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Phase II Study of Dose-Adjusted EPOCH+/- Rituximab in Adults With Untreated Burkitt Lymphoma, C-Myc Positive Diffuse Large B-Cell Lymphoma and Plasmablastic Lymphoma

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A. Obtain information by intervening or interacting with living individuals for research purposes
B. Obtaining identifiable private information about living individuals
C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing coded, linked data or specimens for research purposes
G. Some/all research activities performed outside NIH

Commercial Products:

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

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Roster of NCTN sites with study activation in **APPENDIX E

This trial is supported by the NCI Cancer Trials Support Unit (CTSU). Participation is limited to the Lymphoid Malignancies Branch, Center for Cancer Research, NCI (NCILYMB, CCR, NCI); and the NCI-supported Participants and Special Member sites . All will participate through the CTSU mechanism as outlined below and detailed in the protocol.

- **Access and communications:** To participate in this trial, enroll patients via the Oncology Patient Enrollment Network (OPEN), and access the Medidata Rave Clinical Data Management System (CDMS), investigators and research staff must be registered members of the CTSU and have an active **CTEP IAM account** (https://eapps-ctep.nci.nih.gov/iam). Instructions on obtaining a CTEP IAM account are outlined in the Registration Procedures section of this protocol. The CTSU Web site and CTSU Bi-Monthly Broadcast will be the primary vehicle for communicating study-related updates to clinical sites. In addition, each

site must identify at least one Site Administrator and one Data Administrator to facilitate communications with the CTSU, and at least one Registrar to facilitate patient enrollments, and designate at least one person as a Rave CRA to facilitate data entry.

- The **study protocol and all related forms and documents** may be downloaded from the 9177 Web page of the CTSU Web site (https://www.ctsu.org).Refer to the Registration Procedures section of this protocol for details.
- Send **site registration documents** to the CTSU Regulatory Office in Philadelphia as outlined in the Registration Procedures section of this protocol. The CTSU Regulatory Office will track documents in the CTSU Regulatory Support System (RSS) and transmit approval data to CTEP.
- **Patient registration** will be conducted by sites using the Oncology Patient Enrollment Network (OPEN) as outlined in the Registration Procedures section of this protocol. To perform an enrollment, the site user must have been assigned the 'Registrar' role on the relevant Organization roster. OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.
- **Data management activities** will be performed by CTSU Data Operations and all sites will submit data and respond to all queries electronically using the Medidata Rave Clinical Data Management System (CDMS). Details are provided in the Data Collection section of this protocol. The Rave CDMS application is available to those individuals assigned the Rave CRA role on the relevant Organization roster and who have completed their Rave eLearning assignments. Required trainings will be assigned as eLearnings to site staff within Rave as staff are invited to the study.

The treating PI will be expected to review patient data and to document at Off Study certifying the data is accurate and complete. If documenting directly in Rave, the PI will need to be assigned a PI role on the relevant roster and will need to obtain a Rave account. For additional information about Rave, login to the CTSU members' website and access the Rave tab.

- **Contact Information:**

  Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal:

  Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

  Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

  Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.

For answers to **patient eligibility or treatment-related questions**:
Please contact the Responsible Research Nurse listed on the protocol cover page or Dr. Mark Roschewski.

All other questions (including OPEN and form-specific and remote data capture system questions) should be communicated by phone or e-mail to the CTSU Help Desk at:
CTSU General Information Line 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. CTSU Help Desk hours are 9:00 am – 6:00 pm. E.T. Mon-Fri (excluding holidays).

The CTSU Public Web site is located at www.ctsu.org. A CTEP-IAM username and password is required to access the members' section of the Web site as well as the OPEN and Rave applications.

PRÉCIS

Background:

- Burkitt lymphoma/leukemia (BL) is highly curable. Standard treatment employs dose-intense multi-agent chemotherapy and though effective is associated with high morbidity. Therefore, novel approaches are needed that improve the therapeutic index of BL while maintaining or improving efficacy. In HIV+ BL, outcome has been poor, mainly due to the use of CHOP-based regimens in this disease.
- Two NCI phase II trials have used EPOCH chemotherapy with 1 or 2 doses of rituximab (R) per cycle in untreated BL. (Dose-adjusted) DA-EPOCH-Rituximab has been used in 16 HIV negative BL, and 8 HIV positive patients have received 3 to 4 cycles of EPOCH-RR to minimize toxicity and risk of opportunistic infections. All patients remain in continuous remission. Treatment was very well tolerated and represents a novel therapeutic strategy in BL.
- This trial seeks to assess the effectiveness of a risk adaptive approach with DA-EPOCH-R in untreated BL (HIV+/-). Because this treatment represents a major conceptual departure from standard treatment, it is important to obtain additional Phase II results in limited/advanced stage BL
- c-MYC positive DLBCL is a rare variant of DLBCL. There is very little data on the biology of this disease and what the optimal therapeutic approach should be has not been defined. Therefore, based on our impression that this behaves aggressively and is likely characterized by a high tumor proliferation rate, we plan to accrue patients with this disease in addition to BL patients.
- Plasmablastic lymphoma, another variant of DLBCL is frequently characterized by the activation of MYC and has had a poor outcome historically with standard treatment. We plan to include these patients in the study also. As they are CD20 negative, they will receive DA-EPOCH without Rituximab.

Objectives:

- Determine PFS, EFS and OS of risk adaptive DA-EPOCH-R in untreated BL and c-MYC + DLBCL and DA-EPOCH in c-MYC+ plasmablastic lymphoma
- Assess predictive value of early FDG-PET/CT scans on PFS
- Obtain pilot comparative molecular profiling in HIV negative and positive BL and c-MYC + DLBCL, including c-MYC+ plasmablastic lymphoma.

Eligibility:

- Burkitt lymphoma, c-MYC + DLBCL and c-MYC + plasmablastic lymphoma age ≥ 18 years.
- No prior treatment except limited-field radiotherapy, short course of glucocorticoids and/or cyclophosphamide for an urgent problem at diagnosis.
- Adequate major organ function unless impairment due to lymphoma.

Study Design:

- Phase II Study of risk adapted DA-EPOCH-R in BL, c-MYC + DLBCL and DA-EPOCH in c-MYC+ plasmablastic lymphoma

- Low risk: DA-EPOCH-RR x 3 cycles.
- High risk, c-MYC + DLBCL and c-MYC+ plasmablastic lymphoma: DA-EPOCH (+/-) R x 6 cycles or 8 cycles in select patients.
- CSF cytology and flow cytometry for analysis of BL.
- High Risk CSF negative ⇒ Prophylactic intrathecal treatment
- CSF positive ⇒ Active intrathecal treatment
- FDG-PET/CT pre- and post-cycle 2 in all patients.
- A total of 194 patients will be enrolled in the protocol.

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1 INTRODUCTION

1.1 Primary Objectives

- Determine PFS, EFS and OS of risk adaptive DA-EPOCH-R in newly diagnosed Burkitt Lymphoma, c-MYC + DLBCL and DA-EPOCH in c-MYC+ plasmablastic lymphoma ≥ 18 years

1.2 Secondary Objectives

- Assess predictive value of early FDG-PET/CT scans on PFS
- Obtain pilot comparative molecular profiling of HIV negative and positive BL, c-MYC + DLBCL and c-MYC+ plasmablastic lymphoma
- Assess the toxicity of risk adaptive DA-EPOCH-R in newly diagnosed Burkitt Lymphoma, c-MYC + DLBCL and DA-EPOCH in c-MYC+ plasmablastic lymphoma ≥ 18 years

2 BACKGROUND

2.1 Burkitt Lymphoma (BL)

Burkitt Lymphoma mostly occurs in the first two decades of life and accounts for 1-2% of all lymphomas. Three clinical variants are recognized: Endemic BL which is primarily found in equatorial Africa[1]; Sporadic BL which presents worldwide but is the most common type in Western countries [2] and; Immunodeficiency associated BL which occurs in the setting of HIV infection. [3] There are important clinical differences in these variants (Table 1) with endemic BL involving the jaw, orbit, and paraspinal regions in half of the cases as well as the mesentery and gonads, while sporadic BL mostly involves the distal ileum, cecum and/or mesentery, and rarely the jaw. When bulky or disseminated disease is present, extranodal involvement of the ovaries, kidney, breasts, and/or CNS may be seen. Clinical presentation in a Berlin-Frankfurt-Munster Group (BFM) series of 152 pediatric patients included advanced stage (III/IV) disease in 38%, bone marrow involvement in 33% and central nervous system (CNS) disease in 4%.[4] Overall, 27% of the patients in this series presented as acute leukemia and are usually referred to as the L3 subtype of acute lymphoblastic leukemia (ALL) within the French-American-British (FAB) classification.[5] BL infrequently presents in adults, but does occur with increased frequency in patients with HIV infection.

Table 1. Comparison of Endemic, Sporadic, and HIV-associated Burkitt Lymphoma

	ENDEMIC	SPORADIC	HIV-ASSOCIATED
Epidemiology	Equatorial Africa and Papua, New Guinea. Geographic association with malaria.	United States and Europe	United States and Europe
Incidence	5-10 cases per 100,000	2-3 cases per million	6 per 1,000 AIDS cases
Age and Gender	Malignancy of childhood Peak Incidence: 4-7 years Male: Female of 2: 1	Malignancy of childhood and young adults. Median age: 30 years Male: Female of 2-3:1	Malignancy of adults. Associated with higher CD4 counts > 100/mm3
Clinical Presentation	Jaw and facial bones in ≈ 50%. Also involves mesentery and gonads. Increased risk of CNS dissemination.	Abdomen most common presentation often involving the ileo-cecal region. Other extranodal sites include bone marrow, ovaries, kidneys, and breasts. Increased risk of CNS dissemination.	Nodal presentation most common with occasional bone marrow. Increased risk of CNS dissemination.

2.1.1 Staging

Staging is a critical component of treatment for lymphomas. In particular, the recognition that early stage BL requires less treatment than advanced stage disease has led to risk adaptive strategies that are dependent on the accuracy of the staging classification systems. The Ann Arbor staging system, which is the most commonly used system for lymphomas, was initially developed for radiation treatment of Hodgkin lymphoma. As such, it is relatively useful for identifying nodal and extranodal regions involved by disease but much less so for disease bulk or specific disease sites. The occurrence of BL and LBL in pediatrics led to the St Jude staging system [6] which was developed to more accurately reflect tumor bulk and high risk disease sites (Table 2). Overall, the Ann Arbor system is the staging system most commonly used for Burkitt lymphoma and this is the system to be used in this study. A table of both the Ann Arbor and St. Jude systems is provided.

Table 2. Staging Systems

Stage	St. Jude Staging	Ann Arbor Staging
I	♦Single site (excluding abdomen or mediastinum)	♦Single node region or extranodal site (IE)
II	♦Single extranodal site with regional nodes ♦ > 2 nodal sites, same side of diaphragm ♦2 extranodal sites, same side of diaphragm ♦Primary GI, completely resected (IIR)	♦> 2 node regions, same side of diaphragm +/- Localized contiguous extranodal site (IIE)
III	♦2 extranodal sites, both sides of diaphragm ♦> 2 nodal sites, both sides of diaphragm ♦Primary thoracic ♦Primary GI, extensive ♦Paraspinal, epidural	♦ > 2 node regions, both sides of diaphragm +/- Localized contiguous extranodal site (IIIE) Spleen (IIIS) or Both (IIIES)
IV	♦ CNS and/or bone marrow (< 25%)	♦ Bone Marrow or Liver Diffuse extranodal disease not encompassed in a single radiation field.
		E: Single extranodal site contiguous with a known nodal site A: No symptoms B: Fever, weight loss, night sweats

2.2 Rationale

2.2.1 Standard Treatment of Burkitt Lymphoma

BL is a systemic disease and requires chemotherapy for all disease stages. Importantly, locoregional radiation does not improve survival and should be avoided. While older studies showed that surgical resection of abdominal disease improves outcome, indicating the importance of tumor volume, more effective and risk adapted treatments have made surgical resection unnecessary except for specific complications like obstruction, perforation, fistula or bleeding.

Early treatment strategies for BL were modeled on ALL regimens which employed dose intense and prolonged treatment with induction, consolidation and maintenance phases. These approaches stand in contrast to the significantly less dose intense regimens used in adults with “intermediate-grade” lymphoma, such as CHOP and CHOP-based regimens, that only produced a 50-60% EFS. While dose intensity and dose density are important treatment components for BL, later studies indicated that shorter treatment durations were equally effective. Furthermore, the recognition that tumor volume is an important prognostic feature led to the use of risk adaptive approaches and a further reduction in treatment for early stage patients. Several biological characteristics of BL have helped guide treatment strategies including its high proliferative fraction. It has been recognized for years that BL is sensitive to multiple chemotherapy classes and in endemic BL, cures were occasionally achieved with single agent cyclophosphamide. Despite initial sensitivity, however, patients frequently relapsed, particularly

those with higher volume disease. This apparent dichotomy can potentially be explained by the high tumor proliferation rate. The role of tumor cell kinetics was raised some 30 years ago by Skipper et al [7] who observed that the fraction of cells undergoing DNA replication, termed the "growth fraction," greatly influenced drug sensitivity; a finding that likely reflects the greater sensitivity during S phase to many drug classes. Although a high growth fraction would predict greater drug sensitivity, it could also lead to greater tumor proliferation between cycles. Depending on the relative impact of these two effects, cure rates might increase due to higher fractional cell kill or decrease if tumor proliferation between cycles leads to a “kinetic” failure. One strategy to overcome “kinetic” failure is to increase dose density through frequent chemotherapy administration, a strategy employed in most current BL regimens. Another strategy is to increase the fractional cell kill or efficacy of chemotherapy, thereby reducing the number of tumor cells which can survive and proliferate between cycles. Hence, BL regimens commonly employ multiple chemotherapy agents in high doses and alternating cycles. They typically include anthracylines, epipodophyllotoxins, vinca alkaloids, and alkylators, as well as methotrexate and cytarabine which are cell cycle active agents and take advantage of the high tumor proliferation. These agents, however, are administered in a variety of combinations and schedule, indicating the empiric nature of the actual combinations (Table 3). Indeed, the optimal dose and schedule of cyclophosphamide, methotrexate and cytarabine remain unknown and vary among the major regimens (Table 3).

The risks of tumor lysis syndrome and propensity for CNS dissemination in BL also have important treatment implications. To reduce tumor lysis, which can produce life threatening electrolyte imbalances and renal failure, many regimens employ a pre-phase whereby relatively low dose cyclophosphamide and prednisone are administered. This strategy has been incorporated into the regimens of the French Society of Pediatric Oncology (SFOP), German Multicenter ALL Group (GMALL), and BFM, but not CODOX-M or Hyper-CVAD (Table 4). The high risk of CNS involvement is handled by the use of relatively high dose intravenous methotrexate and cytarabine, both of which have CNS penetration, and intrathecal administration. An important advance has been to reduce intrathecal treatment and eliminate whole brain radiation for prophylaxis, which has significantly reduced CNS toxicity. A recently published FAB/LMB study demonstrated that patients with early stage Burkitt lymphoma had a high cure rate and very low rate of CNS relapse without the use of intrathecal chemotherapy[8].

Table 3. Comparison of Dose and Dose Intensity among Burkitt Lymphoma Regimens

	CODOX-M/ IVAC CODOX-M/ IVAC [9]	LMB 89 LMB 89 [10]	BFM 90 BFM 90 [11]	Dose Range
Doxorubicin				
Dose∗,‖	40	60	50	40-50
Dose intensity∗,‖	13	20	25	13-25
Cyclophosphamide				
Dose	1600	1500	1000	1000-1600
Dose intensity	533	500	500	500-533
Vincristine				
Dose	3	2	1.5	1.4-2
Dose intensity	1.0	0.63	0.75	0.63-0.93
Etoposide				
Dose	300	800	200	200-800
Dose intensity	100	266	100	100-266
Methotrexate				
Dose	6720	8000	5000	5000-8000
Dose intensity	2240	2666	2500	2240-2666
Cytarabine				
Dose	8000	9000	600	600-9000
Dose intensity	2666	3000	200	200-3000
Ifosfamide				
Dose	7500	NA	4000	7500-4000
Dose intensity	2500	NA	2000	2500-2000
Other drugs	NA	Prednisone	Dexamethasone	NA

‖ Dose is expressed as mg/m2. Dose intensity is expressed as planned dose intensity and calculated as mg/m2/week.

Table 4. Selected Regimens for Burkitt Lymphoma

Regimen	No. of Patients	Histology (No.)	Median age yrs (Range)	Stage (%)	CR (%)	EFS (%)	OS (%)
LMB 89 LMB 89 [12]	561	Burkitt and L3 ALL (420)	8 (0.17-18)	III-IV 79%	97 %	92% @ 5 yrs	92% @ 5 yrs
Modified LMB Modified LMB [13]	72	Burkitt and L3 ALL	33 (18-76)	III-IV 67%	72 %	65% @ 2 yrs	70% @ 2 yrs
GMALL B-NHL 86 B-NHL 86 [14]	35	L3 ALL	36 (18-65)	N/A	74 %	71% @ 4 yrs for DFS	51% @ 4 yrs
Modified GMALL	92	Burkitt and L3 ALL	47 (17-78)	III-IV 89%	74 %	45-52% @ 3 yrs	50-54% @ 3 yrs
BFM 90 BFM 90 [4]	413	Burkitt and L3 ALL (322)	9 (1.2-17.9)	III-IV 60%	N/A	89% @ 6 yrs	14 deaths
CODOX-M/ IVAC	21 peds 20 adult	Burkitt	12 (3-17) 25 (18-59)	III-IV 78%	95 %	85% (peds) and 100% (adults) @ 2 yrs	2 deaths
CODOX-M/ IVAC IVAC [9]	52	Burkitt	35 (15-60)	III-IV 61%	77 %	65% @ 2 yrs	73% @ 2 yrs
Hyper-CVAD Hyper-CVAD [15]	26	L3 ALL	58 (17-79)	N/A	81 %	61% @ 3 yrs for DFS	49% @ 3 yrs
Intensive sequential and SCT Intensive sequential and SCT [16]	27	Burkitt	36 (15-64)	III-IV 44%	81 %	73% @ 5 yrs	81% @ 5 yrs
DA-EPOCH-R	25	Burkitt	30 (18-66)	III-IV 54%	100 %	96% @ 28 mos	100% @28mos

There are multiple highly effective regimens for BL and L3 B-ALL, most of which have been based on leukemia platforms (Table 4). Due to high toxicity and the recognition that some patients require less treatment, risk adaptive strategies were tested. The SFOP conducted a series of protocols to refine the treatment of BL and L3 ALL (LMB). These studies demonstrated that short dose intense treatment was effective in patients without CNS involvement, and that dose

intensification of methotrexate, cytarabine and etoposide with cranial irradiation improved the EFS of patients with CNS involvement to 75%. Based on these findings, a risk adapted protocol (LMB 89 protocol) was developed in which treatment was based on tumor burden and early response to chemotherapy (Table 4). Using the St Jude (Table 1) staging, group A included stage I or II with abdominal resection; group B included unresected stage I, non-abdominal stage II, any stage III or IV disease and/or L3 ALL (CNS negative and < 70% marrow blasts); and group C patients had CNS involvement and/or > 70% marrow blasts. Based on these risks, group A only received induction, group B received pre-phase, induction, consolidation and limited maintenance and group C also received extended maintenance and cranial irradiation if the CNS was involved. If a CR was not achieved in groups B and C after the third or fourth induction-consolidation course, patients underwent high dose therapy with autologous stem cell transplant. This strategy was highly successful in pediatric patients with 5 year event-free and overall survivals of 92% (Table 4). The success of LMB 89 in pediatrics led to its testing in adults with minor modifications (Table 4). The outcome in 72 adult patients, mostly with advanced disease, was favorable with EFS and OS of 65% and 70%, respectively, at 2 years.[13] Toxicity remains a problem for advanced stage patients due to the treatment intensity. Treatment-related deaths from infection were higher in adults compared to pediatrics with incidences of 5% and 1.6%, respectively, among patients in groups B and C. Myelosuppression was the primary treatment complication with over 40% of adults experiencing febrile neutropenia. Tumor lysis syndrome requiring dialysis was prevented by the pre-phase treatment and associated supportive care.

The GMALL reported excellent results with an intensive 18 week regimen in adult patients with L3 ALL. In an effort to reduce CNS toxicity, the Cancer and Leukemia Group B (CALGB) studied a modified version in which intrathecal methotrexate was reduced and cranial radiation was only administered to high risk patients (Table 4). These patients were compared to another cohort who received the standard CNS prophylaxis. Overall 92 patients enrolled on the two cohorts. There were no differences in outcome with EFS and OS of 45-52% and 50-54%, respectively, at 3 years. This study suggested that short-duration treatment with less intensive CNS prophylaxis was equally effective to more aggressive prophylaxis and with significantly less neurotoxicity.

Another highly effective regimen for BL was developed by the BFM (Table 4). Like other regimens for BL, the BFM approach was based on short, intensive cycles and over the course of several protocols led to a reduction in the number of cycles based on risk stratification. The BFM 90 protocol continued to further refine the risk stratification and to improve the outcome of patients who had an incomplete initial response with further treatment intensification. Among 322 pediatric patients with BL or L3 ALL treated with the BFM 90 regimen, the overall EFS was 89% at 6 years. Importantly, this represented a significant improvement for advanced stage patients compared to the previous BFM 86 protocol.

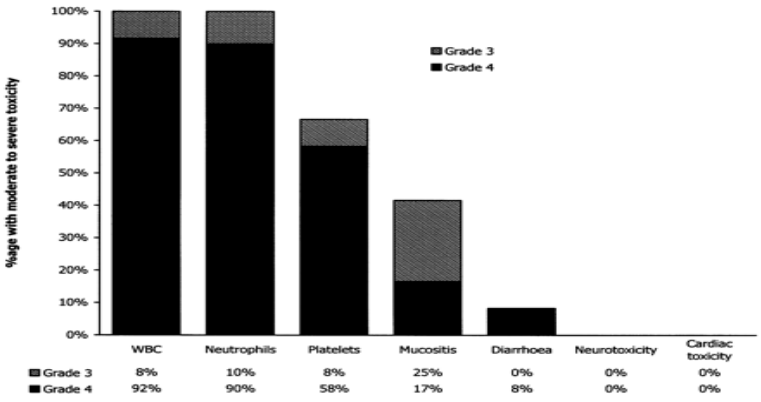
Two clinical trials conducted at the National Cancer Institute (NCI protocols 77-04 and 89-C-41) diverged from the leukemia model of treatment and investigated the role of more limited treatment (Table 4). In the 77-04 protocol, 3 cycles of intravenous cyclophosphamide, vincristine, doxorubicin, methotrexate and leucovorin rescue with cytarabine intrathecal prophylaxis (CODOX-M) showed that intensive combination chemotherapy produced an event-free survival (EFS) of 66% in patients with low risk disease. However, patients with high risk disease (i.e., St. Jude Stage IV) fared poorly with a 19% EFS. Based on the observation that some patients were salvaged with combination ifosfamide, etoposide, and cytarabine (IVAC), a

successor protocol 89-C-41 was developed in which CODOX-M was alternated with IVAC and administered for 4 cycles in high risk patients. This approach yielded an overall EFS of 85% compared to 55% for all patients treated on CODOX-M alone with no difference in low and high risk disease. When the CODOX-M/IVAC regimen was tested in an adult cooperative group trial, however, they only achieved an EFS of 65% at two years.[9]

The Hyper-CVAD regimen was based on a modification of a regimen developed by Murphy et al for pediatric L3 ALL (Table 4). In this regimen, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone were alternated with methotrexate and cytarabine for a total of 8 cycles. The results in 26 adults with L3 ALL were quite favorable with EFS of 73% at five years. Based on these results in L3 ALL, this regimen has also been used for BL.

DA-EPOCH-R has been investigated in a pilot study in untreated Burkitt lymphoma based on the efficacy of the regimen in DLBCL and the ability of the regimen to overcome tumors with a high proliferation rate. Recently reported results demonstrated an EFS and OS of 96% and 100% respectively at a median follow-up time of 28 months in a group of 25 patients treated with the regimen. This strategy and the results of this pilot study, which have led to this study, are discussed in the next section.

