SUMMARY OF CHANGES

A Pilot Study of Ibrutinib and R-da-EPOCH for Front Line Treatment of AIDS-Related Lymphomas

Version 9.0

NCI Protocol #: AMC-101
Local Protocol #: AMC-101

NCI Version Date: 20DEC2024
Protocol Date: 20DEC2024

I. Scientific and Substantive Changes

#	Section	Description of Changes
1.	Table 6-A	The CAEPR risk profile for Ibrutinib (PCI-32765) Version 2.8, dated November 4, 2024 was added.
2.	Table 6-C	Expedited Reporting Requirements for Adverse Events dated August 30, 2024 was added.

II. Administrative and Editorial Changes

#	Section	Description of Changes
3.	Global	Protocol version was updated to 9.0 and date was updated to 20DEC2024.
4.	Protocol Roster	Sylvia Silver was removed as the AMC Biorepository Director.

AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL #101

A Pilot Study of Ibrutinib and R-da-EPOCH for Front Line Treatment of AIDS-Related Lymphomas

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	CTEP, Division of Cancer Treatment and Diagnosis National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT03220022
NCI Supplied Agent	Ibrutinib (NSC 748645; NCI IND#)
Pharmaceutical Support	Pharmacyclics LLC
Commercially Available Agents:	Rituximab (NSC 687451) Etoposide (NSC 141540) Prednisone (NSC 10023) Doxorubicin hydrochloride (NSC 123127) Vincristine sulfate (NSC 67574) Cyclophosphamide (NSC 26271)
Protocol Chair:	Ida Wong-Sefidan, MD
Protocol Co-Chair:	Erin Reid, MD

Version 9.0, 20DEC2024
NCI Version Date 20DEC2024

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol # 101 – A Pilot Study of Ibrutinib and R-da-EPOCH for Front Line Treatment of AIDS-Related Lymphomas (Version 9.0, 20DEC2024),** as written according to AMC, NCI, and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (DDMMMYYYY)

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PROTOCOL ROSTER

AMC Protocol # 101
A Pilot Study of Ibrutinib and R-da-EPOCH for Front Line Treatment of AIDS-Related Lymphomas

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PROTOCOL SYNOPSIS

Title:	A pilot study of ibrutinib and R-da-EPOCH for front line treatment of AIDS-related lymphomas (ARL)
Phase of Study:	Pilot study with a dose-finding and a dose-expansion cohort
Participating Institutions:	This protocol will be open to all AMC domestic member sites.
Accrual Target:	Forty (40) participants with adequate tissue for cell-of-origin (COO) analysis with a minimum of 15 participants with non-germinal B-cell (GCB)-like subtype diffuse large B-cell lymphoma (DLBCL) subtype by immunohistochemistry (IHC) as confirmed by central pathology. To compensate for the possible misclassification of COO, this study will accrue a minimum of 22 participants of non-GCB DLBCL subtype by IHC, as determined by local pathology. To ensure target accrual, 14 participants will be allowed on study as replacement participants should the participant not have adequate tissue for COO analysis. In order to guarantee the minimum participant requirement of non-GCB ARL, if after enrollment of 20 and 30 participants on trial, there are <50% non-GCB subtypes (as determined by the local pathology), non-GCB will be the preferentially enrolled to meet the minimum number of participants required in the trial.
Population:	Participants with histologically documented CD20 positive or negative AIDS-related diffuse large B-cell lymphoma (DLBCL). Participants must have stage II-IV disease, measurable disease by imaging, and ECOG Performance Status score of 0-2. Participants may be untreated or have received a maximum of one cycle of treatment with R-da-EPOCH or R-CHOP. Participants with CD4 ≥ 100 will be enrolled in the dose-finding portion of the study; participants with any CD4 counts, including <100, will be allowed in the dose-expansion cohort after safety is confirmed in dose-finding portion of the study. Participants with asymptomatic leptomeningeal disease by lymphoma may be enrolled in the dose-expansion cohort, at the physician's discretion. Participants must not be on medications with moderate or strong CYP3A4 inhibition, including antiretroviral (ARV) regimens; if on a moderate or strong CYP3A4 inhibitor regimen prior to study enrollment, participants must be switched to a qualifying regimen with the last dose of the moderate and/or strong CYP3A4 inhibitor taken at least one week before administration of protocol therapy due to effects on ibrutinib.

