, thrombocytopenia, anemia, myalgia, arthralgia, dizziness, and rhinitis. Bowel obstruction and perforation have been rarely reported. Skin reactions, some of them life threatening, have been noted in patients receiving rituximab. The FDA currently has a database of 18 patients who have had Stevens-Johnson or toxic epidermic necrolysis (TEN) after rituximab and 7 of those patients have died. The time to onset typically was during or within a few weeks of receiving rituximab. Patients may initially have mucositis with sore throat or mouth ulcers followed by diffuse skin rash, which rapidly progressed to a total body desquamative rash. In fatal cases, sloughing of the skin over 80-90% of the body surface area was seen, followed by fulminate infection, multi-organ failure and death. In addition, hepatitis B virus reactivation with fulminant hepatitis, hepatic failure and death has been reported. In patients with Rheumatoid Arthritis, serious cardiac events have

occurred.

12.12 TRIMETHOPRIM/SULFAMETHOXAZOLE

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

12.12.1 Supply

Will be given as PCP prophylaxis to patients receiving chemotherapy. It will be supplied by the Clinical Center Pharmacy.

12.12.2 Toxicities

The most common side effects are hypersensitivity, rash, nausea, vomiting, diarrhea, GI upset, and photosensitivity. Stevens-Johnson syndrome, bone marrow suppression, hepatic toxicity, and renal toxicity may occur. This agent should be stopped immediately if rash develops. See package insert for additional information.

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14 APPENDIX 1: EPOCH ADMIXTURES: PREPARATION AND ADMINISTRATION

Preparation:

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

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

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

[1] Purge all air from the drug product container,

[2] Attach an administration set appropriate for use with a portable pump,

[3] The set will be primed close to its distal tip, and

[4] The set will be capped with a Luer-locking cap.

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

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

Administration:

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

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

*DO NOT attempt to infuse the overfill

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

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