While current treatments are quite effective in BL, improvements are needed in patients with high risk disease. Furthermore, toxicity of the regimens for high risk disease is particularly problematic for older adults, and treatment related mortality is excessive. Indeed, the high dose methotrexate and cytarabine in standard BL regimens has led to significant toxicity as illustrated by the CODOX-M/IVAC regimen (Figure 1 and 2). With this regimen, myelosuppression is severe and tumor lysis syndrome is high. Hence, new strategies are needed to improve the therapeutic index of treatment and to increase efficacy. The success of rituximab in diffuse large B-cell lymphoma has prompted its testing in BL. Rituximab has been incorporated in the Hyper-CVAD regimen with a three year disease free survival of 88% in 31 patients, most of whom had advanced stage disease.[17, 18] Rituximab has also been incorporated into ongoing CALGB (Phase II study of rituximab and short-duration, high-intensity chemotherapy with GCSF support in previously untreated patients with Burkitt lymphoma/leukemia – P.I. John Byrd – NCT00039310) and COG (rituximab, rasburicase, and combination chemotherapy in treating young patients with newly diagnosed advanced B-cell leukemia or lymphoma – Study Chair: Michael S.Cairo - NCT00057811) protocols for BL.



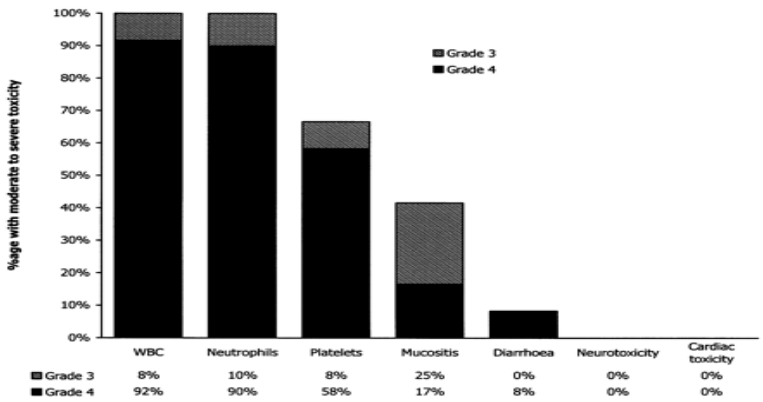


Figure 1: Percent of patients with Grade 3 or 4 WHO toxicity on CODOX-M for low risk BL.

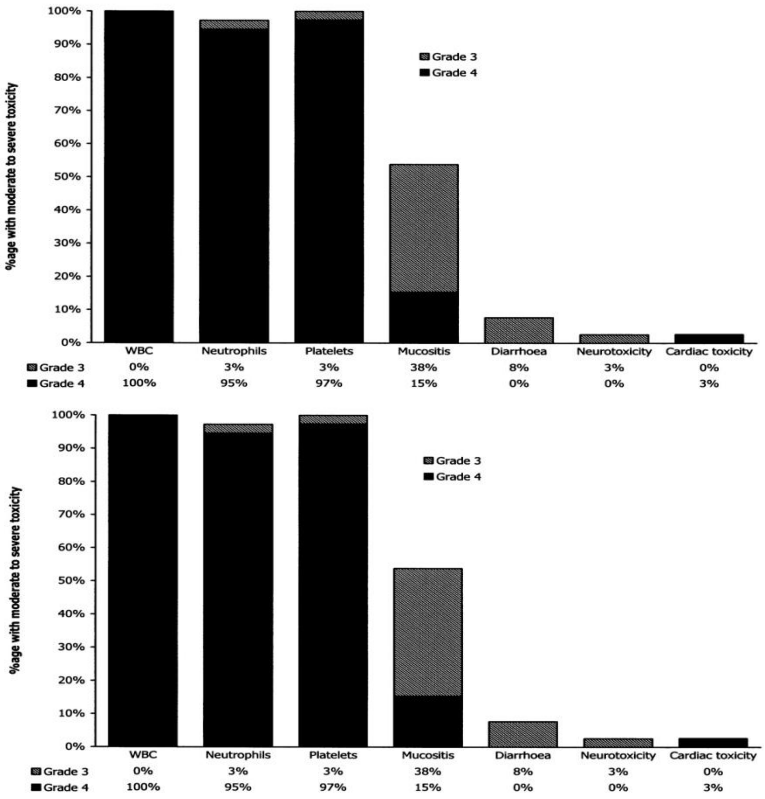


Figure 2: Percent of patients with Grade 3 or 4 WHO toxicity on CODOX-M/IVAC for high risk BL.

2.2.2 c-MYC Positive Diffuse Large B-Cell Lymphoma

Approximately 5% of DLBCLs are c-MYC positive .Though the presence of a MYC break has been linked with a very unfavorable prognosis, there has been very little published on this subtype of DLBCL and there are have not been clinical trials done to investigate how patients with this subtype do. These tumors are usually associated with a high proliferation index and in this respect may preferentially benefit from regimens that can overcome high tumor proliferation like DA-EPOCH-R. We are therefore very interested in investigating these diseases and also

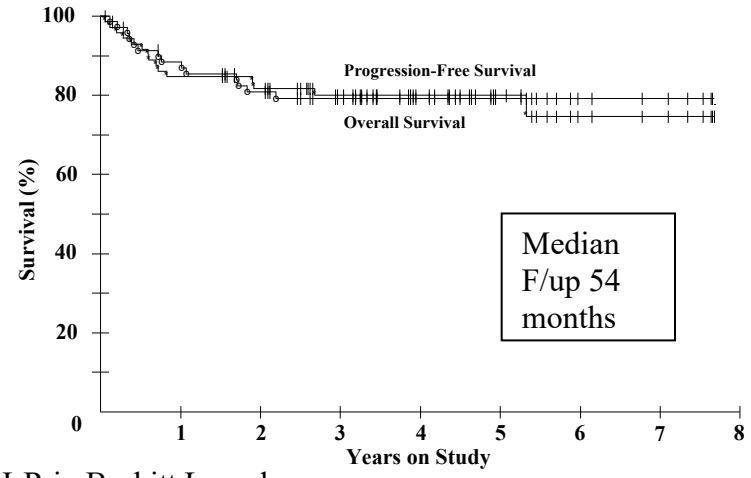
performing gene expression profiling of these tumors, as this has not been well described and this is the reason for their inclusion.

Plasmablastic lymphoma, which is a variant of DLBCL, is associated with a very high rate of c-MYC activation. The outcome for patients with plasmablastic lymphoma has been poor with standard therapies. Plasmablastic lymphomas that are c-MYC + are included in this study. As they are CD20 negative, they will receive DA-EPOCH alone (no rituximab). As they historically have had a poor outcome with standard therapy, they will be treated on the high risk arm (i.e. 6 cycles of DA-EPOCH).

2.2.3 DA-EPOCH-R Background

DA-EPOCH-R is a pharmacodynamic-based infusional regimen with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab. DA-EPOCH was designed to improve the therapeutic index of chemotherapy by taking advantage of increased sensitivity of highly proliferative tumors to prolonged exposure to low concentrations of chemotherapy. A prospective multi-institutional study of DA-EPOCH in 50 patients with previously untreated large B-cell lymphomas showed that highly proliferative tumors were sensitive to treatment, unlike CHOP-based treatments[19]. A Phase II study of DA-EPOCH-R in 72 patients with untreated DLBCL has also been completed. Patients had a median age of 50 years (range, 20-88 years) and 40% had high-intermediate or high risk disease according to International Prognostic Index (IPI) criteria. At 5 years, the progression-free and overall survivals are 79% and 80% respectively (figure 3) with a median follow-up time of 54 months (in press). As seen with DA-EPOCH, high tumor proliferation was not an adverse biomarker. A CALGB multicenter study of 75 patients at 18 centers has also reported similar results (W. Wilson, personal communication). Based on these studies, DA-EPOCH-R is currently being compared to CHOP-R in a phase III multicenter CALGB trial.

DA-EPOCH-R NCI Clinical Trial Results: figure 3



2.2.4 DA-EPOCH-R in Burkitt Lymphoma

Based on the hypothesis that DA-EPOCH-R may be effective in BL, given its established efficacy in DLBCL and its ability to overcome highly proliferative tumors, we assessed in a pilot fashion if DA-EPOCH-R could maintain the high cure rates of standard therapy in BL while minimizing treatment related toxicity in HIV negative patients. We also treated a cohort of HIV positive patients with Burkitt lymphoma employing a modified version of DA-EPOCH-R. All

patients had untreated BL of which 8 were HIV positive and 17 ere HIV negative. HIV negative patients received standard DA-EPOCH-R for 6-8 cycles (median 6 cycles) and HIV positive patients received 3-6 cycles of DA-EPOCH-RR for 1 cycle beyond CR for a minimum of 3 cycles (median 3 cycles). All patients received intrathecal methotrexate prophylaxis. A total of 25 patients with BL have been treated at the NCI on two protocols using EPOCH and rituximab (#93-C-0133 (DA-EPOCH-R in untreated DLBCL and BL), #01-C-0030 (DA-EPOCH-RR in untreated ARL)). Characteristics of all 25 patients (see table) included median age (range) 30 (18-66); male sex 20 (80%); median (range) ECOG PS 1 (1-3); stage III/IV 54%; LDH > N 56%; extranodal sites 79% and ileocecal disease 54%. 8/25 (32%) had low-risk disease and 17/25 (68%) had high-risk disease. No patients had CNS involvement at diagnosis. All patients achieved a CR/CRu with one patient receiving consolidative radiation to a site of residual disease. OS and PFS are both 100% and EFS 96% at a median potential follow-up of 28 months. Significant toxicities included tumor lysis syndrome (TLS) in only one patient and fever/neutropenia in 16% of cycles. There were no treatment related deaths. These pilot results suggest that DA-EPOCH-R is effective regimen in newly diagnosed BL and is associated with low toxicity and low rates of TLS compared to “standard” high dose regimens used in BL. Hence, these results suggest that DA-EPOCH-R may significantly advance the therapeutic index in the treatment of BL[20].

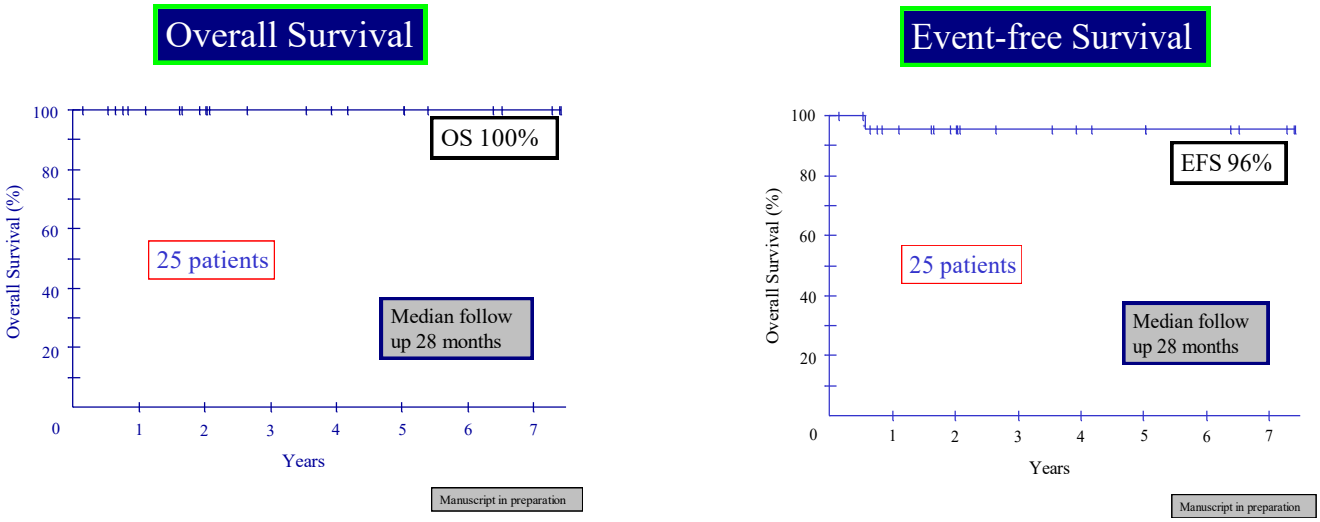
2.2.5 Rationale for Short-Course Treatment in Low-Risk Patients

We investigated reduced cycle EPOCH-RR in 10 patients with newly diagnosed HIV-associated Burkitt lymphoma, 80% of whom had advanced stage III or IV disease. In this study, we administered short-course chemotherapy (minimum of 3 cycles with at least 1 cycle beyond CR) in an attempt to reduce treatment duration and toxicity. We demonstrated that most patients (79%) required 3 cycles of chemotherapy. The efficacy of this approach was outstanding with 100% of patients progression-free at 5 years. Based on these results and the current standard to employ risk adapted therapy, we plan to treat patients with early stage disease with reduced chemotherapy. To increase safety, patients who do not achieve a CR in 2 cycles will be crossed over to receive 6 cycles of treatment and an early stopping rule has been incorporated in the study design.

DA-EPOCH-R in Burkitt Lymphoma: Patient Characteristics

Characteristics	All Patients	HIV -	HIV +
Total Patients	25	17	8
Gender (M/F)	4:1	3:1	5:1
Median age, y (range)	30 (18-66)	25 (18-66)	40 (24-60)
ECOG PS > 1	25%	12%	50%
Stage III or IV	54%	44%	75%
LDH > Normal*	56%	37%	87%
Extranodal sites	79%	75%	87%
Ileo-caecal disease	54%	56%	50%

DA-EPOCH-R Results in Burkitt Lymphoma: figures 4a and 4b



2.2.6 DA-EPOCH Pharmacokinetics

The pharmacokinetics (PK) of DA-EPOCH has been studied in adults with DLBCL (Balis and Wilson, et al, personal communication). Age-related clearance was demonstrated for doxorubicin and etoposide. In 12 patients studied, the mean coefficient of variation of doxorubicin across the 6 cycles of therapy was 34% (range, 13-76%). There was no difference in doxorubicin clearance, but there was a trend toward lower clearance with advancing age (rho=-0.54, p=0.08). We also measured steady state total and free plasma etoposide concentration in 33 patients, ages 22-69, over 164 cycles of EPOCH. Free etoposide clearance gradually increased over the course of therapy. While the mean clearance for total and free etoposide was similar in males and females, there was significantly lower clearance with advancing age (r=-0.45; p=0.034). Pharmacokinetics

and tolerance of doxorubicin and etoposide during treatment of aggressive B-cell lymphomas indicate doses need not be routinely reduced for hepatic dysfunction[21].

2.2.7 PET Scans in Lymphoma

PET scans are used in NHL to evaluate residual masses detected on CT after completion of chemotherapy, with the positive and negative predictive values for outcome of 80% to 100%. [22] PET after one cycle of chemotherapy was superior to PET at completion of chemotherapy in predicting PFS in NHL and HD.[23] In Hodgkin's lymphoma (HL) positive predictive value of a PET-2 (PET after 2 cycles) was 90% and the negative predictive value was 97%. The sensitivity, specificity and overall accuracy of PET-2 were 86%, 98% and 95%, respectively.[24] There is limited experience with PET scans in BL but it is known that this high grade, chemo-sensitive malignancy is generally PET positive at diagnosis and negative at completion of chemotherapy. Early PET scanning in BL may identify a population of poor prognosis chemo-resistant patients who could benefit from alternative treatment. Additionally, it may identify patients who should not receive limited chemotherapy.

2.2.8 FISH and Microarray Profiling

BL is characterized by translocations of the myc-oncogene on chromosome 8 to the IgH locus on chromosome 14 although other myc translocations and activating mutations have been reported. BL has recently been characterized by microarray profiling. [25, 26] It is possible to differentiate between DLBCL and BL using microarray. This study may provide pilot predictive and prognostic data and to investigate whether BL in HIV positive and negative patients have differences in their gene expression profiles. We aim to perform gene expression profiling on Affymetrix whole genome arrays in pre-treatment biopsies from patients enrolled in the study. Gene expression profiling provides a comprehensive and highly quantitative overview of tumor biology and can be carried out even from small amounts of tissue. Gene expression signatures that relate to specific cellular functions or to the activity of distinct signaling pathways can be reproducibly monitored and can identify subsets of patients with distinct tumor biology, different prognosis or differential response to therapy.

2.2.9 Burkitt Lymphoma Genome Sequencing Project (BLGSP)

In Amendment I (version date 03/14/14), we added the Burkitt Lymphoma Genome Sequencing Project (BLGSP) protocol to this study to allow us to contribute samples from Burkitt Lymphoma patients to the Genomic Databank for Burkitt Lymphoma being created by the Foundation for Burkitt Lymphoma Research (FFBLR) (APPENDIX F). The effort will be coordinated through the Foundation for the National Institutes of Health (FNIH). The NCI, through the Office of Cancer Genomics (OCG), will provide the administrative, physical and analytical infrastructure in order to carry out this project. This will enable the FFBLR to utilize existing Standard Operating Procedures (SOPs) developed by OCG, as well as relationships OCG has established with other organizations, in order to carry out this project. This effort will enhance the scientific integrity and credibility of the BLGSP, and be consistent with the conduct and methodologies used in other NCI sponsored cancer sequencing projects.

2.2.10 Study Rationale and Design

The DA-EPOCH-R regimen represents a major paradigm shift for the treatment of BL. Whereas standard treatment relies on dose density and intensity based on methotrexate and cytarabine to achieve adequate cell kill, DA-EPOCH-R relies on a pharmacodynamic based infusional

schedule to improve the therapeutic index of chemotherapy. Based on our pilot results, DA-EPOCH-R appears to provide a high rate of cure with significantly lower treatment toxicity and tumor lysis syndrome compared to standard treatment. As such, DA-EPOCH-R may provide a major treatment advance in BL by lowering morbidity, mortality and cost, while maintaining or possibly improving efficacy. The current protocol is written to confirm our pilot results of DA-EPOCH-R in BL and in particular to obtain further results in patients with advanced stage disease. We also plan to obtain pilot information on potential differences in the microarray of BL in HIV positive and negative patients.

Regarding the toxicity of DA-EPOCH-R compared to other treatments for Burkitt lymphoma: In the UK Lymphoma Group LY06 study (Mead et al. Annals of Oncology 13: 1264-1274, 2002) - which was a very large multicenter study comparing CODOX-M and CODOX-M-IVAC in 52 patients, the major toxicities were as follows: there were 6 toxic deaths in total: 5 of these were in patients receiving CODOX-M-IVAC and 1 was in patients receiving CODOX-M. This is an overall treatment related mortality of 12%. This study accrued patients from 16 years to 60 years. While appreciating that toxicity may be somewhat less overall in a pediatric population, this treatment-related mortality with these regimens is very significant. Thus far, in treating 27 Burkitt lymphoma patients with DA-EPOCH-R, we have encountered 0% mortality and have included patients older than 50 years some with immunodeficiency. Overall hematological toxicities and notably mucositis (grade 3 or 43%) are significantly higher for CODOX-M and CODOX-M-IVAC than for DA-EPOCH-R but our principal concern with these regimens is treatment related mortality. It is also notable that across several studies that have looked at toxicity with CODOX-M and CODOX-M-IVAC, dose reductions, particularly of methotrexate, have been required and in our study of DA-EPOCH-R in Burkitt lymphoma, we have not needed to make any dose reductions. The concern of dose reductions in curable lymphomas is that they may compromise cure rates.

Based on our excellent albeit limited results with short-course (median 3 cycles) DA-EPOCH-RR (Rituximab day 1 and 5) in HIV associated BL, we hypothesize that low risk BL may only require 3 cycles of treatment. Thus far, in our Burkitt lymphoma study, of HIV positive patients with Burkitt lymphoma, most just required 3 cycles of therapy. We administered one cycle of therapy beyond CR. There is much literature that patients with low-risk Burkitt lymphoma can be cured with shorter courses of therapy (and of course this is associated with less toxicity) and based on this and our excellent results with short-course therapy in the HIV positive population, we are confident that 3 cycles of therapy should be adequate for patients with low risk disease. Of course patients will be closely monitored and if they have not achieved a CR after 3 cycles of therapy, they will receive further courses. Hence, we have developed a risk adaptive paradigm in which low risk patients will receive 3 cycles of DA-EPOCH-RR and high risk patients and patients with c-MYC+ DLBCL will receive 6 cycles of DA-EPOCH-R (Rituximab day 1). Thus, all patients will receive the same amount of rituximab, but the treatment duration will be shorter for low risk patients. We used this approach (the administration of 2 doses of rituximab on days 1 and 5 of the EPOCH cycle) empirically in our study of abbreviated EPOCH-R in ARL, as we wanted all patients to receive at least 6 doses of the drug – at this point in time, we do not have any data to show that fewer than 6 cycles are as effective as 6. In addition, we hypothesized that levels of the drug would rise higher and be sustained over a longer period of time (potentially improving tumor cell kill) when 2 doses were given compared to 1 and this strategy, with PK

studies, is being investigated by the German High-Grade NHL group and initial PK results demonstrate higher levels over a longer period of time.

To provide a measure of safety in patients with low risk disease, and to assess the predictive value of PET/CT scans, all patients will undergo a clinical PET/CT scan after two cycles of treatment. Low risk patients who respond with a negative PET/CT scan will receive 3 cycles of treatment whereas low risk patients with persistently positive PET/CT scan after 2 cycles will cross over to the high risk arm to receive a total 6 cycles of treatment. All patients with a positive PET/CT scan after 2 cycles will have a repeat PET/CT scan after treatment completion. Low risk patients with a negative CSF by cytology and flow cytometry will not receive prophylactic IT chemotherapy, as we deem the risk of CNS dissemination in this group to be extremely negligible based on the recent FAB/LMB study; high risk patients with a negative CSF by cytology/flow cytometry will receive prophylactic treatment of the CSF with IT methotrexate and/or cytarabine and patients with a positive CSF by cytology/flow cytometry will receive active treatment of the CSF with IT/Intraventricular methotrexate/cytarabine.

For patients who receive prophylactic intrathecal chemotherapy, this therapy is commenced on Cycle 3. The rationale for this is as follows: in previous studies using the EPOCH regimen in aggressive lymphomas, we have noted increased toxicity from the EPOCH drugs on the cycles when intrathecal therapy is administered. In treating Burkitt and other aggressive B-cell lymphomas, dose intensity on the initial cycles (and dose adjustment potentially) are critical (in avoiding kinetic failures). Adding intrathecal therapy early may enhance cytotoxicity and limit the doses of EPOCH drugs that can be administered on these cycles. We feel that this approach is safe in view of the fact that every patient's CSF is analyzed by flow cytometry at diagnosis and this detects very small volumes of tumor cells.

3 ELIGIBILITY ASSESSMENT AND ENROLLMENT

3.1 Eligibility Criteria

3.1.1 Patients must have Burkitt Lymphoma. Effective with Amendment J (version date: 06/24/2014), the following histologies were removed as the maximum number allowed for these sub-groups has been reached: B-cell lymphoma: unclassifiable with features intermediate between Diffuse Large B–cell lymphoma and Burkitt Lymphoma; c-MYC + DLBCL and c-MYC+ plasmablastic lymphoma.

If questions arise related to diagnosis, please contact the NCI Principal Investigator, Dr. Mark Roschewski or the NCI study coordinator, A. Nicole Lucas.

3.1.2 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of EPOCH-R in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

3.1.3 Pathology confirmed by treating institution's Pathology Department.

3.1.4 No prior treatment except patients may be entered if they have had prior limited-field radiotherapy, a short course of glucocorticoids, cyclophosphamide for an urgent problem at diagnosis (e.g. epidural cord compression, superior vena cava syndrome) and/or a single dose of intrathecal methotrexate (MTX) at the time of the pre-treatment diagnostic lumbar puncture.

3.1.5 All disease stages

3.1.6 HIV negative or positive

3.1.7 HIV positive patients on antiretroviral therapy regimen must be willing to suspend all Highly Active Antiretroviral Therapy (HAART) except in circumstances described in Section **6.5**.

3.1.8 ECOG 0-4

3.1.9 Ability of patient or durable power of attorney (DPA) for healthcare to give informed consent

3.1.10 Hepatitis B + patients may be enrolled at the discretion of the investigator.

3.2 Exclusion Criteria

3.2.1 Patients with Primary CNS Lymphoma.

3.2.2 Inadequate renal function, defined as serum Cr > 1.5 mg/dL or creatinine clearance < 50 ml/min/1.73m2 unless lymphoma related.

3.2.3 Inadequate hepatic or hematological function, as follows, unless lymphoma-/disease-related: bilirubin > 2 mg/dl (total) except > 5 mg/dl in patients with Gilbert's syndrome as defined by > 80% unconjugated, ANC < 1000 and platelets < 75,000.