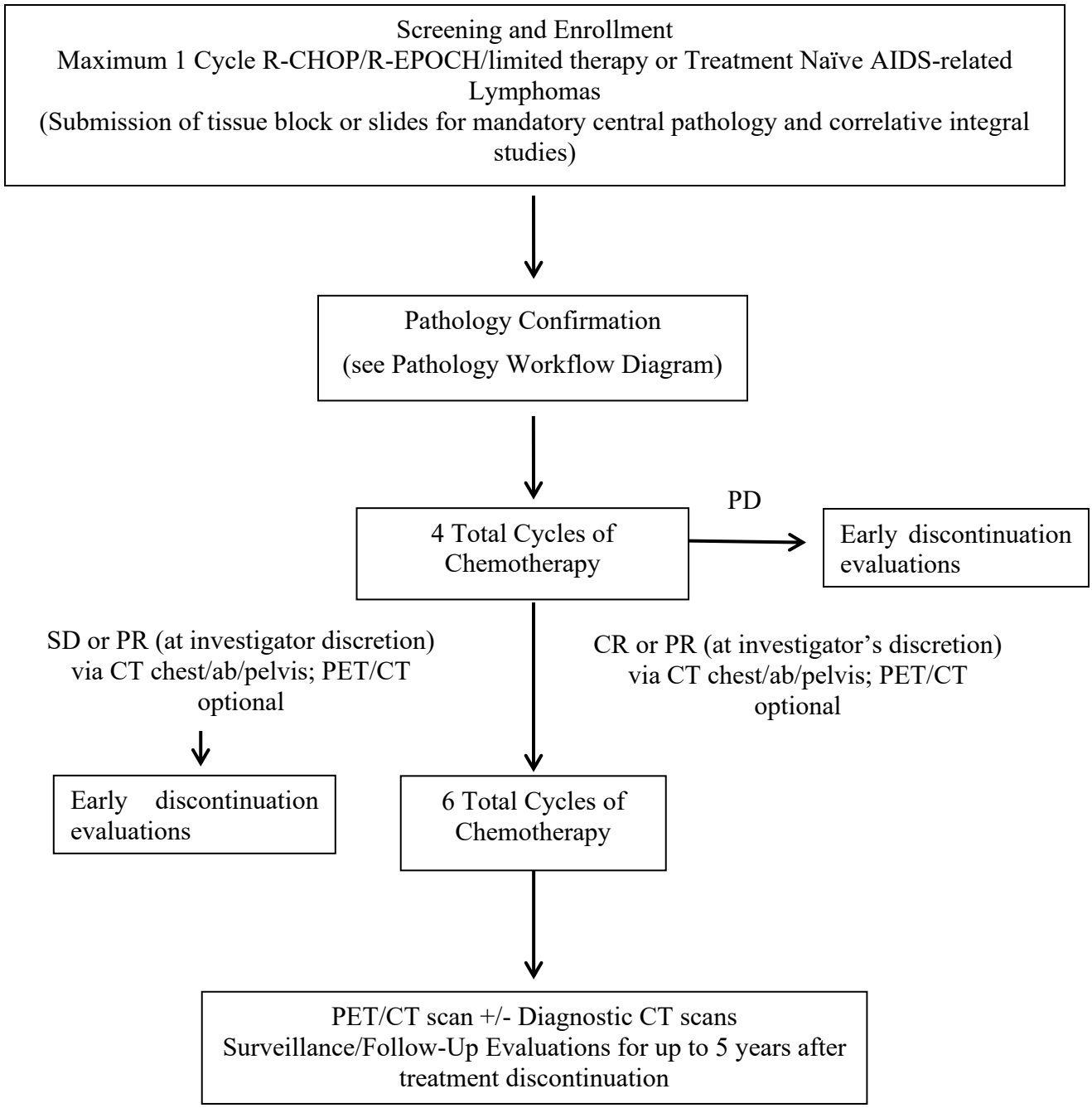
Treatment:	Ibrutinib will be evaluated in a 3+3 dose de-escalation design in the dose-finding portion of the study. Ibrutinib will be given in combination with R-da-EPOCH in CD20 positive disease, and da-EPOCH will be given in CD20 negative disease. In this portion of the study, ibrutinib will begin at dose level 1 (560 mg PO), and de-escalate to dose -1 (420 mg PO) and -2 (280 mg PO) if excessive toxicity is seen at dose levels 1 and -1, respectively. Once the recommended maximum tolerated dose (MTD) or recommended phase II dose (RP2D) of ibrutinib in combination with R-da-EPOCH is determined, additional participants will be enrolled into the dose-expansion portion of the study. In the dose-expansion stage of the study, participants will be treated at the MTD of ibrutinib, with intra-participant dose escalation and de-escalation of ibrutinib, in addition to dose-adjustment of R-EPOCH. Dose adjustment for R-EPOCH and/or ibrutinib will be based on laboratory measurements of the previous cycle ANC or platelet nadir, whichever is lower.
Duration:	Participants will be treated for a maximum of 6 cycles (21-day cycle length) of chemotherapy. Participants with complete response (CR) after Cycle 4 will receive two additional cycles of chemotherapy. Participants who achieve a partial response (PR) after Cycle 4 may continue on protocol therapy or be removed from the study at the discretion of a CTEP-registered AMC investigator). Participants will be followed for 5 years after completion of treatment (defined as day 21 of the final treatment cycle), with follow-up visits every 3 months for years 1-2 post-treatment, and then every 6 months for 3-5 years post-treatment.
Anticipated Trial Duration	34 months
Primary Objectives:	To assess the safety and tolerability of ibrutinib and R-da-EPOCH in participants with ARL. This will define the RP2D of ibrutinib in combination with R-da-EPOCH in participants with ARL.