3.2.4 The effects of EPOCH-R on the developing human fetus are unknown. For this reason and because chemotherapy agents are known to be teratogenic, female subject of child-bearing potential not willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study and one year beyond treatment completion will not be eligible to participate in the study.

3.2.5 Female subject pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for women without child-bearing potential.

3.2.6 The effects of EPOCH-R on the developing human fetus are unknown. For this reason and because chemotherapy agents are known to be teratogenic, male subject unwilling to use an acceptable method for contraception for the duration of the study and one year beyond treatment completion, will not be eligible to participate in the study.

3.2.7 History of a prior invasive malignancy in past 5 years

3.2.8 Active symptomatic ischemic heart disease, myocardial infarction or congestive heart failure within the past year. If echo is obtained the LVEF should exceed 40%.

3.2.9 Serious concomitant medical illnesses that would jeopardize the patient's ability to receive the regimen with reasonable safety.

3.2.10 HIV positive patients with advanced immune suppression and evidence of HIV resistant to all combinations of antiretroviral therapy considered at high risk of non-lymphoma related death within 12-months due to other AIDS complications should not be enrolled on the study.

3.3 Screening Evaluation

Evaluation pre-treatment (within 4 weeks of treatment except **3.3.2.1**and **3.3.2.6** must be done within 72 hours of treatment):

3.3.1 Clinical evaluation

3.3.1.1 Complete History and Physical examination

3.3.1.2 Height, weight and performance status

3.3.1.3 CT scan of chest, abdomen and pelvis

3.3.1.4 Clinical PET/CT (fluorine 18-FDG) scan. This PET/CT scan is optional, but it is strongly encouraged that it be obtained if possible.

3.3.1.5 Magnetic Resonance Imaging of head and/or spine if clinically indicated

3.3.1.6 Unilateral Bone marrow biopsy and aspirate

3.3.1.7 Lumbar Puncture for flow cytometry, glucose, protein, cell count and cytology.

3.3.2 Laboratory Evaluation

3.3.2.1 CBC, differential, PT, PTT, AST, ALT, LDH, alkaline phosphatase, bilirubin, albumin, calcium, phosphate, uric acid, creatinine (24 hour creatinine clearance if serum creatinine > 1.5 mg/dL), electrolytes, glucose, urinalysis.

3.3.2.2 HIV antibody, Anti-HCV antibody, & hepatitis B surface antigen.

3.3.2.3 Serum EBV viral load by PCR (NIH Clinical Center only).

3.3.2.4 Lymphocyte enumeration (TBNK) for HIV + patients only

3.3.2.5 HIV viral load for HIV + patients only

3.3.2.6 Serum HCG in females of childbearing potential.

3.3.2.7 Peripheral blood flow cytometry

3.3.2.8 All patients (except Burkitt Lymphoma patients) must have confirmation of cMYC rearrangement [(8,14) translocation by FISH or cytogenetics] prior to enrollment.

3.4 Baseline Studies

3.4.1 A fresh tissue biopsy of accessible lymph node will be obtained in patients who consent to the optional biopsy where possible and if it does not delay the initiation of treatment significantly, as judged by the PI or designee. These biopsies are optional but highly encouraged.

3.5 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN) or Rave or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL)

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

4.2 Site Registration (Applies to all participating sites, including NCILYMB)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office

before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federalwide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

Site registration. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS. forms can be downloaded from the 9177 protocol page located on the CTSU Web site.

- Go to https://www.ctsu.org
- Log in to the members' section on the left side of the page using your CTEP IAM username and password
- Click on the Protocols tab in the upper left portion of your screen; enter "9177" in the search box, then click the Go button.
- Click on the LPO Documents tab and scroll down the page to the Site Registration Documents links.
- Download and complete the following forms:
- CTSU IRB/Regulatory Transmittal
- CTSU IRB Certification Form

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.3 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). All site staff (including NCILYMB) will use OPEN. OPEN is a web-based registration system available on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

Prior to accessing OPEN site staff should verify the following:

4.3.1 All eligibility criteria have been met within the protocol stated timeframes.

4.3.2 If applicable, all patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form.

4.4 Access requirements for OPEN:

4.4.1 Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.

4.4.2 To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Organization roster. Role assignments are handled through the Groups in which

you are a member

4.4.3 Site and/or Data Administrators can manage roster roles (including assignment of the Registrar role) within the Regulatory tab/Site Roles sub-tab of the CTSU members' web site.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

A PDF version of the Eligibility Checklist is available on the CTSU web site under the patient enrollment documents link for the protocol. If a paper EC is used for source documentation it must be signed and dated.

4.5 On-study Procedure for NIH Clinical Center Only

In addition to registering patients through the OPEN system, authorized staff at the NCI 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.

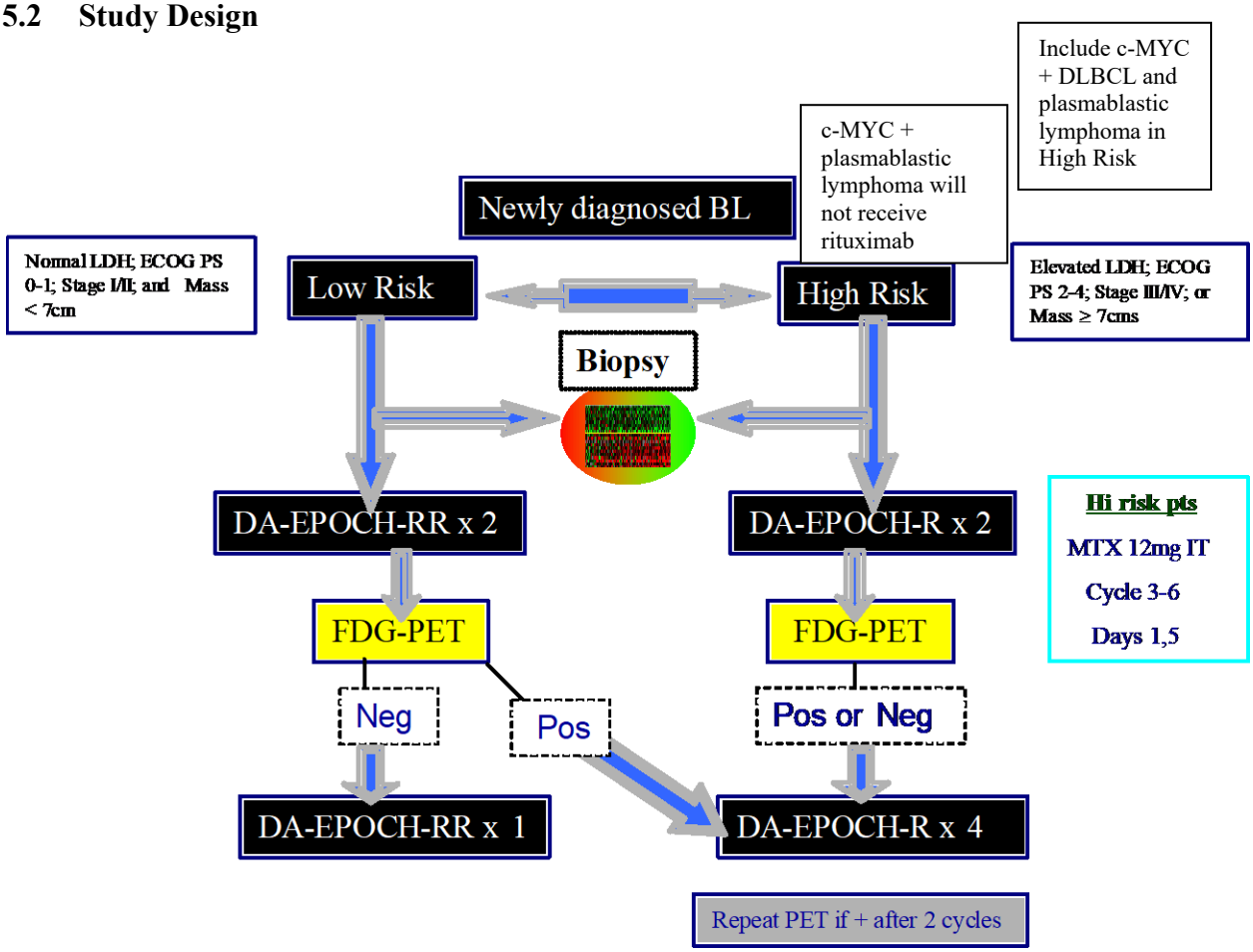
5 TREATMENT PLAN

Effective with Amendment L (version date: 11/21/2016) this protocol is no longer on Administrative Hold. The investigators at the Clinical Center may resume patient enrollment. Effective with Amendment K (version date: 10/18/2016) this protocol is on Administrative Hold at the Clinical Center only. No new patients will be enrolled at the NIH Clinical Center; however, patients currently on-study will continue to be followed per protocol. Enrollment will continue at Participating Sites with current IRB Approval.

5.1 Agent Administration

Treatment will be administered on an outpatient basis, as a general rule. At times, it may be necessary to administer the treatment on an inpatient basis. Reported adverse events and potential risks are described in Section **14**. Appropriate dose modifications are described in Section **5.4**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2 Study Design



5.2.1 Definition of Low and High Risk Patients

5.2.1.1 Low Risk (LR) Patients must meet all of the following criteria:

- Normal LDH
- ECOG PS 0-1 or Karnofsky 100%-70%
- Ann Arbor stage I-II
- No tumor mass ≥ 7 cm

5.2.1.2 High Risk (HR) Patients

All patients not considered low risk (LR) and all patients with c-MYC + DLBCL. Note that patients with c-MYC + plasmablastic lymphoma (who are CD20 negative) will NOT receive rituximab and will receive 6 (or 8 if applicable) cycles of DA-EPOCH.

5.2.2 Systemic Treatment

Systemic treatment is determined by risk as described in Section **5.2.1**. The treatment paradigm is described in Section **5.3**.

5.2.3 Central Nervous System (CNS) Treatment

CNS treatment is determined by disease status as described in Section **5.2.1**.

Patients with low risk disease will not receive prophylactic intrathecal chemotherapy.

If initial CSF flow cytometry and cytology and brain scan negative, high risk patients (including patients with c-MYC+ DLBCL and c-MYC+ plasmablastic lymphoma) will receive prophylactic intrathecal chemotherapy beginning on cycle 3.

If initial CSF flow cytometry or cytology is positive, patients will receive active intrathecal chemotherapy beginning on cycle 1. At the discretion of the Principal Investigator or lead associate investigator, patients with abnormal clinical neurological findings, or suspicious flow cytometry or cytology may receive active intrathecal chemotherapy beginning on cycle 1.

5.3 Study Drug Administration (Dose-Adjusted-EPOCH-Rituximab)

5.3.1 Low Risk Patients

LR patients will receive 3 cycles of DA-EPOCH-RR (two doses of rituximab per cycle). As a safety measure and secondary endpoint, FDG-PET/CT will be performed after cycle 2 completion. If the FDG-PET/CT is positive, the patient will complete treatment as outlined for high risk patients (i.e. receive 4 additional cycles of DA-EPOCH-R), with a repeat FDG-PET/CT after completion of cycle 6.

Dose-Adjusted-EPOCH-RR

Drugs	Dose/Schedule
Rituximab	375 mg/m2 IV day 1 (before infusions) and day 5 (before cyclophosphamide); see Section **14.1.5** for administration instructions
Etoposide	50 mg/m2/day CIV days 1- 4 (96 hour infusion)
Doxorubicin	10 mg/m2/day CIV days 1-4 (96 hour infusion)
Vincristine	0.4 mg/m2/day CIV days 1-4 (96 hour infusion)
Cyclophosphamide	750 mg/m2 IV day 5 over 30 minutes.
Prednisone*	60 mg/m2 PO BID days 1-5; (first dose should be given at least 60 minutes before starting day 1 rituximab)
Filgrastim**	480 mcg/day SC days 6-15 or ANC > 5000/µl past the nadir.
Cycle Length	Repeat cycle every 21 days

Delay cycle until ANC > 1000/µl and platelets >75,000/µl. Use filgrastim to increase ANC and begin next cycle as soon as ANC recovers. If no recovery after 2 weeks, contact Dr. Roschewski for guidance.

*For patients who cannot tolerate oral steroids, please contact the Hospital Pharmacist for guidance on dosing equivalents of other steroid preparations.

** In circumstances where it is not feasible to use filgrastim, pegfilgrastim may be substituted but using filgrastim is encouraged if at all possible. If pegfilgrastim is used, the dose is 6 mg SC on Day 6 (as close as possible to 24 hours after completion of chemotherapy).

5.3.2 High Risk Patients including Patients with c-MYC+ DLBCL and c-MYC+ plasmablastic lymphoma

HR patients will receive 6 cycles of DA-EPOCH-R (one dose of rituximab per cycle). Patients with c-MYC+ plasmablastic lymphoma will receive 6 cycles of DA-EPOCH (no rituximab). As a secondary endpoint, FDG-PET/CT will be performed after cycle 2 completion. If that FDG-PET/CT is positive, it will be repeated after completion of cycle 6. High risk patients who have achieved only a Partial Response at the completion of cycle 6 may receive up to 2 additional cycles of DA-EPOCH-R at the discretion of the PI. FDG-PET/CT will be repeated after cycle 8, for those patients who receive 8 cycles of therapy.

Dose-Adjusted-EPOCH-R

Drugs	Dose/Schedule
Rituximab	375 mg/m2 IV day 1 (before infusions); see Section **14.1.5** for administration instructions
Etoposide	50 mg/m2/day CIV days 1- 4 (96 hour infusion)
Doxorubicin	10 mg/m2/day CIV days 1-4 (96 hour infusion)
Vincristine	0.4 mg/m2/day CIV days 1-4 (96 hour infusion)
Cyclophosphamide	750 mg/m2 IV day 5 over 30 minutes.
Prednisone*	60 mg/m2 PO BID days 1-5; (first dose should be given at least 60 minutes before starting day 1 rituximab)
Filgrastim**	480 mcg/day SC days 6-15 or ANC > 5000/µl past the nadir.
Cycle Length	Repeat cycle every 21 days

Delay cycle until ANC > 1000/µl and platelets >75,000/µl. Use filgrastim to increase ANC and begin next cycle as soon as ANC recovers. If no recovery after 2 weeks, contact Dr. Roschewski for guidance.

*For patients who cannot tolerate oral steroids, please contact the Hospital Pharmacist for guidance on dosing equivalents of other steroid preparations.

**In circumstances where it is not feasible to use filgrastim, pegfilgrastim may be substituted but using filgrastim is encouraged if at all possible. If pegfilgrastim is used, the dose is 6 mg SC on Day 6 (as close as possible to 24 hours after completion of chemotherapy).

5.3.3 CNS Treatment

5.3.3.1 Prophylactic CSF treatment: High risk CSF negative patients (including patients with c-MYC+ DLBCL and c-MYC+ plasmablastic lymphoma) will receive prophylactic CNS treatment with intrathecal methotrexate (MTX) on the following schedule: methotrexate 12 mg IT on days 1 and 5 of cycles 3, 4, 5 and 6 (total of 8 treatments). The days of treatment may be adjusted +/- 3 days to accommodate scheduling issues such as holidays, etc.

5.3.3.2 Active Meningeal Lymphoma treatment: If the CSF is positive for malignant cells by flow cytometry/cytology, or the patient has neurological or radiological evidence consistent with leptomeningeal lymphoma, the CSF should be treated with methotrexate as follows:

Induction: MTX (12 mg by lumbar or 6 mg by Ommaya route) twice a week for 2 weeks past negative cytology with a minimum of 4 weeks treatment. Patients will then receive consolidation with MTX weekly x 6 doses and maintenance with MTX monthly x 6 doses.

The above therapy may be modified as clinically indicated. In some cases, it may be necessary to administer radiation to the head and/or spine and/or to substitute cytarabine (70 mg by lumbar or 30 mg by Ommaya route) for MTX. Patients who fail to clear or relapse in the CSF will be considered for alternative intraventricular therapy and/or radiation.

The methods of IT administration should be performed according to institutional procedures.

Patients should remain in prone or Trendelenburg position for 1 hour post LP to facilitate drug circulation throughout the CNS.

5.3.3.3 Parenchymal CNS lymphoma: Patients with evidence of a parenchymal mass may be treated with radiation.

5.3.3.4 Chemical Arachnoiditis: If signs or symptoms of chemical arachnoiditis occur, administer 15 mg hydrocortisone (HDC) with the methotrexate or cytarabine as per the institutional standard. Cytarabine (Ara-C). Cytarabine may be used in place of methotrexate after discussion with the local principal investigator if methotrexate is contraindicated.

5.4 DA-EPOCH-R "Dose Adjustment"

Doses for doxorubicin, etoposide and cyclophosphamide will be based on measurements of the previous cycle ANC or platelet nadir whichever is lower. Dose adjustment is based on measurements of twice weekly CBC only, even if additional CBCs are obtained. Twice weekly CBCs must be at least 3 days apart.

• If Nadir ANC ≥ 500/µl on all measurements:	↑ One level above last cycle
•If Nadir ANC < 500/µl on 1 or 2 measurements:	Same level as last cycle
• If Nadir ANC < 500/µl ≥ 3 measurements:	↓ One level below last cycle
Or	
• If nadir platelet < 25,000/µl ** on ≥ 1 measurement:	↓ One level below last cycle

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

When moving to a higher dose level, adjustments apply only to etoposide, doxorubicin and

cyclophosphamide. When moving to dose levels below dose level 1, adjustments apply only to cyclophosphamide and involve 20% reductions in cyclophosphamide.

Drugs	Drug Doses per Dose Levels							
	-2	-1	1	2	3	4	5	6
Doxorubicin (mg/m2/day)	10	10	10	12	14.4	17.3	20.7	24.8
Etoposide (mg/m2/day)	50	50	50	60	72	86.4	103.7	124.4
Cyclophosphamide (mg/m2/day)	480	600	750	900	1080	1296	1555	1866

5.5 Adverse Event Management (Dose Modification Guidelines)

5.5.1 Ileus and Constipation

Symptomatic ileus/constipation may occur. Because the severity of constipation is dose related, it is usually unnecessary to stop the vincristine altogether. Every effort should be made to not unnecessarily reduce vincristine doses. Ileus/constipation is usually worse on the first cycle, so prophylactic bowel care is essential. If vincristine dose is reduced for this toxicity, it can often be increased to full dose on subsequent cycles without recurrence of severe ileus/constipation. If ileus or constipation requires hospitalization, reduce vincristine 25% on the subsequent cycle. If symptoms resolve after vincristine reduction, increase dose to previous level on subsequent cycles.

Recommended Bowel Regimen – goal of at least one soft bowel motion every 24 hours while on study

Adults: Sodium Docusate 100mg capsule; take one to two capsules once a day Days 1-7 of each cycle. If needed can double the frequency to two capsules every 12 hours. If needed add oral lactulose 15-30 ml prn/ every 6 hours.

5.5.2 Neurological Adverse Events

5.5.2.1 Sensory neuropathy

Grade	% Dose of Vincristine
2	100
3	50
4	0

5.5.2.2 Motor neuropathy

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

If neuropathy resolves to a lower grade, doses for that lower grade may be reinstituted at investigator discretion. If the grade of neuropathy increases after being re-escalated, doses must be reduced for the appropriate toxicity grade and may not be re-escalated, even if neuropathy resolves again to a lower grade.

5.5.3 Hepatic and Renal Dysfunction

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

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

5.5.4 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.

5.5.5 Rituximab Infusional related Adverse Events

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

5.5.6 Supportive Therapies

Supportive therapies, such as blood and/or platelet transfusion and medications to prevent nausea and vomiting are permitted as clinically indicated.

5.6 Study Calendar

Studies[A]	Pre-therapy[A]	Pre-Cycles 1-6[E]	BIW Cycles 1-6[E]	Pre-Cycle 3	Post Cycle 3 (Low Risk)	Post- Cycle 6 and Post-Cycle 8, if applicable (High risk)	Follow Up (see 5.9)
Hx; PE; VS	x	x		x	x	x	x
Height	x						
*PS and weight	x	x					
Tumor Measurement	x			x	x	x	x
*CBC/diff	x	x	x	x	x	x	x
*PT/PTT	x	x					
*Electrolytes, glucose, BUN, Creatinine, ALT, AST, Bilirubin, Alk Phos, LDH, Ca++, Albumin, Phos, Mg, uric acid	x	x		x	x	x	x
*Urinalysis	x						
HIV and Hepatitis B and C serology, Pregnancy Test (serum)*	x						
Lymphocyte enumeration (TBNK) HIV + patients only	x				x	x	x[F]
HIV viral load for HIV + patients only	x				x	x	x[F]
EBV viral load (NIH Clinical Center only)	x			x	x	x	x
CT chest/abd/pelvis	x			x	x[G]	x	x
MRI Brain and/or spine if clinically indicated	x						
PET/CT scan[B]	x			x		If positive after Cycle 2	
Bone marrow biopsy & aspirate, peripheral blood flow cytometry[C]	x			x		x	

Studies[A]	Pre-therapy[A]	Pre-Cycles 1-6[E]	BIW Cycles 1-6[E]	Pre-Cycle 3	Post Cycle 3 (Low Risk)	Post- Cycle 6 and Post-Cycle 8, if applicable (High risk)	Follow Up (see **5.9**)
Lumbar puncture with chemistries, cell count, cytology and flow cytometry	x			x[D]			
10 cc red top for serum storage (NIH Clinical Center only)	x			x	x	x	x
Tumor Biopsy Optional	x						
Adverse Events, Symptoms/Toxicity Assessment	x	x ..... x[H]					x[H]

- **A—**Initial assessment is to be performed within 4 weeks prior to starting treatment, except as marked with * which must be performed within 72 hours of treatment.
- **B—**Clinical PET/CT scans may be performed at other time points throughout this protocol if the investigator deems it medically necessary. If obtaining PET/CT scan will delay initiation of treatment, pre-treatment PET/CT scan may be waived. PET/CT scan will be obtained after cycle 2 in all patients. If PET/CT scan post cycle 2 is positive, a post cycle 6 (and post cycle 8, if applicable) PET/CT scan will be obtained.
- **C—**If flow cytometry or bone marrow positive, repeat test as indicated until negative.
- **D—**High Risk patients only.
- **E—**also applies to Cycle 7 and 8, if applicable.
- **F—**To be performed one year after end of treatment and as clinically indicated.
- **G—**CT scan may be delayed for up to 2 weeks after Low Risk patients complete Cycle 3.
- **H—**Every effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy; this may be completed by phone if the subject is not seen in the clinic.

5.7 Correlative Studies

5.7.1 In Amendment I (version date 03/14/2014), the Burkitt Lymphoma Genome Sequencing Project (BLGSP) protocol was added to this study to allow for contribution of samples from Burkitt Lymphoma patients to the Genomic Databank for Burkitt Lymphoma that was created by the Foundation for Burkitt Lymphoma Research (FFBLR). Details related to the BLGSP protocol are described in APPENDIX F and for the samples to be collected in **APPENDIX D**.

Biopsies may be obtained for cytogenetics, immunophenotype, molecular analyses including Fluorescent In Situ Hybridization for myc and polymerase chain reaction for Immunoglobulin gene rearrangement. Tissue will be frozen for microarray analysis. 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.

Standard techniques will be used for biopsies which may include CT and/or ultrasound guided biopsy. In some cases, such biopsies may be expedited and facilitated with the use of navigation tools such as an automated laser angle selector connected to CT scan, or a standard needle guide connected to a protractor to determine which exact angle the biopsy needle will be inserted. These guiding techniques may occur as maneuvers to facilitate the biopsy, which will take place in the usual conventional fashion, with standard, disposable, conventional spring-loaded biopsy equipment. Accurate spatial tissue acquisition may lead to more reliable, accurate and precise tissue characterization, which in turn should be more reproducible. Please See Section **7.1** for details of sample handling.

5.7.2 Structural and Functional Genomics of Tumor Cells

The present study proposes to perform a comprehensive analysis of somatic alterations to the tumor genome. Included in this analysis will be DNA sequencing of all or part of the tumor, which can be achieved by classical DNA sequencing of individual genes or by utilizing high-throughput DNA sequencing technologies. Recently, in diffuse large B cell lymphoma (DLBCL), a number of recurrent oncogenic abnormalities have been uncovered by DNA sequencing. These abnormalities track with known molecular subtypes of this disease. For example, in the ABC subtype of DLBCL, recurrent mutations in CARD11, CD79B and MYD88 have been described.

The activity of the tumor genome will be assessed by profiling the expression levels of mRNAs and microRNAs in a tumor biopsy sample using microarray and multiplexed PCR methods. The mRNA expression profiling of samples on CALGB 50303 have been used to identify molecular subtypes of DLBCL and to predict therapeutic responses. In addition, new methods have been developed recently to identify new RNA species that are expressed from the genome. For example, digital gene expression is based on the high-throughput resequencing of mRNA, an effort that can uncover previously unannotated genes and new alternatively spliced isoforms of known genes. This effort would be exploratory, aiming to identify new aspects of the biology of aggressive B cell tumors that are related to therapeutic response. In addition, microRNAs have the capacity to identify molecular subtypes of DLBCL and can yield additional functional information because of their ability to regulate the expression of a large repertoire of

5.7.3 Methods

The technology platforms that are able to interrogate genomic structure and function are constantly in flux. Therefore, the exact nature of the methodologies that will be employed will be assessed at the time that the samples are collected and ready for analysis. The following are technologies in use for each task at the time of protocol writing/amendment:

5.7.3.1 DNA/RNA sequencing

Genomic DNA and total RNA will be extracted from tumor samples using a Qiagen All-prep kit. MicroRNAs will be extracted from the samples using a QiagenmiRNeasy Mini Kit.

For investigating individual target genes, classical Sanger sequencing will be performed on PCR amplicons, using primers surrounding the known sites of mutation in DLBCL.

A related technology, RNA-Seq, utilizes RNA from the tumor specimen to create a cDNA library for high-throughput sequencing. RNA-seq will be performed using Illumina kits followed by high-throughput sequencing on an Illumina HighSeq 2000 machine. The cutoffs for coverage and percent mutant calls mentioned above will also be used to identify putative SNVs. RNA sequencing will also be used to read out digital gene expression across the genome as described[60].

MicroRNAs will be profiled using an Illumina kit to construct a library from tumor RNA samples and will be sequenced using the Illumina HighSeq 2000 platform.

5.7.3.2 Molecular Analyses

Molecular analyses using fluorescent In Situ Hybridization and polymerase chain reaction may be performed on tissue samples.

5.7.3.3 Flow Cytometric Analysis

FACS analysis is a standard methodology for studying hematologic malignancy cell phenotype and biology. A variety of standard and new flow cytometric techniques will be applied in attempt to improve understanding of cancer biology, investigate mechanisms of chemotherapy resistance, and identify new potential therapeutic targets.

5.7.4 Certificate of Confidentiality

As part of study efforts to provide confidentiality of subject information, this study will obtain a Certificate of Confidentiality which helps to protect personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.

5.7.5 Management of Results

The analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform participants of the results of testing on the tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding during the course of the study that could be clinically relevant, we will contact the participant if he/she agrees to be contacted. We will ask if he/she would like to meet with a genetic healthcare provider and have an additional tube of blood drawn to verify the findings we have seen in our lab. If the health history, family history, or tumor diagnosis from the Laboratory of Pathology at the NIH Clinical Center suggests that the participant might benefit from genetic testing, we will discuss this with him/her.

Note: incidental findings that may be considered clinically relevant will be discussed at the NCI Lymphoid Malignancies Branch monthly conference and determined as significant or not by the Senior Staff. It is anticipated that this study will be ongoing for at least 10 years; incidental findings will only be reported to the patient while the study is on-going.

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

5.7.6 Genetic counseling

Should any incidental findings be discovered, the NCI CCR Genetics Branch will be asked to provide genetic counseling.

Subjects will be contacted with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at the patient's expense).

5.8 Criteria for Removal from Protocol Therapy and Off-Study Criteria

Every effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy for reporting of toxicities; this may be done by phone if the subject is not seen in the clinic.

5.8.1 Criteria for removal from protocol therapy

- Patient completes therapy as outlined in section **5.3**
- Voluntary withdrawal from treatment
- 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

5.8.2 Off-Study Criteria

- Voluntary withdrawal from the protocol and follow-up
- Death
- Non-compliance which affects safety or endpoints of the study.
- Physician's determination that withdrawal is in the patient's best interest.

5.8.3 Off Protocol Therapy and Off-Study Procedure for NIH Clinical Center Only

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

5.9 Post-Treatment Evaluation

5.9.1 Patients in complete remission (CR), complete remission-unconfirmed (CRu), partial remission (PR) or stable disease (SD) at the end of treatment will proceed to follow up. CT scans will be performed every 4 months for the first two years after the completion of therapy.

- At the two year post-treatment visit, patients with Burkitt lymphoma whose scans are negative will return yearly. At these yearly follow up visits, patients will undergo a physical examination and laboratory testing but will not undergo a CT scan unless this is clinically indicated.
- At the two year post-treatment visit, patients with other than Burkitt lymphoma whose scans are negative will return yearly. At these yearly follow up visits, patients will undergo a physical examination and laboratory testing and a CT scan for up to 5 years post treatment. After the five years post-treatment visit, these patients will continue to have yearly visits; at which time, they will undergo a physical examination and laboratory testing but will not undergo a CT scan unless this is clinically indicated.

  NOTE: Following Amendment N, follow-up will stop at 3 years.

5.9.2 If patients have progressive disease, they will be followed for survival and any further therapy for their lymphoma, which should be documented by regimen name and dates of treatment only. This follow-up may be done via telephone contact with the patient and/or the patient's local physician.

Burkitt lymphoma and very aggressive B-cell lymphomas are characterized by early relapses if they occur and given the concern for radiation exposure, the PI does not believe that is justified to perform routine CTs in this population beyond 2 years. Adverse event data that occurs during the follow-up period that is unrelated to study treatment will not be reported.

6 SUPPORTIVE CARE

6.1 Prophylaxis of Pneumocystis jiroveci (previously known as Pneumocystis carinii)

All patients will receive prophylaxis for Pneumocystis during EPOCH chemotherapy.

- Adult Dosing: trimethoprim/sulfamethoxazole 1 DS P.O. QD for three days each week.
- Patients allergic to either component may receive other standard treatments.

6.2 Prophylaxis for hepatitis B reactivation

Patients who receive chemotherapy and/or rituximab may undergo hepatitis B virus (HBV) reactivation. Patients who are hepatitis B Core Ab+ but hepatitis B s Ag Ab- may have low levels of hepatitis B viremia and should undergo a blood PCR test for hepatitis B viral load. All patients at risk of reactivation will have a PCR analysis of blood for viral loads performed pretreatment and after cycles 2, 4 and 6 of chemotherapy treatment. Additionally, these patients will receive appropriate treatment for hepatitis B reactivation prophylaxis.

Please note: HBV prophylaxis for HIV **positive** patients should not include tenofovir or lamivudine. Other HBV agents must be used in those patients.

6.3 Additional Prophylaxis for HIV positive patients

6.3.1 MAC prophylaxis

Initiate in all patients with CD4 cells ≤ 100/mm3 and for patients whose CD4 cells fall below this level while on study. Recommend azithromycin 1200 mg once weekly, but other agents are acceptable.

6.3.2 Fungal Infections

Oral Candidiasis – if asymptomatic, recommend clotrimazole troches. If symptomatic, recommend oral fluconazole. Fluconazole interacts with many drugs, and can alter EPOCH pharmacokinetics and therefore must be held during chemotherapy infusions.

Esophageal Candidiasis – recommend oral fluconazole, but if no response, consider amphotericin B. Fluconazole interacts with many drugs, and can alter EPOCH pharmacokinetics and therefore must be held during chemotherapy infusions.

6.4 Tumor Lysis Syndrome

All patients with BL will receive allopurinol starting 24 hours prior to the initiation of therapy and continued for the first week of the initial cycle of therapy. Adult dosing: 600 mg x 1 dose followed by 300 mg daily PO. The 600 mg dose may be omitted if the patient is already receiving allopurinol. Additional measures such as hospitalization with aggressive IV hydration will be used at the discretion of the investigator.

6.5 Antiretroviral therapy for HIV infection

It is recommended that antiretroviral therapy be suspended until the completion of systemic chemotherapy treatment for Lymphoma. If antiretroviral therapy is used concurrently, the following conditions should be met:

1. The patient does not have renal or hepatic abnormalities
2. The patient is already on a stable regimen of antiretroviral therapy that does not include ritonavir, zidovudine, or stavudine.
3. For patients who are not already on antiretroviral therapy, they may begin antiretroviral therapy (exclusive of the agents in #2 above) after completion of cycle 2 infusions provided there were no treatment related events in cycle one such as mucositis that would impair oral intake, and there are no hepatic or renal abnormalities.
4. If the patient develops renal or hepatic abnormalities at any time, antiretroviral therapy must be suspended until completion of all therapy for lymphoma.

7 BIOSPECIMEN COLLECTION

7.1 Sample Storage, Tracking and Disposition

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.

7.1.1 Procedures for stored serum specimens

- The Clinical Support Laboratory, Leidos Biomedical Research Inc., processes and cryopreserves samples in support of IRB-approved, NCI clinical trials. All laboratory

personnel with access to patient information annually complete the NIH online course in Protection of Human Subjects. The laboratory is CLIA certified for anti-IL 15 and certain cytokine measurements, 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, 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 (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. At a minimum, the lab needs confirmation that one has been executed or an exception was granted from an office authorized to make such exceptions, e.g. NCI Technical Transfer Center. 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.

7.1.2 Procedures for Collecting, Processing and Storing of Tumor Biopsies

- Orders for tumor biopsies and research blood samples collections should be placed in CRIS (Clinical Research Information System, Clinical Research Center, NIH, Bethesda, MD)
- 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 may be viably frozen, typically at concentrations of 20-100x106/mL in FCS with 10% DMSO using a temperature controlled freezing process to optimize sample viability. Samples will be transferred to Nitrogen tanks for long term storage.
- Tumor 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. Tumor biopsies and processed biologic material (RNA, protein) is stored at -80C in a temperature controlled, alarm secured -80C freezer.
- Tumor tissue may be stored by the NCI 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.

7.1.3 Procedures for shipping Tumor Biopsies from participating sites to NCI

Contact one of the following individuals to obtain shipping packages:

Andrea Nicole Lucas, RN 10 Center Drive Building 10 Room 4N115 Bethesda, MD 20892 240-760-6252 lucasan2@mail.nih.gov	Saleema Osman 10 Center Drive Building 10 Room 4N115 Bethesda, MD 20892 240-858-3184 saleema.osman@nih.gov	Hong Zhao 10 Center Drive Building 10 Room 6N105 Bethesda, MD 20892 240-858-3550 zhaoho@mail.nih.gov

Shipping packages will be sent to each participating institution. To ensure timely arrival of shipping packages, place a request for multiple packages (at least 2 more than is needed) at the time of local IRB review. Packages will consist of the following items:
(1) Fresh (Frozen) Tumor Biopsy Sample Procurement Instructions
(1) Styrofoam Box
(1) Cardboard Box
(1) Biohazard Labeled Ziplock Bag
(10) 2 mL cryopreservation screw cap tube

Each package should be used to mail only one set of samples from a single patient. DO NOT CONSOLIDATE SAMPLES FROM MULTIPLE PATIENTS INTO A SINGLE BOX.

- Remove the collection tubes from the styrofoam container.
- Label all tubes with the CTSU patient ID number, NCI CTEP protocol number, institution, date of acquisition, and tissue source.
- Use the 2 mL cryotubes to collect tumor samples. A minimum of a hundred milligrams (100 mg) of tissue should be provided. This corresponds to a minimum of 4 core needle biopsy specimens (16 gauge needle at least) or an excisional biopsy that is at least 100 cubic mm in volume (i.e., the size of a pea). Fill the Nunc tubes 2/3 full and use as many Nunc tubes as necessary.
- **REMOVE ALL LIQUID FROM SAMPLE BEFORE FREEZING. Immediately preserve by freezing in dry ice or liquid nitrogen and transfer them from the liquid nitrogen or dry ice container, to a -70°/-80° C freezer (preferable), or to a -20°C freezer for storage until time of shipment**.

Fresh (Frozen) Tumor Biopsy Sample Shipment
Note: Must have patient identification number before shipping sample.

- Place all tubes with samples into the styrofoam box filled with at least 2 lbs. of dry ice. Position the tubes so that they are roughly in the center of the container (i.e., surrounded by dry ice).
- Remember: ONE PATIENT SAMPLE SET PER "ZIPLOCK" BAG/BOX.
- Complete the Tumor Biopsy Specimen Submission Form (**APPENDIX D**: Tumor Biopsy Submission Form) and place in the document compartment of the waterproof "Ziplock" plastic bag. Place in the styrofoam box.
- Send a copy of form to Hong Zhao via email: zhaoho@mail.nih.go.
- Tape the styrofoam box. Put the box inside the provided cardboard box. Close with tape.
- Affix a FedEx label. Make a note of the air bill number on the FedEx label.
- Please mail overnight on a Monday through Thursday so shipment will arrive during the week.
- After mailing, send an e-mail to: lucasan2@mail.nih.gov and zhaoho@mail.nih.gov with the subject: "URGENT: NCI Protocol 10C0052_9177 Fresh/Frozen Biopsy Sample Sent" indicating the DAY, TIME, INSTITUTION, CTSU PATIENT ID NUMBER AND AIR BILL NUMBER OF THE PACKAGE in which the sample set was mailed.
- Mail the samples to:

Louis M. Staudt, MD, PhD
Lymphoid Malignancies Branch, CCR, NCI
Building 10/ Room 6N105
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
lstaudt@mail.nih.gov

Questions or problems with sample procurement or shipment should be directed to the following individuals:

Hong Zhao, Phone: 240-858-3550 (Primary Contact)
Louis Staudt, MD, PhD, Phone: 240-781-13394
Mark Roschewski, MD, Phone: 240-760-6183

7.1.4 Protocol Completion/Sample Destruction

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **11.2**.

7.2 Samples for Genetic/ Genomic Analysis

7.2.1 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors, including circulating tumor (ctDNA)/cell-free (cfDNA) DNA. In addition, whole exome sequencing may include evaluation for known lymphoma mutations. For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

7.2.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Section **7.1**). In addition, a Certificate of Confidentiality has been obtained for this study.

8 DATA COLLECTION AND EVALUATION

8.1 Data Collection

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the Lead or Participating Organization roster at the enrolling site. To hold the Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Data will be directly entered into the Medidata Rave database by each site. Data should be entered into the database no later than 2 weeks after the completion of each cycle. Data in section 3 must be entered within 2 weeks of registration.

The CTSU will be responsible for data management and abbreviated CDUS reporting. NCI will be responsible for data analysis.

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 **11.2.1**.

8.1.1 The following is a list of specific data elements that **will** be collected and recorded in the database:

1. All data elements of the International Prognostic Index (IPI) at baseline
2. All transfusions of blood products
3. All infections
4. All hospitalizations, regardless of reason and the reason for hospitalization and the duration of hospitalization
5. As patients will potentially remain on protocol until the time they die, the name(s) of subsequent regimens and date(s) received if patient has progressive disease.
6. PET/CT results will be reported as positive or negative. (PET/CT and CT scan reports will be loaded into the database).
7. All Unexpected Grade 2 adverse events
8. Only the following **expected** Grade 2 adverse events:
    a. Neuropathy-motor
    b. Neuropathy-sensory
    c. Constipation
    d. Ileus
    e. Allergic Reaction
    f. Hemorrhagic Cystitis
    g. Febrile Neutropenia
9. All other adverse events grade 3 or higher
10. **Special Note**: Record only the highest grade of each adverse event **(and the dates corresponding to the highest grade)** during each cycle of treatment.

8.1.2 Refer to Section **12.2.5** for a list of adverse events that do not require expedited reporting.

8.1.3 The following is a list of specific data elements that **will not** be collected or recorded in the database:

- Grade 1 adverse events
- Grade 2 expected adverse events, except as listed above
- Any adverse events which occur during subsequent regimens administered for progressive disease.
- Concomitant medications
- Results of physical exams
- Vital Signs

Complete records must be maintained on each patient including supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will serve as the primary source material that forms the basis for the research record. The primary source documentation will assure the following:

- The patient satisfied each eligibility criterion.
- Signed informed consent was obtained prior to registration and treatment.

- Treatment was given according to protocol or any protocol violations documented and justified.
- Toxicity and response were assessed according to protocol.
- Drug accountability records were kept on each patient.

8.2 Accessing Case Report Forms and Related Documents

8.2.1 All clinical case report forms and supporting documentation associated with this study will be available through Medidata Rave. Instructions for accessing and using Rave are located on the 9177 Web page located on the members' section of the CTSU Web site.

- Go to www.ctsu.org
- Log in to the members' section on the left side of the page
- Click on the Protocols tab in the upper left of your screen
- Click on by Lead Group, then NCILYMB and select trial #9177
- Click on the 9177 Study Specific RDC Instructions link

8.3 Data Submission

8.3.1 The Medidata Rave Clinical Data Management System (CDMS)

8.3.1.1 All participating sites will submit patient data via the Medidata Rave Clinical Data Management System. Rave CDMS allows sites to enter patient data into the 9177 database in Rave over a secure Internet connection. Rave also allows for data correction at the point of entry, and is used to communicate and resolve issues relating to discrepant data. Rave is available to those individuals who have completed their assigned eLearnings and are ready to enter actual patient data into the system.

8.3.1.2 In addition to submitting patient data electronically via Rave, sites may be required to submit clinical reports to CTSU. Reports (if required) will be uploaded into the applicable Rave CRF.

8.3.2 The Clinical Data Update System (CDUS)

8.3.2.1 This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Abbreviated CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

8.3.2.2 Responsibility for Data Submission: Study participants are responsible for submitting CDUS data and/or data forms to the CTSU quarterly at least 2 weeks before CTEP's due date to allow time for CTSU compilation, Principal Investigator review, and timely submission to CTEP (Section **13.2.2**). The CTSU is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

8.3.3 Rave Training

8.3.3.1 Required trainings will be assigned as eLearnings to site staff within Medidata as staff are invited to the study.

8.4 Data Submission Questions

The CTSU help desk is available to answer questions regarding data submission at 1-888-823-5923 or by email at ctsucontact@westat.com. Hours are between 9:00 A.M. and 6:00 P.M. Eastern Time, Monday through Friday (excluding holidays).

8.5 Toxicity Criteria

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

8.6 Response Criteria

This trial will use the IWC criteria when evaluating primary end points. The IWC+PET criteria will be documented and compared with the IWC.

IWC Response criteria for lymphomas: Responses must last for at least 4 weeks off treatment.

For detailed explanations of combined IWC and PET criteria, please refer to J Clin Oncol, 2005. 23(21): p. 4652-61.

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	< 1 cm	< 1 cm	Normal
CRu	Normal	> 1 cm	> 75% decrease	Indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Progression	Enlarging liver/spleen; new sites	New or increased > 50%	New or increased > 50%	Reappearance

IWC (International Workshop Criteria)+PET-Based Response Designations Based on the IWC Designations and PET Findings [22]

IWC+PET-Based Response Designations	Description

CR	CR by IWC with a completely negative PET
	CRu, PR, or SD by IWC with a completely negative PET and a negative BMB if positive prior to therapy
	PD by IWC with a completely negative PET and CT abnormalities (new lesion, increasing size of previous lesion) ≥1.5 cm (≥ 1.0 cm in the lungs) and negative BMB if positive prior to therapy
CRu	CRu by IWC with a completely negative PET but with an indeterminate BMB
PR	CR, CRu, or PR by IWC with a positive PET at the site of a previously involved node/nodal mass
	CR, CRu, PR, or SD by IWC with a positive PET outside the site of a previously involved node/nodal mass
	SD by IWC with a positive PET at the site of a previously involved node/nodal mass that regressed to < 1.5 cm if previously > 1.5 cm, or < 1 cm if previously 1.1-1.5 cm
SD	SD by IWC with a positive PET at the site of a previously involved node/nodal mass (i.e., residual mass)
PD	PD by IWC with a positive PET finding corresponding to the CT abnormality (new lesion, increasing size of previous lesion)
	PD by IWC with a negative PET and a CT abnormality (new lesion, increasing size of previous lesion) of < 1.5 cm (< 1.0 cm in the lungs)

Abbreviations: IWC+PET, International Workshop Criteria plus positron emission tomography; CR, complete response; BMB, bone marrow biopsy; CT, computed tomography; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

8.7 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

9 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to provide DA-EPOCH-R to patients with either high or low risk Burkitt lymphoma and to estimate the event free survival (EFS) in both groups. In addition, a cohort of MYC+ patients with large cell lymphoma will be enrolled and treated in the same fashion, in order to estimate the event free survival in those patients.
Secondary objectives are to perform exploratory analyses as they relate to identifying markers or molecular characteristics of patients and to determine if they may be related to clinical outcomes including response, event free and progression free survival (PFS) and overall survival (OS); to

explore whether PET is able to provide an early prediction of clinical outcome; to perform microarray analyses to see if there are differences between high and low risk patients. Patients with Burkitt lymphoma enrolled prior to amendment F will have their EFS evaluated in a secondary analysis in which their data may be reported separately or combined with that of patients enrolled subsequent to amendment F, if the results are sufficiently similar to do so.

Patients with Burkitt lymphoma have been treated on the previous NCI trial of DA-EPOCH-R as one of several histologies being evaluated. In this trial, at a 35 month median potential follow-up, none of the 25 patients with Burkitt lymphoma enrolled between 2000 and 2008 have experienced a disease progression or have died from any cause. There was one event which was unrelated to disease progression: one patient required radiation at the completion of chemotherapy for localized residual disease. It is the goal of this trial to continue to offer DA-EPOCH-R to additional patients with Burkitt lymphoma in order to determine if the results seen previously can be replicated. The new results will be used to estimate the EFS to the DA_EPOCH-R regimen with reasonable precision.

Data from a published trial of CODOX-M (low risk) or CODOX-M + alternating IVAC) high risk) indicated that the two year EFS was 83.3% for low risk (95% CI: 59.0-99.0%) and 59.5% (43.0-76.0%) for high risk patients (Mead GM, Sydes MR, Walewski et al, Annals of Oncology 13: 1264-1274, 2002). In this trial of DA-EPOCH-R, low risk patients will be treated with 3 cycles of therapy while high risk patients will be treated with 6 cycles of therapy. The goal will be to estimate the EFS for patients treated with DA-EPOCH R at 2 years and to informally describe the results relative to those found with CODOX-M (alone or with IVAC, as appropriate and to report the toxicity profile in this study.

In the cohort with low risk patients, CODOX-M was associated with an 83.3% two year EFS probability with a lower 95% confidence bound of 59.0%. It would be desirable to have reasonable precision to estimate the EFS at two years for low risk patients receiving DA-EPOCH R. In this cohort, 55 evaluable patients will be enrolled and followed for EFS for the primary analysis. If the fraction of patients who have not had an event by 2 years were similar to that of CODOX-M, it would be expected to be approximately 83%. With 55 low-risk patients, the two-sided 95% confidence interval for the expected proportion of 0.83 without an event will extend +/- 0.10. In practice, in addition to determining the number of patients who have not had an event by two years, a Kaplan-Meier curve will also be constructed, with 80% and 95% confidence intervals determined at 1, 2, and 3 years. The results may also be informally compared with those from the published CODOX result in similar patients.

In the cohort with high risk patients, CODOX-M + IVAC was associated with a 59.5% two year EFS probability with a lower 95% confidence bound of 43.0%. It would be desirable to have reasonable precision to estimate the EFS at two years for the high risk patients receiving DA-EPOCH R. In this cohort, 41 evaluable patients will be enrolled and followed for EFS for the primary analysis. If the fraction of patients who have not had an event by 2 years is similar to that of CODOX-M+ IVAC, it would be expected to be approximately 60%. With 41 high-risk patients, the two-sided 95% confidence interval for the expected proportion of 0.60 without an event will extend +/- 0.15. In practice, in addition to determining the number of patients who have not had an event by two years, a Kaplan-Meier curve will also be constructed, with 80% and 95% confidence intervals determined at 1, 2, and 3 years. The results may be informally compared with those from the published CODOX + IVAC result in similar patients.

The following stopping rule will apply for patients with low-risk Burkitt lymphoma (HIV negative patients only) who receive 3 cycles of therapy. A stopping rule will apply to monitor for <90% durable CR (defined as maintaining CR for one year beyond completion of therapy) among those with low risk BL who receive only 3 cycles of therapy. The first 10 patients in this category will be monitored for this outcome over one year. If < 8/10 has a durable CR, then this will be considered insufficient since the upper one sided 90% CI for 7/10 is 88.4%, which would indicate that this regimen is likely to not have results which are consistent with a desirable 90% CR rate. If this stopping rule is invoked, all patients (regardless of risk) will be treated as in the high risk arm.