Secondary Objectives:

(includes all participants unless specified)

- To evaluate the CR rates of ARL to ibrutinib and R-da-EPOCH.
- To measure the 1-year and 2-year overall and progression-free survival (OS, PFS) of participants with ARL treated with combination ibrutinib and R-da-EPOCH, including preliminary comparison of non-GCB with historical controls treated with R-da-EPOCH.
- To categorize and compare the cell-of-origin by GEP gene expression-based classification (GCB, activated B-cell-like, unclassifiable) to IHC classification (GCB, non-GCB), estimate the discordant classification, and correlate each biological classification (IHC and GEP) with treatment response rates and survival.
- To calculate the percentage of participants who receive two or more cycles of R-da-EPOCH, and are able to continue on a minimum dose level of cyclophosphamide of -1 and above after dose adjustments for hematologic toxicities.
- To determine the average number of days per cycle participants are able to stay on planned dose of ibrutinib at the RP2D.
- To assess the effect of ibrutinib and R-da-EPOCH on levels of circulating tumor DNA.
- To assess the effect and degree of ibrutinib and R-da-EPOCH on T-cell receptor signaling via ITK inhibition.
- To assess the effect of ibrutinib and R-da-EPOCH on B-cell receptor signaling pathway including BTK activity in ARL.
- To evaluate the soluble cytokine response to ibrutinib and R-da-EPOCH.
- To characterize the pharmacokinetics of doxorubicin, etoposide, and vincristine in the presence of ibrutinib, and vice versa, and assess the clinical relevance of any drug-drug interaction and correlate with pharmacodynamics outcomes.