In addition, a stopping rule will be implemented for patients who enroll with documented CNS disease. If within the first 10 patients enrolled with active CNS disease, there are 4 patients who attain a failure in the CNS, the study will not accrue any more patients with documented CNS disease. A separate cohort of patients with c-MYC positive DLBCL (including plasmablastic subtype) will also be eligible and may be enrolled onto this trial. A total of 30 patients will be enrolled in order to provide an approximate estimate of the EFS for this group of patients being treated in a relatively homogeneous fashion. This will allow the trial to determine a preliminary estimate of the effect of DA-EPOCH-R in Myc+ DLBCL. All of these patients will be treated using 6 cycles of DA-EPOCH-R (as written for high-risk Burkitt lymphoma).

Markers and molecular characteristics of the patients will be obtained and evaluated for their association with EFS, PFS and OS using Kaplan-Meier curves and two-tailed log-rank tests. These evaluations will be done separately for low and high risk patients, and may be evaluated in an overall analysis stratified by risk category as well. Results may also be compared between responders and non-responders using a Wilcoxon rank sum test. In general, all secondary analyses will be performed with exploratory intent, and any findings which result from these analyses will be used to generate hypotheses which can be investigated in later studies.

This trial will be opened to multiple centers through the CTSU mechanism. When most enrolling centers have opened the protocol, it is expected that approximately 27 Burkitt lymphoma and 8 myc+ DLBCL can be accrued per year. Thus, it is expected that the study will require 3.5 years in order to accrue a total of 55 low risk and 41 high risk patients to the trial (total 96), and up to 30 of the patients with c-MYC positive DLBCL and c-MYC positive plasmablastic lymphoma. The patients enrolled on the trial prior to this amendment will be considered a separate cohort for evaluation purposes, as required by an external scientific committee. The results from this earlier cohort may be examined in combination with those patients enrolled after the present amendment if the results are shown to be sufficiently similar. This would be done in an exploratory fashion only, in addition to main analyses restricted to newly enrolled patients.

In order to allow for a very small number of non-evaluable patients, the accrual ceiling will be set at 153 (up to 18 from earlier enrollment + 96 low and high risk Burkitt + 30 with c-MYC positive DLBCL and c-MYC positive plasmablastic lymphoma, and up to 9 extra to allow for inevaluable patients).

In April 2014, an interim analysis that looked at accrual of the MYC + DLBCL and BL arms showed that the accrual ceiling in the MYC + DLBCL arm, which included plasmablastic lymphoma and B-cell lymphoma with features intermediate between BL and DLBCL, had been exceeded – therefore, accrual to this arm was suspended. At the same time, the analysis revealed

that only 35 patients had been accrued to the BL arm which is significantly short of the initial accrual goal for this arm (96 patients).

Effective with Amendment J (version date: 06/24/2014): In order to reach the BL arm initial accrual goal, we elected to amend the study to increase the overall accrual goal to 194 – allowing for the following breakdown:

- 31 patients enrolled prior to Amendment F (The patients enrolled on the trial prior to Amendment F will be considered a separate cohort for evaluation purposes, as required by an external scientific committee (CTEP).
- 96 Burkitt Lymphoma
- 47 DLBCL (initially planned for 30; but 47 enrolled after Amendment F—we need to add slots for them). No more patients will be enrolled in this subgroup.
- 20 inevaluable patients
- Effective with Amendment N, all patients on trial will be followed for PFS for up to 3 years from the date they sign the consent form. Any future analysis will focus on evaluations taking place no more than 3 years after study entry. This will apply both to previously enrolled patients as well as to any patients who enroll after this amendment is in effect.

10 HUMAN SUBJECTS PROTECTIONS

10.1 Rationale for subject selection

BL affects all races and genders. However, males are more likely than females to be affected and this will be reflected in the gender distribution of our cases. The incidence of BL is increased in HIV positive patients. In the US HIV is more prevalent in ethnic minorities and Men who have Sex with Men (MSM). Our experience to date suggests that most of our patients will be HIV negative. Some of our HIV positive patients may come from ethnic minorities and/or be MSM. Strategies/procedures for recruitment: This trial will be available on the cancer.gov website as a dedicated trial for BL. We have excellent relations with medical schools, oncologists and infectious disease doctors who refer us patients for second opinions and clinical trials. Patients or their physicians contact the lead research nurse who arranges for a medical doctor to contact them or to screen them in clinic. Patients who are hospital in-patients with a diagnosis of untreated BL can be directly admitted to our in-patient unit for assessment. Justification for exclusions: Pregnant or nursing mothers are excluded because of the potential teratogenic effects of therapy. These are standard exclusions from clinical trials of chemotherapy. There are case reports of pregnant patients with BL being successfully treated in the second and third trimester with existing chemotherapy regimens who delivered healthy infants. [27] We do not have experience in using EPOCH-R during pregnancy and feel it would expose the fetus to unnecessary and unquantifiable risks. The risks of cytotoxic agents being excreted in breast milk outweigh the benefits of breastfeeding to the infant. Mothers who are willing to stop breastfeeding are eligible for this study. Procedures or practices that will be used in the protocol to minimize the susceptibility of children and vulnerable subjects to undue influences and unnecessary risks: All patients will be informed that different chemotherapy regimens exist to treat their BL and that they are under no obligation to participate in this research. This is particularly relevant to HIV negative patients where excellent outcomes are

achieved with current regimens. All patients will be given the opportunity to decline research biopsies.

Adults who are unable to consent are included in this protocol because the protocol offers a prospect of direct benefit and should therefore exclude participants only when scientifically necessary or participants with this condition are at risk of losing capacity at least temporarily and enrollment might be compromised without their involvement. Capacity to consent will be evaluated by the Principal or Associate Investigator(s). For adults whose ability to consent is uncertain, The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. The PI or AI will obtain permission for decisionally-impaired adults via their appointed surrogate decision-maker or another legally authorized representative (such as legal guardian or holder of the durable power of attorney) in accordance with NIH Policy and Communications Bulletin Number 87-4 (rev.). Procedures described in NIH Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed. The risks and benefits of participation for adults unable to consent should be no different than those described for less vulnerable patients.

In cases where the patient's DPA is unable to be present in person at the Clinical Center, the procedures described in Section **10.5** and **10.5.2** will be followed.

10.2 Participation of Children

Pediatric patients <18 years of age will not be eligible to participate in this protocol.

10.3 Evaluation of benefits and risks/ discomforts

The potential benefit of this protocol for patients is cure of life threatening malignancy with fewer side effects and shorter duration of chemotherapy than existing regimens for all patients enrolled on this protocol. The main danger to participants in this study is drug toxicity. Therefore, this protocol involves greater than minimal risk for adults, but presents the potential for direct benefit to individual subjects. Patients may or may not obtain direct benefit from EPOCH-R or DA-EPOCH. Results from two phase II studies of EPOCH-R show promising initial results and acceptable toxicity. In particular toxicity is less than with commonly used regimens such as CODOX-M/IVAC and response rates and survival is similar or superior especially in HIV positive patients. Adults with HIV BL have very poor outcomes with existing chemotherapy regimens which are either too toxic or non-curative.

10.4 Risks Benefit Analysis

Patients may derive direct benefit from DA-EPOCH-R or DA-EPOCH based on prior research results. The potential toxicity of this combination is reasonable in relation to the potential benefit to this group of patients who have treatable diseases. In HIV positive patients the increased risks of opportunistic infection and reactivation of Hepatitis B are outweighed by the potential for cure. Additionally, the knowledge that will be gained from this trial is potentially important and may be of direct benefit to patients.

10.5 Consent Processes and Documentation

All patients will read and sign the informed consent document prior to enrollment. Members of the protocol team will describe the protocol, alternative therapies, and the risks and benefits of each to the individual signing the consent. In cases where the patient is unable to give informed consent, an appropriate surrogate, such as a DPA, will be identified as per the NIH Clinical Center (CC) Institutional policy. In that case, members of the protocol team will describe the protocol, alternative therapies, and the risks and benefits of each to the patient's DPA for health care and the DPA may give informed consent on behalf of the patient. If possible, verbal assent will be obtained from patients unable to give informed consent. As this is potentially curable therapy, and a DPA is being used because the patient is unable to understand the consequences of their assent or dissent, the Study PI has determined that the designated DPA should be allowed to make the decision for the patient to enroll in this protocol. The investigational nature and research objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts and potential benefits, and alternative therapies will be carefully explained to the patient or their DPA. An informed consent document will be obtained prior to entry onto the study. In cases where the patient's DPA is unable to be present in person at the Clinical Center, obtaining informed consent via technology and/or electronic processes is permissible. In these cases, the informed consent discussion will be carried out over telephone and giving of informed consent may be done by phone, fax or email. The informed consent process will be documented in the patient's medical record and on the informed consent document. This process will be performed by the local Principal Investigator or designee.

10.5.1 Subjects who become unable to give consent (NIH Clinical Center)

Subjects could become decisionally impaired during participation on this study. For this reason and because there is a prospect of direct benefit from research participation (Section Error! Reference source not found.), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.5.2 Telephone Consent and Re-consent (NIH Clinical Center)

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.

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 in the medical record.

In cases of telephone reconsent of subjects unable to give consent (i.e., those who are decisionally impaired upon enrollment or who become decisionally impaired), reconsent may take place with the patient's DPA by phone with verbal assent from the subject, if possible.

11 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

11.1 Definitions (NIH only)

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

11.2 OHSRP Office Of Compliance And Training / IRB Reporting (NIH Only)

11.2.1 Expedited Reporting

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

11.2.2 IRB Requirements for PI Reporting at Continuing Review

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

11.3 NCI Clinical Director (CD) Reporting (NIH Only)

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

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

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

11.4 NIH Required Data And Safety Monitoring Plan

11.4.1 Principal Investigator/Research Team

The Coordinating Center research team will meet on a monthly at least weekly when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the Coordinating Center principal investigator. Events meeting requirements for expedited reporting as described in section **11.2.1** will be submitted within the appropriate timelines.

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

12 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following characteristics of an observed AE (Sections **12.1.1** and **12.2)** will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting.

12.1 Definitions

12.1.1 Adverse Event Characteristics

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

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Document AEs from the first study intervention, though 30 days after the last administration of study drug. AEs and serious adverse events (SAEs) that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **12.2**, Error! Reference source not found., and **12.3**.

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.

Attribution of the AE:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

12.1.2 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.

12.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in or consistent with the risk information described in the package insert or is not listed at the

specificity or severity that has been observed, or is not consistent with the general investigational plan or elsewhere in the current application.

12.1.4 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.

12.1.5 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.

12.1.6 Disability

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

12.1.7 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.

12.1.8 Protocol Deviation (NIH Definition)

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

12.1.9 Protocol 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.

12.1.10Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
- the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
- 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.

12.1.11Procedures 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.

12.2 Expedited Adverse Event Reporting

12.2.1 CTEP-AERS

Expedited AE reporting for this study must use CTEP Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to the NCI Study Coordinator, Andrea Nicole Lucas, RN at 240-760-6252 or lucasan2@mail.nih.gov. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

12.2.2 Distribution of Adverse Events

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

12.2.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires BOTH routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5** "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in **Section 12.2.4**

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

Grade 3 adverse events

Effective Date: May 5, 2011

12.2.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, only events that are both **serious** and **unexpected** as defined in section **12.2.3** should be reported via CTEP-AERS. Institutes should follow their own Institutional guidelines for reporting events to their local IRBs.

12.2.5 Routine Adverse Event Reporting

All Adverse Events (AEs) must be recorded in the database, including AEs reported through CTEP-AERS .

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in

future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

12.2.6 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. In addition, the Pregnancy Information Form included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

12.2.7 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be recorded in the database.

12.2.8 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** recording in the database.

12.3 NCI Guidance for Reporting Expedited Adverse Events for Multi-Center Trials

The site PI must immediately report to the NCI-LYMB PI any serious adverse event as defined above in Section **12.2.3**; using CTEP Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP Web site (http://ctep.cancer.gov).

Report events to the Reviewing IRB as per its policy. Please also notify the coordinating center PI and study coordinator of your submission at the time you make it.

13 MULTI-INSTITUTIONAL GUIDELINES

13.1 IRB Approvals

The NIH IRB must approve the addition of each participating institution to the protocol and will require a copy of the local IRB approval from each participating institution before NIH IRB approval will be granted. The CCR PI will provide the NIH IRB with copies of all consents and IRB approvals from each participating institution. The **Cancer Trials Support Unit** (CTSU) Regulatory Office is responsible for collecting and maintaining IRB approvals and informed consent documents for all participating institutions and will provide digital copies to the NCI for submission to the NIH IRB.

The PI will provide the NIH IRB with a copy of the participating institution's approved yearly continuing review. The CTSU Regulatory Office is responsible for collecting and maintaining yearly continuing review approvals for all participating institutions and will provide digital copies to the NCI for submission to the NIH IRB. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH IRB.

13.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are listed below. The Principal Investigator/Coordinating Center is responsible for distributing all Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

13.2.1 Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

13.2.2 Responsibilities of the Coordinating Center:

Each participating institution will have an appropriate assurance on file with the Office for Human Research Protections (OHRP), HHS. The CTSU is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site. Prior to the activation of the protocol at each participating institution, documentation of initial IRB approval must be submitted to the CTSU Regulatory Office

- The CTSU is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for ensuring each participating site is accruing a representative sample consistent with the estimate of population representation in the site's geographical location for race and ethnic groups as determined by the Census Bureau to assure overall target goals are met.
- The CTSU is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. Participating institutions will report directly to CTEP with a copy to the Coordinating Center. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit; or, (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

14 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.

14.1 Rituximab

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

14.1.1 Supply

Genentech/IDEC will supply the agent for this protocol to DFCI, MGH, BIDMC and MD Anderson Cancer Center. It is otherwise commercially available.

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.

14.1.2 Storage

Rituximab for clinical use should be stored in a secure refrigerator at 2º to 8°C.

14.1.3 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

14.1.4 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.

14.1.5 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/m2 (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/m2 on day 1 of each cycle of EPOCH, immediately prior to starting etoposide + doxorubicin + vincristine administration. For Low Risk Patients receiving EPOCH-RR, Rituximab will also be administered on day 5 of each cycle, following etoposide + doxorubicin + vincristine but prior to cyclophosphamide 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.

14.1.6 Safety Profile

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, asthenia, and hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate.

Fatal Infusion Reactions: Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.

Cardiac Events: Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

Tumor Lysis Syndrome: Tumor lysis syndrome, some with fatal outcome, has been reported and is characterized in patients with a high number of circulating malignant cells (≥25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

Renal Events: Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases has led to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (≥25,000/mm2) or high tumor burden who experience tumor lysis syndrome and in patients administered concomitant cisplatin.

Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis and paraneoplastic pemphigus, have been reported in patients treated with rituximab. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single

occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported.

In addition, there have been a limited number of post-marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia.

Infectious Events: Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1-588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

Hepatitis B Reactivation: Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

Other Serious Viral Infections: The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or post-marketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituxan and have resulted in death.

Progressive multifocal leukoencephalopathy (PML)

PML is a rare disease caused by the reactivation of latent JC virus in the brain. Immunosuppression allows reactivation of the JC virus which causes demyelination and destruction of oligodendrocytes resulting in death or severe disability. Rare cases of PML, some resulting in death, have been reported in patients with hematologic malignancies who have received rituximab. The majority of these patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Cases of PML resulting in death have also been reported following the use of rituximab for the treatment of autoimmune diseases. The reported cases had multiple risk factors for PML, including the underlying disease and long-term immunosuppressive therapy or chemotherapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Physicians should consider PML in any patient presenting with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, rituximab should be discontinued and reductions or discontinuation of any concomitant chemotherapy or immunosuppressive therapy should be considered.

Bowel Obstruction and Perforation: Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving Rituxan in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1−77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain,

especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

Immunogenicity: Patients may develop a human anti-chimeric antibody (HACA) response with rituximab treatment. The clinical significance of this is unclear.

Pregnancy: B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in utero.

Immunization: Response rates may be reduced with non live vaccines.

Additional Safety Signals: The following serious adverse events have been reported to occur in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), eye disorders (uveitis and optic neuritis), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), that may result in fatal outcomes, and fatal cardiac failure.

See the rituximab Investigator Brochure for additional details regarding safety experience with rituximab.

14.2 Cyclophosphamide

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

14.2.1 Supply

Commercially available as a lyophilized powder for reconstitution, in 100 mg, 200 mg, 500 mg, 1gm, and 2 gm vials.

14.2.2 Storage and preparation

Intact vials should be stored at room temperature (not to exceed 30ºC). Reconstituted solution is stable up to 6 days if refrigerated (2-8ºC). Discard solution after storage for 24 hours at room temperature.

14.2.3 Administration

Cyclophosphamide will be diluted in 100 mL of D5W or 0.9% NaCl and infused over 30 minutes or according to institutional standard. Patients will be instructed to drink an adequate amount of fluids and empty their bladders frequently during cyclophosphamide administration.

14.2.4 Toxicities

Myelosuppression, nausea and vomiting, hemorrhagic cystitis, and 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. Please refer to the package insert for a complete listing of all toxicities.

14.2.5 Hydration Guidelines

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

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

14.3 Doxorubicin

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

14.3.1 Supply

Commercially available as a lyophilized powder for reconstitution in 10, 20, 50 and 100 mg vials. Also available as a 2 mg/mL solution for injection in 10, 20, 50, and 200mg vials.

14.3.2 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/m2. The drug causes local necrosis if infiltrated into subcutaneous tissue. Please refer to the package insert for a complete listing of all toxicities.

14.4 Vincristine

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

14.4.1 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 2º-8ºC and should be protected from light.

14.4.2 Toxicities

Peripheral neuropathy, autonomic neuropathy, and alopecia. Local necrosis if injected subcutaneously. Please refer to the package insert for a complete listing of all toxicities.

14.5 Etoposide

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

14.5.1 Supply

Commercially available as a 20 mg/mL solution for injection in 5, 25, and 50 mL vials. Each ml contains, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg of polyethylene glycol 300, and 30.5% alcohol.

14.5.2 Toxicities

Myelosuppression, nausea, vomiting, anaphylactoid reactions, alopecia, and hypotension if infusion is too rapid. Please refer to the package insert for a complete listing of all toxicities.

14.6 Administration of vincristine/doxorubicin/etoposide

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

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.

For NIH Clinical Center Only: Please see **APPENDIX A** for further details.

Each participating site is encouraged to mix the vincristine, doxorubicin and etoposide in one bag. If that is not feasible due to institutional constraints, then a site should prepare the continuous infusion of vincristine, doxorubicin and etoposide according to institutional procedures.

14.7 Prednisone

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

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

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

14.7.2 Toxicities

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

14.8 Filgrastim

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

14.8.1 Supply

Commercially available in single use vials containing 480 mcg/vial (300 mcg/ml, 1.6 mlvial). Should be stored at 2º-8ºC (do not freeze and do not shake) and is stable for at least 1 year at this temperature. Filgrastim will be given by subcutaneous injection; patient or other caregiver will be instructed on proper injection technique.

14.8.2 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. Please refer to the package insert for a complete listing of all toxicities.

14.9 Pegfilgrastim

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

14.9.1 Supply

Commercially available in a prefilled single use syringe containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex).

Should be stored at 2° to 8°C (36° to 46°F) in the carton to protected from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

14.9.2 Toxicities

The most common adverse reactions are bone pain and pain in extremity. Please refer to the package insert for a complete listing of all toxicities.

14.10 Methotrexate

Refer to the FDA approved package insert for complete product information

14.10.1Supply

Commercially available folic acid antagonist, and only the preservative-free preparation may be used for intrathecal injection.

14.10.2Storage

It should be stored at 15-30°C and protected from light. Prior to intrathecal or intraventricular injection, the prescribed dose of methotrexate should be reconstituted/diluted with preservative-free 0.9% sodium chloride to a total volume of 3 to 5 mL. Prepared methotrexate doses should be utilized within 4 hours of preparation.

14.10.3Toxicities

It can cause leukopenia, and as such leucovorin may be administered 24 hours after each dose. It can cause headaches, drowsiness, and blurred vision. It can also cause a transient acute neurologic syndrome manifested by confusion, hemiparesis, seizures, and coma. Please refer to the package insert for a complete listing of all toxicities.

14.11 Cytarabine

Refer to the FDA approved package insert for complete product information

14.11.1Supply

A commercially available pyrimidine nucleoside antimetabolite.

14.11.2Storage

Cytarabine 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 be utilized within 4 hours of preparation. Prior to intrathecal or intraventricular injection, the prescribed dose of cytarabine should be reconstituted/diluted with preservative-free 0.9% sodium chloride to a total volume of 3 to 5 mL.

14.11.3Toxicities

It can cause myelosuppression, fever, dizziness, somnolence, and arachnoiditis. Please refer to the package insert for a complete listing of all toxicities.

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16 APPENDIX A: EPOCH Admixtures: Preparation and Administration NCI CC only

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).

17 APPENDIX B: 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.

18 APPENDIX C: NIH IRB form for participating sites Reporting of Deviations Non-compliance and Unanticipated problems

Participating sites should contact Nicole Lucas, RN at lucasan2@mail.nih.gov or 240-760-6252 and request a WORD version of this form to be completed and returned to NCI.

NIH PROBLEM REPORT FORM

NCI Protocol #: 10-C-0052_9177	**Protocol Title: Phase II Study of Dose-Adjusted Epoch+/- Rituximab in Adults with Untreated Burkitt Lymphoma, C-Myc Positive Diffuse Large B-Cell Lymphoma and Plasmablastic Lymphoma**
	Report version: *(select one)* ____Initial Report ____Revised Report ____Follow-up
Site Principal Investigator:	
Date of problem:	**Location of problem:** *(e.g., patient's home, doctor's office)*
Who identified the problem? *(provide role (not name of person): nurse, investigator, monitor, etc…)*	
Brief Description of Subject *(if applicable)* (*Do NOT include personal identifiers)*	Sex: ___ Male ___ Female Age: ___ Not applicable (more than subject is involved)
Diagnosis under study:	
Name the problem: *(select all that apply)* [ ] Adverse drug reaction [ ] Abnormal lab value [ ] Death [ ] Cardiac Arrest/ code [ ] Anaphylaxis [ ] Sepsis/Infection [ ] Blood product reaction [ ] Unanticipated surgery/procedure [ ] Change in status (e.g. increased level of care required) [ ] Allergy (non-medication) [ ] Fall [ ] Injury/Accident (not fall) [ ] Specimen collection issue [ ] Informed consent issue	

[ ] Ineligible for enrollment
[ ] Breach of PII
[ ] Tests/procedures not performed on schedule
[ ] Other, brief 1-2 word description: _____

Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*):

***Is this problem unexpected?** *(see the definition of unexpected in the protocol))* __YES __NO
Please explain:

***Is this problem related or possibly related to participation in the research?** __YES __NO
Please explain:

***Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized?** __YES __NO **Please explain:**

Is this problem? (*select all that apply*)
[ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious
[ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious
[ ] Non-compliance
**Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*

Is the problem also *(select one)* [ ] AE [ ] Non-AE

Have similar problems occurred on this protocol at your site? __YES __NO
If "Yes", how many? ____ Please describe:

Describe what steps you have already taken as a result of this problem:

In addition to the NIH IRB, this problem is also being reported to: (*select all that apply*)
[ ] Local IRB
[ ] Study Sponsor
[ ] Manufacturer : _____
[ ] Institutional Biosafety Committee
[ ] Data Safety Monitoring Board
[ ] Other: _____
[ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	**DATE:**

19 APPENDIX D: Tumor Biopsy Submission Form

9177 Tumor Biopsy Specimen Submission Form

9177 Patient ID: _____ Date form submitted: ___/__/____

Patient Initials: _____ Participating Group Study No.: _____

Patient Hospital No: _____ Participating Group Patient ID: _____

Institution/Affiliate: _____

TO BE COMPLETED BY SUBMITTING INSTITUTION

Does specimen accompany this form?
(NOTE: Core needle biopsy specimens for each patient should be submitted with this form. If specimens will not be submitted, specify the reason and submit the form as required by protocol.)

No, specify reason: _____

Institution error: ____ Sample lost or destroyed: ____ Other, specify: _____

Yes: Date specimen collected: ____/____/_____

Number of core needle biopsy specimens sent with this form: _____
Sample period: Pre-treatment: Y:____ N: ____

Submitted by: _____ Phone number: _____

Institution/Affiliate: _____ NCI institution code: _____

TO BE COMPLETED BY RECEIVING INSTITUTION

Date Specimen received: _____ Specimen ID number: _____

Specimen condition (Mark one with an X)

_____Usable ____ No specimen received _____ Insufficient amount

_____ Damaged or unusable _____Thawed ____ Clotted

Received by: _____ Phone number: _____

20 APPENDIX E: Roster of NCTN Sites with Study Activation

NOTE: Effective with Amendment M, the Roster of NCTN Sites has been removed from the protocol document. This information will be reported within the NIH IRB application. Participating sites may find this information on the CTSU and ClinicalTrial.gov websites.

21 APPENDIX F: Burkitt Lymphoma Genome Sequencing Project (BLGSP)

FOUNDATION FOR BURKITT LYMPHOMA RESEARCH

BURKITT LYMPHOMA GENOME SEQUENCING PROJECT (BLGSP) 04/17/13

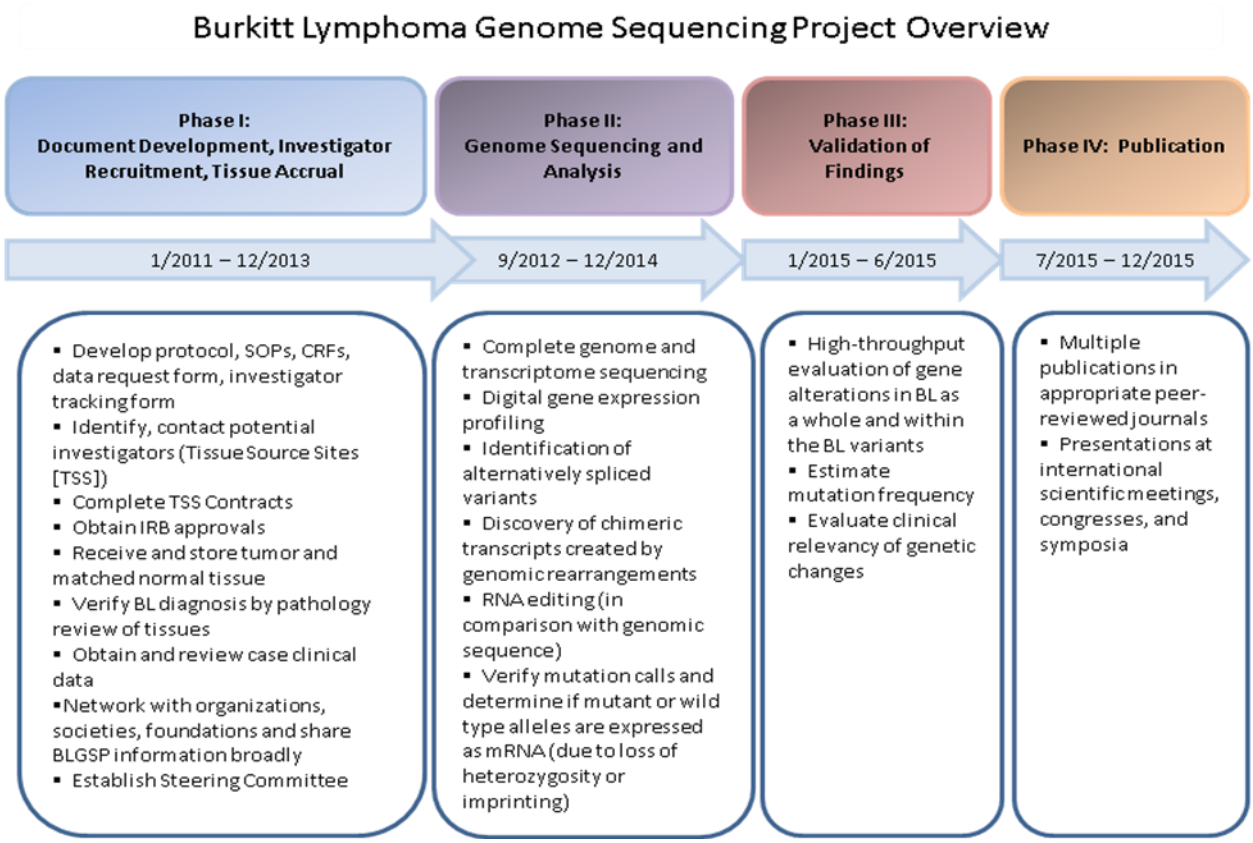
EXECUTIVE SUMMARY

The Foundation for Burkitt Lymphoma Research (FFBLR) has established a collaborative effort with the National Cancer Institute (NCI), in order to develop a genomic databank for Burkitt Lymphoma (BL). The BLGSP will compile genetic changes present in BL tumors, analyze the data to identify diagnostic, prognostic, or therapeutic markers or targets, and publish the results. As with other cancer sequencing projects, the goal is to identify potential genetic changes in patients with BL that could lead to better prevention, detection and treatment of the cancer.

The effort will be coordinated through the Foundation for the National Institutes of Health (FNIH). The NCI, through the Office of Cancer Genomics (OCG), will provide the administrative, physical and analytical infrastructure in order to carry out this project. This will enable the FFBLR to utilize existing Standard Operating Procedures (SOPs) developed by OCG, as well as relationships OCG has established with other organizations, in order to carry out this project. This effort will enhance the scientific integrity and credibility of the BLGSP, and be consistent with the conduct and methodologies used in other NCI sponsored cancer sequencing projects.

The FFBLR will assist in the accrual of the tissues by identifying sites in the US, Europe and Africa, making the initial contacts and providing administrative support. NCI will establish the contracts and protocols for accrual and quality control that are already in place as part of ongoing projects, such as the Cancer Genomic Characterization Initiative (http://cgap.nci.nih.gov/cgci.html). The FFBLR will participate in the scientific leadership of the BLGSP, including having members of its Scientific Advisory Board review the data from the project; provide the biologic context for publication and dissemination within the appropriate scientific communities.

It is anticipated that the project timeline will be 3-4 years; approximately 2 years to identify and collect appropriate tissue and data from approximately 120 qualifying patients with BL (Phase I), about 6-12 months to complete the sequencing and analysis (Phase II), 6 months for validation studies (Phase III), and another 3-6 months to publish the data (Phase IV).



INTRODUCTION

Dr. Jean Paul Martin and Dr. Marie Reine Martin have established a Foundation for Burkitt Lymphoma (BL) Research in Geneva, Switzerland to further the understanding and the treatment of BL. They made this decision because their son Xavier was diagnosed in July 2009 with BL and passed away from a relapse of the disease in May 2010.

Burkitt Lymphoma, first described by Dr. Denis Parsons Burkitt in 1956, is an uncommon type of Non-Hodgkin Lymphoma, often but not exclusively affecting children. It is a highly aggressive type of B-cell lymphoma and often involves body parts other than lymph nodes. The disease is associated with a chromosomal translocation of the *MYC* gene. The tumor consists of sheets of a monotonous (similar in size and morphology) population of medium size lymphoid cells with high proliferative activity and apoptotic activity described as a "starry sky" appearance under low power magnification.

Currently BL is divided into three main clinical variants: 1. Endemic: This BL variant occurs mainly in equatorial Africa, where the disease was first described and is the most common malignancy in children. In 95% of cases, the children are infected with Epstein-Barr virus, which is presumably key to its etiology. The disease involves children much more than adults. The disease characteristically involves the jaw or other facial bone, and may involve the distal ileum, cecum, ovaries, kidney or the breast. 2. Sporadic: This BL variant is found outside of Africa and is usually not associated with Epstein-Barr virus infection, but has morphological and molecular features in common with endemic BL. The jaw is less commonly involved, whereas the ileo-cecal region is the most common site of involvement. 3. Immunodeficiency-associated:

This variant is usually associated with HIV infection and can be associated with the initial manifestations of AIDS, but can also occur in post-transplant patients who are taking immunosuppressive drugs.

Current chemotherapy regimens are effective in approximately 40-90% of patients depending on age, stage of the disease, treatment regimen, and site of the treatment facility. Hence, new treatments are needed to improve the efficacy of current regiments and potentially to substitute less toxic agents for the high intensity chemotherapeutic drugs that are currently given.

With this as a brief background of BL, the vision of the Foundation is to provide monetary support of prioritized, key pre-clinical and clinical research activities that will provide a better understanding of the mechanisms of the disease and lead to more effective treatment algorithms.

The Foundation has a renowned international Advisory Board including Professor Jane Apperley, Professor Riccardo Dalla-Favera, Professor Gerard Evan, Dr. Stephen Friend, Professor John Gribben, Dr. Ariela Noy, and Dr. Louis Staudt. The Executive Director of the Foundation is Dr. John D. Irvin.

The Foundation's first key research project is to establish a comprehensive databank of genomic and clinical data in patients with BL. The purpose of this document is to outline and describe the activities associated with developing the database.

AIM

This project will establish a comprehensive databank of genomic sequence from patients with BL, utilizing tumor DNA and matched normal DNA as well as tumor RNA. Clinical data will also be collected so that associations between clinical parameters and genetic abnormalities can be discovered.

SIGNIFICANCE

Since the discovery in 1983 of *MYC* translocations in BL, little progress has been made in understanding the molecular pathogenesis of the disease. MYC, the defining oncogene for this cancer, is itself insufficient to transform primary cells and actually induces apoptosis unless growth factors are provided or cooperating oncogenes are activated. Loss of p53 function by mutation or by inactivation of $INK4a^{ARF}$ may contribute to cell survival in a fraction of cases. However, there has yet to be a comprehensive effort to discover new genetic aberrations associated with BL using high throughput methods.

There are several major unmet needs in the clinical management of BL that require urgent attention. First, current chemotherapy is ineffective in roughly 20% of cases, and is associated with therapy induced toxicity and death. Because of the toxicity, patients with BL over the age of 70 are ineligible for this potentially curative therapy. Second, young individuals exposed to these intensive regimens face the real possibility of secondary malignancies years later. Finally, children with endemic BL in Africa in general do not receive these curative chemotherapy regimens because of the lack of hospital support for the management of post-treatment infections, and consequently most will die of their disease.

What is needed, therefore, are new approaches to the therapy of BL that are based on an understanding of its molecular pathogenesis and the regulatory pathways that it utilizes for proliferation and survival. Currently, we have no insight into the possible involvement of kinases and signaling pathways that might promote the high rate of proliferation that

characterizes these tumors. Likewise, mechanisms that prevent apoptosis of BL cells, besides p53 inactivation, have yet to be discovered.

Burkitt Lymphoma is derived from the germinal center stage of B cell differentiation, and as such expresses a professional mutator, activation-induced cytosine deaminase (AID). AID is likely involved in generating the breakpoints that lead to MYC translocations in sporadic BL and almost certainly targets many cellular genes for mutation. Hence, BL may utilize AID-generated mutations to modulate oncogene and tumor suppressor pathways. This BL comprehensive genome characterization project will shed considerable light on the oncogenic capacity of AID and identify other potential disease-causing candidates.

An additional fascinating question is whether genetic alterations in the BL genome may influence the symbiotic relationship with the Epstein-Barr virus in the endemic variant in a proportion of the sporadic and immunodeficiency-related cases. EBV viral proteins can mimic Notch signaling (EBNA2), CD40 signaling (LMP1), and B cell receptor signaling (LMP2). It may be necessary for the BLs to acquire mutations in these pathways to shape the cellular response to these virally derived signals.

Many key clinical questions may be illuminated by knowledge of genomic abnormalities in BL. Why do approximately 10-60% of patients treated with potentially curative chemotherapy nonetheless succumb to their disease? How do the genomic alterations in the BL variants (endemic, sporadic, immunodeficiency-related) differ, and how do these differences affect their response to therapy? What new therapeutic options may be available to augment or supplant high-dose chemotherapy?

STUDY POPULATION

The study population should include fresh tissue samples (case-matched tumor and normal) from 60 adult patients with sporadic BL; and tissue from approximately 20 patients of each of the other three variants, pediatric sporadic, endemic and HIV-associated BL. It is anticipated that about double that number of cases will need to be collected as there is about a 50% failure rate at the pathology and molecular processing stages.

STUDY CONDUCT AND STANDARD OPERATING PROCEDURES

In order to enhance the scientific integrity and credibility of the Burkitt Lymphoma Genome Sequencing Project (BLGSP), the project will be carried out utilizing SOPs developed by the OCG at the NCI. The BLGSP-specific SOPs can be found in the OCG Tumor Molecular Characterization Projects Standard Operating Procedures manual (http://cgap.nci.nih.gov/files/OCG_SOP_Manual.pdf) and are consistent with those currently utilized in the NCI-sponsored HIV+ Tumor Molecular Characterization Project (HTMCP).

Using the SOPs, the tissues will be accrued by collaborators (referred to as Tissue Source Sites [TSS]) with access to BL patients. Each TSS will need to obtain an institutional review board (IRB)-approved study protocol that allows for collection of human tumor tissue and matched normal tissue (preferably blood). Upon approval, all TSS will be required to collect and store the tissues, perform site-capable pathology analysis to determine the BL diagnosis, and provide the BLGSP-required clinical data. The above-referenced OCG Tumor Molecular Characterization Projects SOP Manual includes templates of an informed consent and an institutional certification letter, which can be adapted by each TSS for their use. Every patient studied in the BLGSP must be enrolled in a site-specific protocol, and agree to participate by signing an informed consent.

The institutional certification letter states that the IRB understands that the data generated will be made publicly available with the appropriate patient protection procedures (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/about.html).

TISSUE COLLECTION AND PREPARATION

Procedures for tissue collection, preparation, pathology review and shipment in the BLGSP are detailed in the OCG Tumor Molecular Characterization SOP Manual. Adherence to the SOPs is essential to ensure that the quality of the tissues collected meet the technical requirements of the methods of analysis. The protocols include information on tissue collection and preservation by freezing, pathology review, collection of blood samples for molecular characterization, shipping cryoports containing frozen biosamples for processing and extraction of nucleic acids, sample shipping guidelines, sample identifier standards, and disposition form for remaining macromolecules/tissues that are contributed to the project. Templates for suggested language for prospective tissue collection and the data release policy are also included within the SOPs.

TISSUE REQUIREMENTS

Following is a summary of the tissue requirements for the BLGSP. The specific detailed requirements are included in the above referenced SOPs.

- Paired tumor and matched normal (non-involved tissue or blood) of untreated cases must be available in sufficient quantities.
- If blood is the normal tissue, documentation of normal peripheral white blood cell counts and smears must be provided since in rare instances, BL cells can be in the peripheral blood. There are 2 ways of getting normal tissue without tumors: a) Granulocytes can be separated from lymphocytes with Ficoll. b) Also with Ficoll separation, flow cytometry analysis can be performed with CD10, a BL surface marker.
- Pre-treatment blood sample is preferred as the source of normal tissue. However, if a tumor specimen is pre-existing and the patient is alive and can be re-consented following treatment for the collection of a post-treatment blood sample, then that will be acceptable.
- Tissues (both normal and tumor) need to be snap frozen. Currently the project anticipates that ~100 mg of tumor tissue and 10 ml of blood is required, but this may change as the sequencing characterization technology improves.
- A portion of tumor adjacent to the snap frozen sample will be assessed to estimate % tumor cells, with additional immunohistochemical (IHC) stains and FISH to be performed to validate the diagnosis, as needed (see below). Tumors need to have minimum 70-80% tumor nuclei as assessed on the H&E section from the frozen tissue with ~80% viable cells.
- Standard World Health Organization diagnostic criteria for BL must be fulfilled. Specifically, the tumor cells have the “starry-sky” appearance, be positive for CD10 and/or BCL6 by IHC and >90% of the cells need be Ki67 positive. It would be optimal if the presence of MYC to immunoglobulin locus translocation was confirmed by fluorescent in situ hybridization (FISH). At least 12 paraffin-embedded slides, or even better a block, have to be provided, from each case for pathology review by the project pathologists.
- Clinical data (see SOPs) has to be collected at the time of diagnosis, updated after

treatment, and then every year for the next 2 years

If tumor tissue or blood/constitutional tissue is not available, but clinical information and paraffin-embedded slides or block(s) are, we would consider accepting nucleic acids from pathology review-confirmed cases that meet the following criteria:

- At least 10 µg of RNA with RNA Integrity Number (RIN) > 7 as determined on an Agilent Bioanalyzer or similar system
- At least 20 µg each of tumor and normal high molecular weight (>80% of the molecules are >10 kb) DNA

The tissues will be processed in a single biospecimen-processing center using standard protocols developed for and validated in Therapeutically Applicable Research to Generate Effective Treatments (TARGET) and The Cancer Genome Atlas (TCGA). The RNA and DNA will be quality controlled and the match of the tumor and normal DNA confirmed. As part of the processing, the DNA will be whole genome amplified by the method considered the most optimal for genomic characterization at the time when this project will be ready to do so. One of the BLGSP's outcomes will be the availability of the DNA and/or RNA for other projects.

PATHOLOGY REVIEW/VERIFICATION

The review of all tissues by a central pathology review panel of three board-certified hematology pathologists will ensure that the samples that are molecularly characterized are BL, and remove the subjectivity encountered in standard pathology practice. The pathology criteria for BL diagnosis include: 1) characteristic histological appearance; 2) Ki67 immunohistochemical staining in >90% of tumor nuclei; 3) CD10+ and/or BCL6+ by immunohistochemistry; 4) *MYC/Ig* translocation by FISH analysis; BCL2 staining by IHC and those cases which are positive, will by analyzed by *MYC/BCL2* FISH. A SOP for this review and verification has been established and is available in the BLGSP section of the OCG SOP manual.

SEQUENCING, ANALYSIS AND VALIDATION

One of the major objectives of the BLGSP will be to generate genomic-scale DNA and/or RNA sequence from case-matched tumor-normal pairs from patients with BL. For DNA as well as RNA sequencing, normal DNA needs to be sequenced to define which novel sequence variants are germline and which are somatic changes. The plan is to initiate sequencing once a critical number of cases (12-20) have been collected and continue sequencing in batches throughout the term of this project. We anticipate that the cost of whole genome sequence will be decreasing, though the exact cost cannot be estimated. The analysis of the genomic DNA sequence will provide information of single-nucleotide polymorphisms (SNPs) for loss of heterozygosity, somatic mutations, genomic rearrangements and copy number.

We anticipate that sufficient funds will be available for whole transcriptome sequencing (mRNA-seq and miRNA-seq). The analysis of that data results in digital gene expression profile, identification of alternative spliced variants, discovery of fusion transcripts created by genomic rearrangements, RNA editing (in comparison with the genomic sequence), confirmation of mutation calls, and if mutant or wild type alleles are expressed as mRNA (either due to loss of heterozygosity or imprinting).

While the cost and quality of sequencing (2^{nd}, 3^{rd} generation) in two years is impossible to predict (currently the costs are decreasing rapidly and the quality of the sequence is improving as

well), there is every reason to anticipate that it will be the norm to sequence the genome more than the current 30X (50-100X?) and include the transcriptome as well.

The current proposal does not include epigenetic characterization, however whatever materials will be left over could be used in the future to do genome-wide characterization of the methylation profile.

The NCI project team will develop an analytical protocol for the data generated, including:

- Analysis of the copy number alternations with integration with digital gene expression
- Identification of somatic mutations
- Identification of translocations

Taken together, these analyses will look for recurrent lesions within BL as a whole and within the BL variants. Genetic changes will be placed into biological pathways and integrated using available methods. The findings will be validated in a new population cohort via high-throughput evaluation of gene alterations in BL as a whole and within the BL variants. The validation cohort will include up to 200 patients; the proportion of subtype cases will be selected based on the results obtained in the discovery phase (II). Validation studies performed in this new cohort will allow for mutations uncovered in Phase II to be verified as true and increase the power to estimate the frequency with which they occur. Moreover, validation will enable evaluation of the clinical relevancy of the genetic changes found.

GOVERNANCE

The tissue contributors will be co-authors on the first manuscript and may collaborate in the future in others. The project will have a steering committee (SC) whose membership includes members of the FFBLR's scientific advisory board (Dr. Louis Staudt, Professor Riccardo Dalla-Favera, Dr. Stephen Friend, Dr. Ariela Noy, and Dr. John Irvin, Executive Director FFBLR), one representative each from the contractor(s) doing the sequencing and tissue processing, the members of the pathology review board and 1-2 representatives from OCG as needed. During the first 2 years of the project, the SC will meet by teleconference quarterly, and face-to-face annually to assess the progress in tissue accrual and any issues, which may arise in the process to isolation of the molecular analytes. The sequencing will be performed by contractors, which will be put in place by OCG. Once sequencing starts, the SC needs to meet monthly through teleconferencing and face to face every 6 months.

DATA RELEASE POLICY AND PUBLICATION

The data that are generated will be submitted to publicly accessible databases developed for HTMCP and other projects. The NCI database is called the Data Coordinating Center and it allows an easy access to all data generated (TARGET, CGCI and TCGA) as well as analytical tools developed for other large-scale sequencing projects. The BLGSP will be listed on the CGCI web page and the Foundation acknowledged as a collaborator. The procedures developed for the other projects include submission of the sequence generated to publicly accessible databases (currently called sequence-read archive), which are an NCI-defined resource used by all NCI projects. The BLGSP agrees to abide by the data release policy formulated for the HTMCP (**http**://cgap.nci.nih.gov/files/H_TMCP_Data_Release_Policy.pdf). Every effort will be made to rapidly, and not later than in 3-6 months after validation, publish the first manuscript describing the data and including a high-level analysis.

22 APPENDIX G: BLGSP Enrollment Case Report Form

Instructions: *The Clinical Data needed to complete this Enrollment Form should be collected for each patient in the Burkitt Lymphoma Genome Sequencing Project (BLGSP)* prior *to acquisition of tissues. Upon qualification notice from the Office of Cancer Genomics (OCG), the Tissue Source Site (TSS) should complete this Enrollment form for each qualified case within 60 days.*

Questions regarding this form should be directed to the Nationwide Children's Hospital (NCH) or OCG.

Please note the following definitions for the "Unknown" and "Not Evaluated" answer options on this form.

Unknown: This answer option should only be selected if the TSS does not know this information after all efforts to obtain the data have been exhausted. If this answer option is selected for a question that is part of the BLGSP required data set, the TSS must complete a discrepancy note providing a reason why the answer is unknown.

Not Evaluated: This answer option should only be selected by the TSS if it is known that the information being requested cannot be obtained. This could be because the test in question was never performed on the patient or the TSS knows that the information requested was never disclosed.

Tissue Source Site (TSS): _____TSS Identifier: _____ TSS Unique Patient Identifier: _____

Completed By *(Interviewer Name in OpenClinica)*: _____Completed Date: _____

#	Data Element	Entry Alternatives	Working Instructions
General Information			
BLGSP Project ID:			
*1	Is this a prospective tissue collection?	☐ Yes ☐ No	Indicate whether the TSS providing tissue is contracted for prospective tissue collection. If the submitted tissue was collected after the date the BLGSP contract was executed, the tissue has been collected prospectively. 3088492
*2	Is this a retrospective tissue collection?	☐ Yes ☐ No	Indicate whether the TSS providing tissue is contracted for retrospective tissue collection. If the submitted tissue was collected prior to the date the BLGSP contract was executed, the tissue has been collected retrospectively. 3088528
Patient Information			
Demographic Information			
*3	Date of Birth	____ ____ / (month) ____ ____ / (day) __ __ __ __ (year)	Provide the date the patient was born. 2896950 (month), 2896952 (day), 2896954 (year) *Note: The day of Birth is not required.*
*4	Gender	☐ Female ☐ Male	Provide the patient's gender using the provided categories. 2200604
*5	Race *(check all that apply)*	☐ American Indian or Alaska Native ☐ Asian/East Indian ☐ White ☐ Black/African American ☐ Native Hawaiian or other Pacific Islander ☐ Other (please specify) ☐ Unknown	Provide the patient's race using the defined categories. 3009519 American Indian or Alaska Native: A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment. Asian: A person having origins in any of the original peoples of the far East, Southeast Asia, or in the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. White: A person having origins in any of the original peoples of the four Europe, the Middle East, or North Africa. Black or African American: A person having origins in any of any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." Native Hawaiian or other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. Unknown: Could not be determined or unsure
*6	Other Race	_____	If the patient's race was not defined in the

#	Data Element	Entry Alternatives	Working Instructions
	Only complete if "other" is selected in #5.		previous question, provide the patient's race. 2192205
7	Ethnicity	☐ Not Hispanic or Latino ☐ Hispanic or Latino ☐ Not Reported ☐ Unknown	Provide the patient's ethnicity using the defined categories. 2192217 Not Hispanic or Latino: A person not meeting the definition of Hispanic or Latino. Hispanic or Latino: A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. Not Reported: Not provided or available Unknown: Could not be determined or unsure
8	Height *(at time of diagnosis)*	_____(cm)	Provide the patient's height (centimeters) at the time the patient was diagnosed with the tumor submitted for BLGSP. 649
9	Weight *(at time of diagnosis)*	_____(kg)	Provide the patient's weight (kilograms) at the time the patient was diagnosed with the tumor submitted for BLGSP. 651

Survival Information					
*10	Vital Status *(at date of last contact)*	☐ Alive ☐ Dead			The survival state of the person registered on the protocol. 5
*11	Date of Last Contact	____ ____ / (month)	____ ____ / (day)	____ ____ ____ ____ (year)	If the patient is living, provide the date of last contact with the patient (as reported by the patient, medical provider, family member, or caregiver). 2897020 (month), 2897022 (day), 2897024 (year) *Note: The day of Last Contact is not required.*
*12	Date of Last Known Alive	____ ____ / (month)	____ ____ / (day)	____ ____ ____ ____ (year)	Indicate the last date the patient was known to be alive, regardless of whether the patient, medical provider, family member or caregiver was contacted. 2975722 (month), 2975724 (day), 2975726 (year) *Note: The day of Last Known Alive is not required.*
*13	Date of Death	____ ____ / (month)	____ ____ / (day)	____ ____ ____ ____ (year)	If the patient is deceased, provide the month of death. 2897026, (month) 2897028 (day), 2897030 (year) *Note: The day of Death is not required.*
6	Cause of Death Only complete if patient is deceased.	☐ Cancer Related ☐ Non-Cancer Related ☐ Unknown ☐ Other (please specify)			Indicate the patient's cause of death. 2554674
7	Other Cause of	_____			If the patient's cause of death was not included

	Death Only complete if "other" is selected in #6.		in the provided list, specify the patient's cause of death. 2004150
Patient Status (Regarding Submitted Tumor)			
*14	Did the patient receive neo-adjuvant therapy for the tumor submitted for BLGSP?	☐ Yes *(exclusion criterion)* ☐ No	Indicate whether the patient received treatment (radiation, pharmaceutical, or both) prior to the procurement of the sample submitted for BLGSP. 3382737 *If the answer to this question is "yes", the submitted case is excluded.*
*15	Tumor Status *(at time of last contact or death)*	☐ Tumor free ☐ With tumor ☐ Unknown	Indicate whether the patient was tumor/disease free (i.e. free of the malignancy that yielded the sample submitted for the BLGSP study) at the date of last contact or death. 2759550
16	Performance Status: Eastern Cooperative Oncology Group	☐ 0: Fully active, able to carry on all pre-disease performance without restriction. ☐ 1: 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. ☐ 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. ☐ 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. ☐ 4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. ☐ Unknown ☐ Not Evaluated	Provide the Eastern Cooperative Oncology Group (ECOG) performance status of the patient at the time selected in the "timing" question below. 88
17	Performance Status: Karnofsky Score	☐ 100: Normal, no complaints, no evidence of disease ☐ 90: Able to carry on normal activity; minor signs or symptoms of disease ☐ 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 ☐ 60: Requires occasional assistance, but is able to care for most of his/her needs. ☐ 50: Requires considerable assistance and frequent medical care ☐ 40: Disabled, requires special care and assistance ☐ 30: Severely disabled, hospitalization indicated. Death not imminent. ☐ 20: Very sick, hospitalization indicated. Death not imminent. ☐ 10: Moribund, fatal processes progressing rapidly ☐ 0: Dead ☐ Unknown	Provide the Karnofsky score for the patient at the time selected in the "timing" question below. 2003853

		☐ Not Evaluated	
18	Performance Status Score: Timing	☐ Preoperative ☐ Pre-adjuvant Therapy ☐ Adjuvant Therapy ☐ Post-adjuvant Therapy ☐ Unknown	Indicate the timing of the performance status(es) provided in the previous question(s). 2792763
18	Tumor Response	☐ Progressive Disease ☐ Stable Disease ☐ Partial Response ☐ Complete Response	Indicate the patient's measure of success after their primary treatment for the tumor submitted for HTMCP. Treatment includes surgery and adjuvant therapies. 2786727
Treatment			
*19	Indication of Regimen	☐ Initial ☐ Adjuvant ☐ Progression after initial ☐ Recurrence ☐ Palliative ☐ Unknown	Text term to identify the reason for the administration of a treatment regimen. 2793511
*20	Lymphoma Treatment Type	☐ Chemotherapy ☐ Radiation ☐ Radiation and Chemotherapy ☐ Stem Cell Transplant ☐ Surgery ☐ No Treatment ☐ Other Treatment	Text term that describes the kind of treatment that was given for the primary lymphoma. 3284925
*21	If other, specify	_____	Indicate the other treatment type for the lymphoma. 2861111
Chemotherapy			
22	Chemotherapy Start Date	__ __ / __ __ / __ __ __ __	Date chemotherapy started. 2897050 (month), 2897052 (day), 2897054 (year)
23	Did chemotherapy end during this reporting period?	☐ Yes ☐ No	Indicate whether chemotherapy administration ended during this reporting period. 2188260
24	Chemotherapy End Date	__ __ / __ __ / __ __ __ __	Date chemotherapy ended. 2897056 (month), 2897058 (day), 2897060 (year)
*25	Pharmaceutical Regimen	☐ BACOP ☐ C-MOPP ☐ CAP-BOP ☐ CHOP + Bleomycin ☐ CHOP + Etoposide ☐ CHOP-14 ☐ CHOP-14 + Rituximab ☐ CHOP-21 ☐ CHOP-21 + Rituximab ☐ CNOP ☐ CODOX + Rituximab ☐ CVP ☐ DA-EPOCH ☐ DA-EPOCH + Rituxumab	Text term or code to represent the name of a pharmaceutical regimen containing two or more agents which are given together or separately to treat a patient with malignant lymphoma. 3366758

		☐ F-MACHOP ☐ High Dose Methotrexate w/Leucovorin ☐ HyperCVAD-Mtx/AraC + Rituximab ☐ ICE ☐ ICE + Rituxumab ☐ LNH-84 ☐ LNH-87 ☐ M-BACOP ☐ MACOP-B ☐ ProMace-CytaBOM ☐ ProMace-MOPP ☐ VACOP-B ☐ Vanderbilt regimen + Rituximab ☐ Single Agent Therapy (please specify) ☐ Other Pharmaceutical Regimen (please specify) ☐ Unknown	

26	If Other Pharmaceutical Regimen, specify	_____	Text term or abbreviation to represent another name of a pharmaceutical regimen containing two or more agents which are given together or separately to treat a patient with malignant lymphoma that was not already mentioned or specified. 3366930
27	If Single-Agent Therapy, specify	_____	Text name for agent used without other agents in a treatment regimen or study. 3590022
28	Number of Cycles	_____	The total number of cycles administered to the patient of a protocol specified drug or therapy agent as of the current report. 62590
Radiation Therapy			
29	Radiation Therapy Start Date	__ __ / __ __ / __ __ __ __	Date radiation therapy started. 2897100 (month), 2897102 (day), 2897104 (year)
30	Did radiation therapy end during this reporting period?	☐ Yes ☐ No	Indicate whether radiation therapy ended during this reporting period.
31	Radiation Therapy End Date	__ __ / __ __ / __ __ __ __	Date radiation therapy ended. 2897106 (month), 2897108 (day), 2897110 (year)
32	Total Dose of Radiation Therapy	_____ **(Gy)**	A numeric value for the total dose volume of radiation therapy given to a patient, in Gray. 36
33	Radiation Field, extranodal	☐ Abdomen, total ☐ Arm ☐ Body, total ☐ Bone, non-spine ☐ Brain, focal ☐ Brain, whole ☐ Breast ☐ Chest wall ☐ Eye ☐ Gastrointestinal, colon ☐ Gastrointestinal, gallbladder ☐ Gastrointestinal, intestine ☐ Gastrointestinal, Liver ☐ Gastrointestinal, NOS ☐ Gastrointestinal, Pancreas ☐ Gastrointestinal, Stomach ☐ Genitourinary, Bladder ☐ Genitourinary, Kidney ☐ Genitourinary, NOS ☐ Head, Face, or Neck ☐ Leg ☐ Lung ☐ Lymph node, distant (specify site) ☐ Lymph node, locoregional (specify site) ☐ Lymph Nodes ☐ Mantle ☐ Mediastinum ☐ Parametrium ☐ Pelvis ☐ Shoulder ☐ Skin, lower extremity, local ☐ Skin, total ☐ Skin, trunk, local ☐ Skin, upper extremity, local ☐ Spine ☐	Text term to identify anatomically-specified areas or fields that are targeted for radiation therapy. 2416537

		Supraclavicular ☐ Thorax ☐ Trunk ☐ Other ☐ Unknown	
34	Nodal Regions Targeted	☐ Axillary ☐ Cervical ☐ Epitrochlear ☐ Femoral ☐ Hilar ☐ Iliac-common ☐ Iliac-external ☐ Inguinal ☐ Mediastinal ☐ Mesenteric ☐ Occipital ☐ Paraaortic ☐ Parotid ☐ Popliteal ☐ Retroperitoneal ☐ Splenic ☐ Submandibular ☐ Supraclavicular	Identify lymph node sites targeted for radiation therapy. 3762198
35	Other, specify	_____	Specify other field of radiation 62999
Stem Cell Transplantation			
36	Type of Stem Cell Transplantation	☐ Autologous ☐ Syngeneic/Allogeneic related donor ☐ Allogeneic, unrelated donor	Indicate the hematopoietic stem cell source type. 2957417
37	Date of Stem Cell Transplantation	__ __ / __ __ / __ __ __ __	Indicate the date of the hematopoietic stem cell transplant. 3718671
Surgery			
38	Date of cancer debulking surgery	__ __ / __ __ / __ __ __ __	Indicate the date related to the procedure of surgically removing as much of the tumor as possible being executed. 2839523
39	Measure of Success of Outcome at the Completion of Initial First Course Treatment	☐ Progressive Disease ☐ Persistent Disease ☐ Stable Disease ☐ Partial Remission/ Response ☐ Complete Remission/Response ☐ Unknown ☐ Not Applicable (treatment ongoing)	Indicate the patient's measure of success after the initial first course of treatment. 2786727
Patient History of Disease			
HIV Status			
*40	HIV antibody status	☐ Positive ☐ Negative ☐ Unknown	Indicate whether the patient is HIV positive. 2180464
41	Date of HIV	_____ _____ _____ _____ / ___	Provide the month the patient was diagnosed

	Diagnosis (if known)	/ (day) ____ (month) ____ ____ (year)	with HIV. 3579640 (month), 3579644 (day), 3579643 (year) *Note: The day of HIV Diagnosis is not required.*
42	Nadir CD4 Counts *(at time of last contact)*	_____ (cells/mm^3)	Provide the patient's Nadir CD4 counts, which are the lowest CD4 counts the patient has had. 2684395
43	CD4 Counts at Diagnosis of the Submitted Malignancy	_____ (cells/mm^3)	Provide the patient's CD4 Counts at the time the patient was diagnosed with the malignancy submitted for the BLGSP study. 2922654
44	HIV RNA load at Diagnosis of Submitted Malignancy	_____ (counts/mL)	Provide the HIV RNA load (also known as the "viral load") at the time the patient was diagnosed with the malignancy submitted for the BLGSP study. 2922674
45	Prior AIDS Defining Conditions	☐ Candidiasis of bronchi, trachea or lungs ☐ Candidiasis, esophageal ☐ CMV other than liver, spleen or nodes, onset at age >1month ☐ CMV retinitis ☐ Coccidioidomycosis, disseminated or extrapulmonary ☐ Cryptococcosis, extrapulmonary ☐ Cryptosporidiosis, chronic intestinal ☐ Encephalopathy, HIV-related ☐ Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis or esophagitis (onset at age > 1 month) ☐ Histoplasmosis, disseminated or extrapulmonary ☐ Isosporiasis, chronic intestinal (> 1 mon) ☐ Mycobacterium avium complex or Mycobacterium kansasii disseminated or extrapulmonary ☐ Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary ☐ Mycobacterium, other species or unidentified species, disseminated or extrapulmonary ☐ Nocardiosis ☐ Pneumocystis jirovecii pneumonia ☐ Pneumonia, recurrent ☐ Progressive multifocal leukoencephalopathy ☐ Salmonella septicemia, recurrent ☐ Toxoplasmosis of the brain, onset at age >1month ☐ Wasting syndrome, due to HIV	Prior to the malignancy submitted for the BLGSP study, provide any AIDS defining conditions. 2679581

v46	Co-Infections	**Test** **Positive**	**Negative**	**Inconclusive**	**Not Tested**	Using the list provided,

						indicate whether the patient had any co-infections by providing the results of each of the tests listed.
		HBV ☐	☐	☐	☐	2180456
		HCV ☐	☐	☐	☐	2695021
		HPV ☐	☐	☐	☐	2230033
		KSHV/HHV8 ☐	☐	☐	☐	3335773
47	HAART Treatment Prior to Diagnosis of Submitted Malignancy	☐ Yes ☐ No ☐ Unknown				Indicate whether the patient received Highly Active Antiretroviral Therapy (HAART) treatment prior to the diagnosis of the malignancy submitted for the BLGSP study. 3335156
48	HAART Treatment at Time of Diagnosis of Submitted Malignancy	☐ Yes ☐ No ☐ Unknown				Indicate whether the patient received Highly Active Antiretroviral Therapy (HAART) treatment at the time of the diagnosis of the malignancy submitted for the BLGSP study. 2922679
49	CDC HIV Risk Group(s)	☐ Homosexual or bisexual contact ☐ Heterosexual contact ☐ IV drug user ☐ Transfusion recipient ☐ Hemophiliac ☐ Unknown				Indicate whether the patient has a history of any of the listed HIV Risk Groups as defined by the Center for Disease Control (CDC). 2542215
Prior Malignancies						
*50	History of other malignancy	☐ Yes *(exclusion criterion)* ☐ No				Indicate whether the patient has a history of malignancies, including synchronous or bilateral malignancies. 3382736 *If the answer to this question is "yes", the submitted case is excluded. This exclusion does not apply if the patient only has a history of non-melanoma skin cancer OR cervical in situ carcinoma.*
Prior Immunological Disease						
51	Patient History of Prior Immunological Disease	☐ Rheumatoid Arthritis ☐ Sjogren's Syndrome ☐ Systemic Lupus Erythematous ☐ Crohn's Disease ☐ Ulcerative Colitis ☐ Hasimoto's Thyroiditis ☐ Other ☐ Unknown				Indicate whether the patient has a history of any of the listed immunological diseases. 3233628
52	Other Specified Patient History of Immunological Disease Only complete if	_____				Indicate whether the patient has a history of any of the listed immunological diseases. 3233629

	"other" is selected in #5.		
53	Patient History of Prior Immunosuppressive Therapy for Immunological Disease	☐ Methotrexate ☐ Cyclophosphamide ☐ Azathioprine ☐ Anti-TNF therapy ☐ None ☐ Other ☐ Unknown	If the patient received immunosuppressive therapy for the immunological disease selected in the previous question, provide the type of immunosuppressive therapy given. 3233638
54	Other Prior Immunosuppressive Therapy Administered Specify Text Only complete if "other" is selected in #5.	_____	What was the other immunosuppressive therapy administered? 2873928
Prior Infectious Disease			
55	Patient History of Relevant Prior Infectious Disease	☐ Hepatitis B ☐ Hepatitis C ☐ H. Pylori ☐ Malaria ☐ Other ☐ Unknown	Indicate whether the patient has a history of any of the listed infectious disease. 3233642
56	Patient History of Other Relevant Infectious Disease Only complete if "other" is selected in #5.	_____	If the patient has a history of relevant prior disease that was not included in the list, provide the infectious disease. 3233643
Pathologic Information			
*57	Histological Subtype	☐ Burkitt Lymphoma (BL), classic morphology ☐ Burkitt Lymphoma (BL), atypical morphology ☐ Other, specify ☐ Unknown	Using the patient's final diagnostic pathology report, provide the most detailed histological subtype available. 3081934
58	Other Neoplasm Histologic Type, Specify Only complete if "other" is selected in #5.	_____	Free text field to specify the structural pattern of cancer cells used to define a microscopic diagnosis that is not already specified or mentioned. 3294805
*59	Percent Follicular Component	☐ <=10% ☐ > 10% (exclusionary) ☐ Unknown	Using the pathology report, indicate the percentage of the follicular component within the Burkitt lymphoma sample that was removed from the patient. 3770422

*60	Site(s) of Nodal Involvement at Diagnosis *(Please check all that apply)*	☐ Axillary ☐ Cervical ☐ Epitrochlear ☐ Femoral ☐ Hilar ☐ Iliac ☐ Iliac-common ☐ Iliac-external ☐ Mediastinal ☐ Mesenteric	☐ Occipital ☐ Paraaortic ☐ Parotid ☐ Popliteal ☐ Retroperitoneal ☐ Splenic ☐ Supraclavicular ☐ Submandibular ☐ No known nodal involvement	Using the patient's medical record check all applicable boxes to identify the lymph node chain(s) that were involved by Burkitt lymphoma at the time of initial diagnosis. 2180591 *To select multiple sites of involvement, press the control button and select the sites of involvement. Your selections should be highlighted after you've selected.*
*61	Site(s) of Extranodal Involvement At Diagnosis *(Please check all that apply)*	☐ Adrenal Gland ☐ Bone ☐ Bone Marrow ☐ Breast ☐ Peripheral Blood ☐ Skin ☐ Soft Tissue *(muscle, ligaments, subcutaneous)* **ENT & Eye** ☐ Eye ☐ Larynx ☐ Mandible ☐ Maxilla ☐ Nasal Soft Tissue ☐ Nasopharynx ☐ Ocular orbits ☐ Oropharynx ☐ Parotid Gland ☐ Peri-orbital Soft Tissue ☐ Salivary Gland ☐ Sinus(es) ☐ Thyroid gland **Central Nervous System** ☐ Brain ☐ Epidural space ☐ Leptomeninges	**Gastrointestinal/ Abdominal** ☐ Ascites ☐ Appendix ☐ Colon ☐ Esophagus ☐ Gallbladder ☐ Liver ☐ Pancreas ☐ Rectum ☐ Small Intestine ☐ Stomach **Genito-urinary Tract** ☐ Bladder ☐ Epididymis ☐ Kidney ☐ Ovary ☐ Prostate ☐ Testicle ☐ Uterus **Mediastinal/ Intra-thoracic** ☐ Heart ☐ Lung ☐ Mediastinal Soft Tissue ☐ Pericardium ☐ Pleura ☐ Not applicable ☐ Other, please specify	Using the patient's medical record check all applicable boxes to identify the anatomic location of all site(s) of extranodal involvement by Burkitt lymphoma at the time of initial diagnosis. 2735776 *To select multiple sites of involvement, press the control button and select the sites of involvement. Your selections should be highlighted after you've selected.*
62	Other Specified Site of Extranodal Involvement at Diagnosis *(For Primary Clinical Involvement)*	_____		If all extranodal sites of involvement are not included in the list provided, please indicate any sites of extranodal involvement. 3234303

63	Number of Extranodal Sites of Involvement Above *(to calculate the IPI)*	_____		Provide the total number of extranodal sites with lymphoma involvement. Use the previous three questions to determine this number. This information, along with other data provided, will be used by the Analysis Working Group (AWG) to calculate the International Prognostic Index (IPI). 3233242
64	Maximum Tumor Bulk *(Dimension)*	_____ (cm)		After review of the entire medical record, record the length of the largest dimension/ diameter of a tumor, regardless of anatomical plane. 64215
*65	Anatomic Site of Maximum Tumor Bulk *(Select one anatomic site from listing above)*	☐ Adrenal ☐ Bone ☐ Bone Marrow ☐ Brest ☐ Peripheral Blood ☐ Skin ☐ Soft Tissue *(muscle, ligaments, subcutaneous)* **Genito-urinary Tract** ☐ Epididymis ☐ Kidney ☐ Ovary ☐ Prostate ☐ Testes ☐ Uterus **ENT & Eye** ☐ Intraocular ☐ Larynx ☐ Nasal Soft Tissue ☐ Nasopharynx ☐ Oropharynx ☐ Parotid Gland ☐ Peri-orbital Soft Tissue ☐ Salivary Gland ☐ Sinus ☐ Thyroid **Mediastinal/ Intra-thoracic** ☐ Heart ☐ Lung ☐ Mediastinal Soft Tissue ☐ Pericardium ☐ Pleura ☐ Other, please specify ☐ No Known Extranodal Involvement	**Gastrointestinal/ Abdominal** ☐ Ascites/ Peritoneum ☐ Appendix ☐ Colon ☐ Esophagus ☐ Liver ☐ Pancreas ☐ Rectum ☐ Small Intestine ☐ Stomach **Central Nervous System** ☐ Brain ☐ Epidural ☐ Lepomeninges **Lymph Nodes** ☐ Axillary ☐ Cervical ☐ Epitrochlear ☐ Femoral ☐ Ililac ☐ Iliac-common ☐ Iliac-external ☐ Mediastinal ☐ Mesenteric ☐ Occipital ☐ Paraaortic ☐ Parotid ☐ Popliteal ☐ Retroperitoneal ☐ Splenic ☐ Supraclavicular ☐ Submandibular	Using the list of sites in numbers 39 and 40, provide the anatomic site of the maximum tumor bulk. 3233300

			☐ No Known Nodal Involvement	
Pathologic Diagnosis and Surgical Resection				
*66	Date of Initial Pathologic Diagnosis	____ ____ / (month)	____ ____ / (day)	___ ___ ___ ___ (year)	Provide the date the patient was initially diagnosed with the malignancy submitted for BLGSP. This may or may not be the date of the surgical resection that yielded the tumor sample submitted for BLGSP. 2896956 (month), 2896958 (day), 2896960 (year) *Note: The day of Initial Pathologic Diagnosis is not required.*
67	Initial Pathologic Diagnosis Acquisition Method	☐ Incisional Biopsy ☐ Excisional Biopsy ☐ Core Biopsy ☐ Blood Draw ☐ Bone Marrow Aspirate ☐ Other (please specify) ☐ Unknown			Provide the method of the initial pathologic diagnosis. This is the method used on the date provided above. 2757941
68	Other Method of Initial Pathologic Diagnosis	_____			If the method of initial pathologic diagnosis is not included in the list above, provide the method used. 2757948
69	Date of Tumor Collection	____ ____ / (month)	____ ____ / (day)	___ ___ ___ ___ (year)	Provide the date of the surgical resection that yielded the tumor sample submitted for BLGSP. 3008197 (month), 3008195 (day), 3008199 (year)
Staging and Histology of Bone Marrow					
*70	Tumor Stage	☐ Stage IA ☐ Stage IB ☐ Stage IE ☐ Stage IIA ☐ Stage IIB ☐ Stage IIE		☐ Stage IIIA ☐ Stage IIIB ☐ Stage IIIE ☐ Stage IVA ☐ Stage IVB ☐ Stage IVE	Using the Ann Arbor criteria, provide the stage that was used to treat the patient. 2902417 **A**: Absence of the Ann Arbor staging system symptoms including fevers, night sweats, and weight loss. **B**: Presence of the Ann Arbor staging system symptoms including fevers, night sweats, and weight loss. **E**: Presence of lymphoma in extranodal sites.
71	Presence of Malignant Cells in Bone Marrow by Histology	☐ Yes ☐ No ☐ Unknown			Indicate if malignant cells are histologically confirmed in the patient's bone marrow. 2180550
72	Histology of Bone Marrow Samples	☐ Concordant Histology ☐ Discordant Histology ☐ Unknown			If malignant cells are present in the bone marrow at the time of initial staging workup, determine if the histologic diagnosis of the bone marrow is concordant with the diagnosis

			of BL. 3233401
Tests Performed			
LDH Level (at the time of staging)			
*73	LDH Level	_____(IU)	Record the result of the LDH lab test performed during the staging workup. 2798766
*74	LDH Level Upper Limit for Normal at Facility	_____(IU)	Record the upper limit of the normal range of the LDH lab test performed at the reporting facility. 2953115
Genetic Testing			
75	Immunophenotyping	(+) (-) Indeterminate Ki-67 > 90% ☐ ☐ ☐ CD10 > 30% ☐ ☐ ☐ BCL2 ☐ ☐ ☐ CD20 ☐ ☐ ☐ BCL6 > 30% ☐ ☐ ☐ CD3 ☐ ☐ ☐	Indicate all tests performed for immunophenotypic analysis in order to classify clonal subgroups. 3234614, 3234626
76	Other Immunophenotyping (please specify)		Indicate all tests performed for immunophenotypic analysis in order to classify clonal subgroups. 3234626, 2516429
77	B-cell Immunophenotype Methodology	☐ Immunohistochemistry ☐ Flow Cytometry, not otherwise specified ☐ Immunofluorescence ☐ Other	If B-cell genotype was performed, indicate the testing method used. 64540
Genetic Abnormalities			
78	Genetic Abnormalities	N T G A L O C-MYC ☐ ☐ ☐ ☐ ☐ ☐ BCL2 ☐ ☐ ☐ ☐ ☐ ☐ BCL6 ☐ ☐ ☐ ☐ ☐ ☐	Indicate all genetic abnormalities for which the patient was tested. 3234675, 3234680 N = Normal T = Translocation G = Gain L = Loss A = Amplification O = Other
79	Other Genetic Abnormalities *(please specify)*	N T G A L O _____ ☐ ☐ ☐ ☐ ☐ ☐ _____ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ _____ ☐ ☐ ☐ ☐ ☐ ☐	Specify any other genetic abnormalities not in the provided list for which the patient was tested. 3234685, 3234680
80	Methodology Used to Identify Genetic Abnormalities	1 2 3 4 C-MYC ☐ ☐ ☐ ☐ BCL2 ☐ ☐ ☐ ☐ BCL6 ☐ ☐ ☐ ☐	If the patient was tested for a specific genetic abnormality, indicate the testing method used to perform each analysis. 3234684

							Methodology Code: 1 = PCR 2 = Southern Blot 3 = FISH 4 = Cytogenetic
81	Methodology Used to Identify Other Genetic Abnormalities				If the patient was tested for a specific genetic abnormality, indicate the testing method used to perform each analysis. 3234684 Methodology Code: 1 = PCR 2 = Southern Blot 3 = FISH 4 = Cytogenetic		
82	EBV Status of Malignant Cells	☐ Positive ☐ Negative ☐ Unknown			Provide the result of the lab test to detect the presence of Epstein/Barr Virus antibody in the patient. 2003961		
83	If EBV status is positive, provide the percent positive. (does not include background positives)	_____**(%)**			If the patient's EBV status was positive, provide the percentage of EBV positive malignant cells. Do not include the number of background positives. 3233649		
84	Methodology Used to Determine EBV Status of Malignant Cells	☐ EBER in situ Hybridization ☐ LMP Immunohistochemistry ☐ EBV PCR ☐ Unknown			If the patient's EBV status was positive, provide the testing method used to determine the EBV status of the malignant cells. 3233656		

New Tumor Event Information *Complete this section if the patient had a new tumor event. If the patient did not have a new tumor event (or if the TSS does not know) indicate this in the question below, and the remainder of this section can be skipped.*

Note: The New Tumor Event section on OpenClinica can be completed multiple times, if the patient had multiple New Tumor Events.

First Recurrence or Progression

85*	Has the patient developed a first relapse or progression that has not been previously reported?	☐ Yes ☐ No ☐ Unknown		Indicate whether the patient has been diagnosed with a first recurrence or progression. 2002502
86	Date of First Recurrence or Progression	__ __ / __ __ / __ __ __ __		Provide the date documenting the initial identification of reappearance or advancement in extent or severity of cancer. 62998
87	Type of New Tumor Event	☐ Locoregional Recurrence ☐ Locoregional Disease ☐ Distant Metastasis ☐ Recurrence ☐ New Primary Tumor		Indicate whether the patient's new tumor event was a locoregional recurrence, a distant metastasis, or a new primary tumor. 3119721
88	Site of First Malignant Lymphoma	☐ Adrenal ☐ Appendix ☐ Ascites/ Peritoneum	☐ Nasal Soft Tissue ☐ Nasopharynx	Description of the anatomic location of progression of disease for malignant lymphoma.

	Progression	☐ Axillary lymph nodes ☐ Bone ☐ Bone Marrow ☐ Brain ☐ Breast ☐ Cervical lymph nodes ☐ Colon ☐ Conjunctiva ☐ Epididymis ☐ Epidural ☐ Epitrochlear lymph nodes ☐ Esophagus ☐ Femoral lymph nodes ☐ Gastrointestinal/ Abdominal ☐ Heart ☐ Hilar lymph nodes ☐ Iliac-common lymph nodes ☐ Iliac-external lymph nodes ☐ Inguinal lymph nodes ☐ Intraocular ☐ Kidney ☐ Large intestine ☐ Larynx ☐ Leptomeninges ☐ Liver ☐ Lung ☐ Mandible ☐ Maxilla ☐ Mediastinal/ Intrathoracic ☐ Mediastinal lymph nodes ☐ Mediastinal soft tissue ☐ Mesenteric lymph nodes	☐ Occipital lymph nodes ☐ Orbit ☐ Oropharynx ☐ Ovary ☐ Pancreas ☐ Paraaortic lymph nodes ☐ Parotid Gland ☐ Parotid lymph nodes ☐ Peri-orbital Soft Tissue ☐ Pericardium ☐ Peripheral Blood ☐ Pleura/ Pleural Effusion ☐ Popliteal lymph nodes ☐ Prostate ☐ Rectum ☐ Retroperitoneal lymph nodes ☐ Salivary Gland ☐ Sinus ☐ Skin ☐ Small Intestine ☐ Soft Tissue *(muscle, ligaments, subcutaneous)* ☐ Splenic lymph nodes ☐ Stomach ☐ Submandibular lymph nodes ☐ Supraclavicular lymph nodes ☐ Testes ☐ Thyroid ☐ Uterus ☐ No known extranodal	3282650

			involvement ☐ Other Extranodal Site	
89	Other Specified Extranodal Site of First Malignant Lymphoma Progression	_____		If the patient had a new tumor event and the site of this tumor was not included in the provided list, describe the site. 3282651
90	Was Site of First Progression Biopsied?	☐ Yes ☐ No ☐ Unknown		If the patient has had progression of disease, indicate whether the site of first progression was biopsied. 2716366
*91	If biopsied, what was the Histological Subtype?	☐ Burkitt lymphoma, classic morphology ☐ Burkitt lymphoma, atypical morphology ☐ Other Histological Type, specify ☐ Unknown		Using the patient's final diagnostic pathology report, provide the most detailed histological subtype available. 3282652
92	Other Specified Histologic Type	_____		Specify the structural pattern of malignant lymphoma cells at the time of biopsy for first progression of malignant lymphoma different from those already specified or mentioned. 3282653
Additional New Tumor Events				
*93	Has the patient developed a second progression or relapse that has not been previously reported?	☐ Yes ☐ No ☐ Unknown		Indicate whether the patient had a second progression or relapse that has not been previously reported. 3137510
94	Type of New Tumor Event	☐ Locoregional Recurrence ☐ Locoregional Disease ☐ Distant Metastasis ☐ Recurrence ☐ New Primary Tumor ☐ No new Tumor Event ☐ Not applicable		Indicate whether the patient's new tumor event was a locoregional recurrence, a distant metastasis, or a new primary tumor. 3119721
*95	Date of New Tumor Event	____ ____ / (month)	____ ____ / (day)	__ __ __ __ (year)	If the patient had a new tumor event, provide the date of diagnosis for this new tumor event. 3104044 (month), 3104042 (day), 3104046 (year)

*96	Patient Vital Status *(at date of last contact)*	☐ Alive ☐ Dead ☐ Lost to follow-up	Indicate whether the patient was living or deceased at the date of last contact, or has been lost to follow-up as defined by the ACoS Commission on Cancer. This only includes cases where updated follow-up information has not been collected within the past 15 months and all efforts to contact the patient have been exhausted (this includes reviewing death records). *If the patient is lost to follow-up, the remaining questions can be left unanswered. If the patient is **deceased** and a BLGSP follow-up form has not yet been completed, the remaining applicable questions should be completed.* 5
General Comments			

_____/_____

Principal Investigator (*Printed Name*) Principal Investigator (*Signature*) Date

I acknowledge that the above information provided by my institution is true and correct and has been quality controlled.

23 APPENDIX H: BLGSP Follow-Up Case Report Form

Instructions: *The Clinical Data needed to complete this Follow-up Form should be collected for each qualified case in the Burkitt Lymphoma Genome Sequencing Project (BLGSP) at 12 and 24 months after the date of patient consent. The Tissue Source Site (TSS) should complete this Follow-up Form within 60 days after the 12 and 24 month patient consent anniversary for all qualified cases indicated by the Office of Cancer Genomics (OCG). Questions regarding this form should be sent to Nationwide Children's Hospital or OCG.*

Please note the following definitions for the "Unknown" and "Not Evaluated" answer options on this form.

Unknown: This answer option should only be selected if the TSS does not know this information after all efforts to obtain the data have been exhausted. If this answer option is selected for a question that is part of the BLGSP required data set, the TSS must complete a discrepancy note providing a reason why the answer is unknown.

Not Evaluated: This answer option should only be selected by the TSS if it is known that the information being requested cannot be obtained. This could be because the test in question was never performed on the patient or the TSS knows that the information requested was never disclosed.

Tissue Source Site (TSS): _____TSS Identifier: _____ TSS Unique Patient Identifier: _____

Completed By *(Interviewer Name in OpenClinica)*: _____Completed Date: _____

#	Data Element	Entry Alternatives	Working Instructions
Patient Information			
Survival Information			
*1	Patient Vital Status *(at date of last contact)*	☐ Alive ☐ Dead ☐ Lost to follow-up	Indicate whether the patient was living or deceased at the date of last contact, or has been lost to follow-up as defined by the ACoS Commission on Cancer. This only includes cases where updated follow-up information has not been collected within the past 15 months and all efforts to contact the patient have been exhausted (this includes reviewing death records). *If the patient is lost to follow-up, the remaining questions can be left unanswered.* *If the patient is **deceased** and a BLGSP follow-up form has not yet been completed, the remaining applicable questions should be completed.* 5
*2	Date of Last Contact	____ ____ / ____ ____ / ___ ___ ___ ___ (month) (day) (year)	If the patient is living, provide the date of last contact with the patient (as reported by the patient, medical provider, family member, or caregiver). 2897020 (month), 2897022 (day), 2897024 (year) *Do not answer if patient is deceased.* *Note: The day of Last Contact is not required.*
*3	Date Last Known Alive	____ ____ / ____ ____ / ___ ___ ___ ___ (month) (day) (year)	Indicate the last date the patient was known to be alive, regardless of whether the patient, medical provider, family member or caregiver was contacted. 2975722 (month), 2975724 (day), 2975726 (year) *Note: The day of Last Known Alive is not required.*
*4	Date of Death	____ ____ / ____ ____ / ____ ____ ____ ____ (month) (day) (year)	If the patient is deceased, provide the date of death. 2897026, (month) 2897028 (day), 2897030 (year) *Note: The day of Death is not required.*
Patient Status (Regarding Submitted Tumor)			
*5	Tumor Status *(at time of last contact)*	☐ Tumor free ☐ With tumor ☐ Unknown tumor status	Indicate whether the patient was tumor/disease free (i.e. free of the malignancy that yielded the sample submitted for the BLGSP study) at the date of last contact or death. 2759550
6	Performance Status: Eastern Cooperative Oncology Group *(at time of last contact)*	☐ 0: Fully active, able to carry on all pre-disease performance without restriction. ☐ 1: 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. ☐ 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. ☐ 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. ☐ 4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. ☐ Unknown ☐ Not Evaluated	Provide the Eastern Cooperative Oncology Group (ECOG) performance status of the patient at the time selected in the "timing" question below. 88
7	Performance Status: Karnofsky Score *(at time of last contact)*	☐ 100: Normal, no complaints, no evidence of disease ☐ 90: Able to carry on normal activity; minor signs or symptoms of disease ☐ 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 ☐ 60: Requires occasional assistance, but is able to care for most of his/her needs. ☐ 50: Requires considerable assistance and frequent medical care ☐ 40: Disabled, requires special care and assistance	Provide the Karnofsky score for the patient at the time selected in the "timing" question below. 2003853

#	Data Element	Entry Alternatives	Working Instructions
		☐ 30: Severely disabled, hospitalization indicated. Death not imminent. ☐ 20: Very sick, hospitalization indicated. Death not imminent. ☐ 10: Moribund, fatal processes progressing rapidly ☐ 0: Dead ☐ Unknown ☐ Not Evaluated	
*8	Measure of Success of Outcome at the Completion of this Follow-up Submission *(at time of last contact)*	☐ Complete Remission/Response ☐ Partial Remission/Response ☐ Stable disease ☐ Progressive disease ☐ Persistent disease ☐ Unknown	Text term to describe the overall outcome of treatment up to the point of the current data submission. 3104050
HIV Status			
*9	HIV antibody status	☐ Positive ☐ Negative ☐ Unknown	Indicate whether the patient is HIV positive. 2180464
10	Date of HIV Diagnosis (if known)	__ __ / __ __ / __ __ __ __	Provide the date the patient was diagnosed with HIV. 3579640 (month), 3579644 (day), 3579643 (year) *Note: The day of HIV Diagnosis is not required.*
11	Nadir CD4 Counts	_____ (cells/mm^3)	Provide the patient's Nadir CD4 counts, which are the lowest CD4 counts the patient has had. 2684395
Treatment			
*12	Indication of Regimen	☐ Initial ☐ Adjuvant ☐ Progression after initial ☐ Recurrence ☐ Palliative ☐ Unknown	Text term to identify the reason for the administration of a treatment regimen. 2793511
*13	Lymphoma Treatment Type	☐ Chemotherapy ☐ Radiation ☐ Radiation and Chemotherapy ☐ Stem Cell Transplant ☐ Surgery ☐ No Treatment ☐ Other Treatment	Text term that describes the kind of treatment that was given for the primary lymphoma. 3284925
*14	If other, specify	_____	Indicate the other treatment type for the lymphoma. 2861111
Chemotherapy			
15	Chemotherapy Start Date	__ __ / __ __ / __ __ __ __	Date chemotherapy started. 2897050 (month), 2897052 (day), 2897054 (year)
16	Did chemotherapy end during this reporting period?	☐ Yes ☐ No	Indicate whether chemotherapy administration ended during this reporting period. 2188260
17	Chemotherapy End Date	__ __ / __ __ / __ __ __ __	Date chemotherapy ended. 2897056 (month), 2897058 (day), 2897060 (year)
*18	Pharmaceutical Regimen	☐ BACOP ☐ C-MOPP ☐ CAP-BOP ☐ CHOP + Bleomycin ☐ CHOP + Etoposide	Text term or code to represent the name of a pharmaceutical regimen containing two or more agents which are given together or separately to treat a patient with malignant lymphoma. 3366758

#	Data Element	Entry Alternatives	Working Instructions
		☐ CHOP-14 ☐ CHOP-14 + Rituximab ☐ CHOP-21 ☐ CHOP-21 + Rituximab ☐ CNOP ☐ CODOX + Rituximab ☐ CVP ☐ DA-EPOCH ☐ DA-EPOCH + Rituxumab ☐ F-MACHOP ☐ High Dose Methotrexate w/Leucovorin ☐ HyperCVAD-Mtx/AraC + Rituximab ☐ ICE ☐ ICE + Rituxumab ☐ LNH-84 ☐ LNH-87 ☐ M-BACOP ☐ MACOP-B ☐ ProMace-CytaBOM ☐ ProMace-MOPP ☐ VACOP-B ☐ Vanderbilt regimen + Rituximab ☐ Single Agent Therapy (please specify) ☐ Other Pharmaceutical Regimen (please specify) ☐ Unknown	

#	Data Element	Entry Alternatives	Working Instructions
19	If Other Pharmaceutical Regimen, specify	_____	Text term or abbreviation to represent another name of a pharmaceutical regimen containing two or more agents which are given together or separately to treat a patient with malignant lymphoma that was not already mentioned or specified. 3366930
20	If Single-Agent Therapy, specify	_____	Text name for agent used without other agents in a treatment regimen or study. 3590022
21	Number of Cycles	_____	The total number of cycles administered to the patient of a protocol specified drug or therapy agent as of the current report. 62590
Radiation Therapy			
22	Radiation Therapy Start Date	__ __ / __ __ / __ __ __ __	Date radiation therapy started. 2897100 (month), 2897102 (day), 2897104 (year)
23	Did radiation therapy end during this reporting period?	☐ Yes ☐ No	Indicate whether radiation therapy ended during this reporting period.
24	Radiation Therapy End Date	__ __ / __ __ / __ __ __ __	Date radiation therapy ended. 2897106 (month), 2897108 (day), 2897110 (year)
25	Total Dose of Radiation Therapy	_____ **(Gy)**	A numeric value for the total dose volume of radiation therapy given to a patient, in Gray. 36
26	Radiation Field, extranodal	☐ Abdomen, total ☐ Arm ☐ Body, total ☐ Bone, non-spine ☐ Brain, focal ☐ Brain, whole ☐ Breast ☐ Chest wall ☐ Eye ☐ Gastrointestinal, colon ☐ Gastrointestinal, gallbladder ☐ Gastrointestinal, intestine ☐ Gastrointestinal, Liver ☐ Gastrointestinal, NOS ☐ Gastrointestinal, Pancreas ☐ Gastrointestinal, Stomach ☐ Genitourinary, Bladder ☐ Genitourinary, Kidney ☐ Genitourinary, NOS ☐ Head, Face, or Neck ☐ Leg ☐ Lung ☐ Lymph node, distant (specify site) ☐ Lymph node, locoregional (specify site) ☐ Lymph Nodes ☐ Mantle ☐ Mediastinum ☐ Parametrium ☐ Pelvis ☐ Shoulder ☐ Skin, lower extremity, local ☐ Skin, total ☐ Skin, trunk, local ☐ Skin, upper extremity, local ☐ Spine ☐ Supraclavicular ☐ Thorax ☐ Trunk ☐ Other ☐ Unknown	Text term to identify anatomically-specified areas or fields that are targeted for radiation therapy. 2416537
27	Nodal Regions Targeted	☐ Axillary ☐ Cervical ☐ Epitrochlear ☐ Femoral	Identify lymph node sites targeted for radiation therapy. 3762198

#	Data Element	Entry Alternatives	Working Instructions
		☐ Hilar ☐ Iliac-common ☐ Iliac-external ☐ Inguinal ☐ Mediastinal ☐ Mesenteric ☐ Occipital ☐ Paraaortic ☐ Parotid ☐ Popliteal ☐ Retroperitoneal ☐ Splenic ☐ Submandibular ☐ Supraclavicular	
28	Other, specify	_____	Specify other field of radiation 62999
Stem Cell Transplantation			
29	Type of Stem Cell Transplantation	☐ Autologous ☐ Syngeneic/Allogeneic related donor ☐ Allogeneic, unrelated donor	Indicate the hematopoietic stem cell source type. 2957417
30	Date of Stem Cell Transplantation	__ __ / __ __ / __ __ __ __	Indicate the date of the hematopoietic stem cell transplant. 3718671
Surgery			
31	Date of cancer debulking surgery	__ __ / __ __ / __ __ __ __	Indicate the date related to the procedure of surgically removing as much of the tumor as possible being executed. 2839523
32	Measure of Success of Outcome at the Completion of Initial First Course Treatment	☐ Progressive Disease ☐ Persistent Disease ☐ Stable Disease ☐ Partial Remission/ Response ☐ Complete Remission/Response ☐ Unknown ☐ Not Applicable (treatment ongoing)	Indicate the patient's measure of success after the initial first course of treatment. 2786727
New Tumor Event Information *Complete this section if the patient had a new tumor event. If the patient did not have a new tumor event (or if the TSS does not know) indicate this in the question below, and the remainder of this section can be skipped.* Note: The New Tumor Event section on OpenClinica can be completed multiple times, if the patient had multiple New Tumor Events.			
First Recurrence or Progression			
33*	Has the patient developed a first relapse or progression that has not been previously reported?	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient has been diagnosed with a first recurrence or progression. 2002502
34	Date of First Recurrence or Progression	__ __ / __ __ / __ __ __ __	Provide the date documenting the initial identification of reappearance or advancement in extent or severity of cancer. 62998
35	Type of New Tumor Event	☐ Locoregional Recurrence ☐ Locoregional Disease ☐ Distant Metastasis ☐ Recurrence ☐ New Primary Tumor	Indicate whether the patient's new tumor event was a locoregional recurrence, a distant metastasis, or a new primary tumor. 3119721

#	Data Element	Entry Alternatives		Working Instructions
36	Site of First Malignant Lymphoma Progression	☐ Adrenal ☐ Appendix ☐ Ascites/ Peritoneum ☐ Axillary lymph nodes ☐ Bone ☐ Bone Marrow ☐ Brain ☐ Breast ☐ Cervical lymph nodes ☐ Colon ☐ Conjunctiva ☐ Epididymis ☐ Epidural ☐ Epitrochlear lymph nodes ☐ Esophagus ☐ Femoral lymph nodes ☐ Gastrointestinal/ Abdominal ☐ Heart ☐ Hilar lymph nodes ☐ Iliac-common lymph nodes ☐ Iliac-external lymph nodes ☐ Inguinal lymph nodes ☐ Intraocular ☐ Kidney ☐ Large intestine ☐ Larynx ☐ Leptomeninges ☐ Liver ☐ Lung ☐ Mandible ☐ Maxilla ☐ Mediastinal/ Intrathoracic ☐ Mediastinal lymph nodes ☐ Mediastinal soft tissue	☐ Mesenteric lymph nodes ☐ Nasal Soft Tissue ☐ Nasopharynx ☐ Occipital lymph nodes ☐ Orbit ☐ Oropharynx ☐ Ovary ☐ Pancreas ☐ Paraaortic lymph nodes ☐ Parotid Gland ☐ Parotid lymph nodes ☐ Peri-orbital Soft Tissue ☐ Pericardium ☐ Peripheral Blood ☐ Pleura/ Pleural Effusion ☐ Popliteal lymph nodes ☐ Prostate ☐ Rectum ☐ Retroperitoneal lymph nodes ☐ Salivary Gland ☐ Sinus ☐ Skin ☐ Small Intestine ☐ Soft Tissue *(muscle, ligaments, subcutaneous)* ☐ Splenic lymph nodes ☐ Stomach ☐ Submandibular lymph nodes ☐ Supraclavicular lymph nodes ☐ Testes ☐ Thyroid ☐ Uterus ☐ No known extranodal involvement ☐ Other Extranodal Site	Description of the anatomic location of progression of disease for malignant lymphoma. 3282650
37	Other Specified Extranodal Site of First Malignant Lymphoma Progression	_____		If the patient had a new tumor event and the site of this tumor was not included in the provided list, describe the site. 3282651
38	Was Site of First Progression Biopsied?	☐ Yes ☐ No ☐ Unknown		If the patient has had progression of disease, indicate whether the site of first progression was biopsied. 2716366

#	Data Element	Entry Alternatives	Working Instructions
*39	If biopsied, what was the Histological Subtype?	☐ Burkitt lymphoma, classic morphology ☐ Burkitt lymphoma, atypical morphology ☐ Other Histological Type, specify ☐ Unknown	Using the patient's final diagnostic pathology report, provide the most detailed histological subtype available. 3282652
40	Other Specified Histologic Type	_____	Specify the structural pattern of malignant lymphoma cells at the time of biopsy for first progression of malignant lymphoma different from those already specified or mentioned. 3282653
Additional New Tumor Events			
*41	Has the patient developed a second progression or relapse that has not been previously reported?	☐ Yes ☐ No ☐ Unknown	Indicate whether the patient had a second progression or relapse that has not been previously reported. 3137510
42	Type of New Tumor Event	☐ Locoregional Recurrence ☐ Locoregional Disease ☐ Distant Metastasis ☐ Recurrence ☐ New Primary Tumor ☐ No new Tumor Event ☐ Not applicable	Indicate whether the patient's new tumor event was a locoregional recurrence, a distant metastasis, or a new primary tumor. 3119721
*43	Date of New Tumor Event	____ ____ / ____ ____ / ___ ___ ___ ___ (month) (day) (year)	If the patient had a new tumor event, provide the date of diagnosis for this new tumor event. 3104044 (month), 3104042 (day), 3104046 (year)
General Comments			

Principal Investigator (*Printed Name*)

Principal Investigator (*Signature*) Date

I acknowledge that the above information provided by my institution is true and correct and has been quality controlled.