PROTOCOL SCHEMA



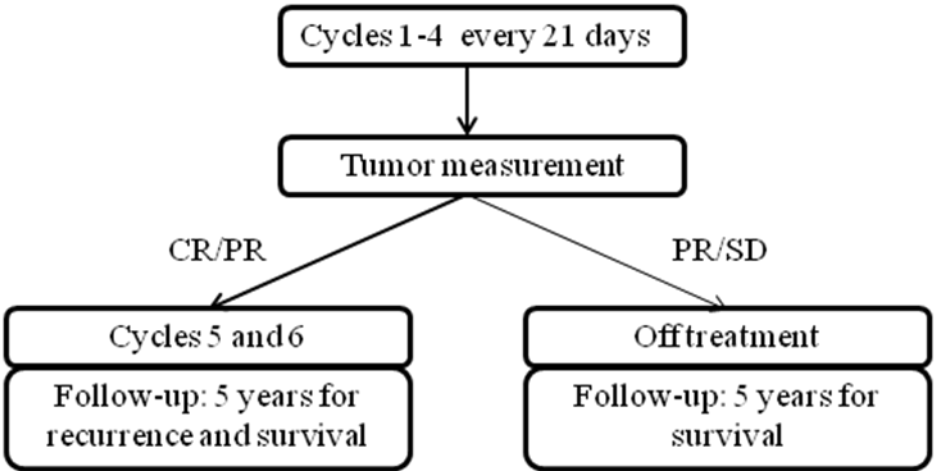
Dose De-Escalation Stage

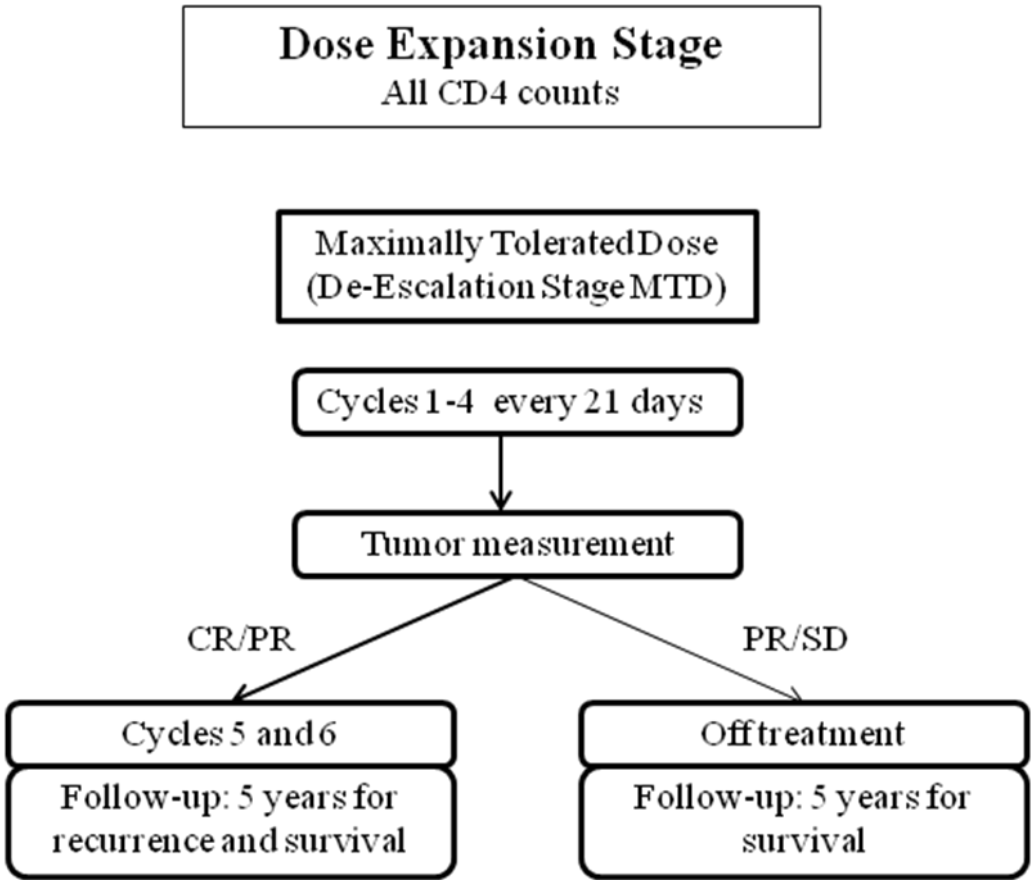
Ibrutinib + R-da-EPOCH

Dose Level	Ibrutinib Dose
+1	560mg
-1	420mg
-2	280mg

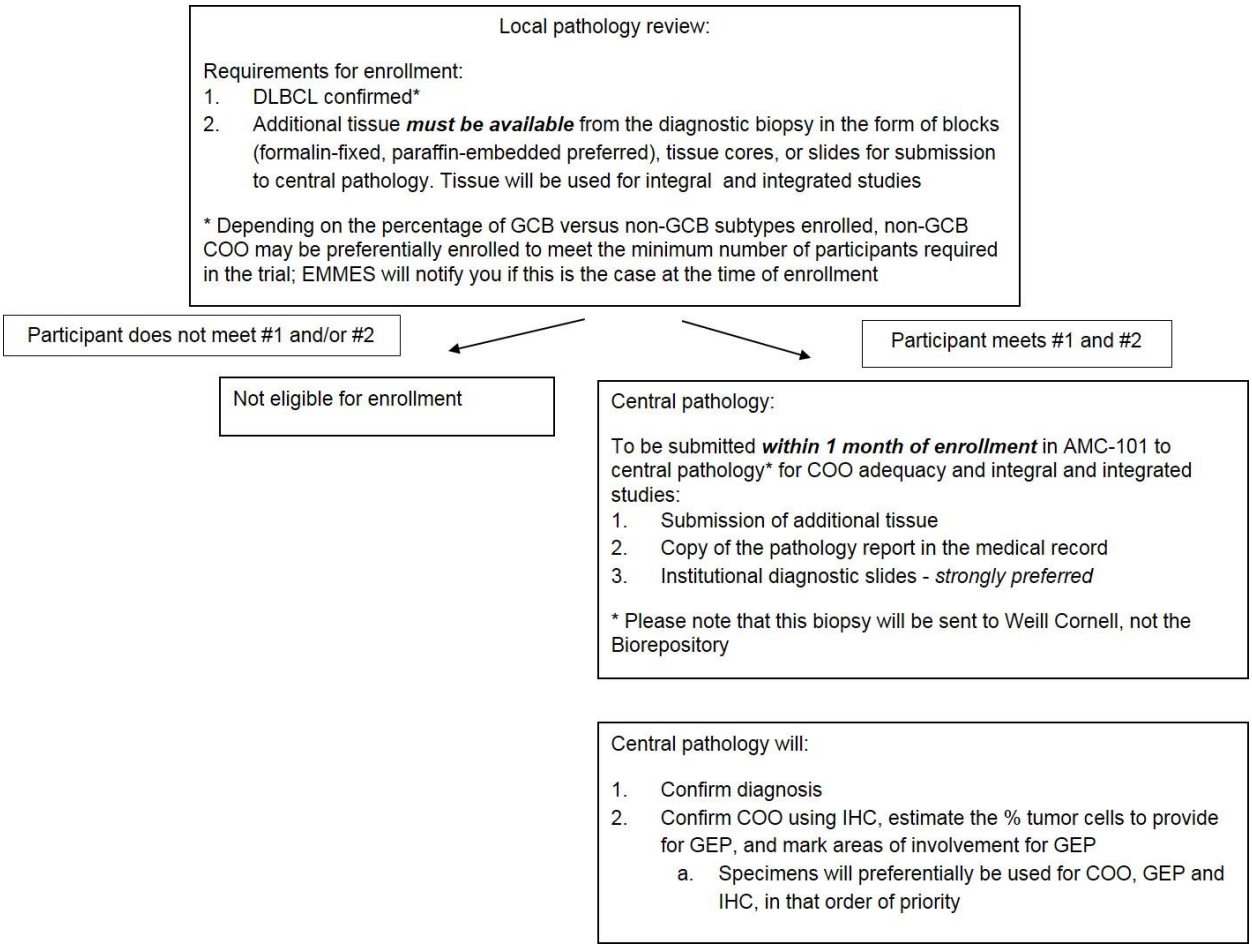
Dose De-Escalation Rules

Number of Participants at Dose Level	Number of Participants with Cycle 1 DLT	Action
3	0	RP2D, move on to dose-expansion cohort
3	1	Treat another 3 participants at the same dose
6	1	RP2D, move on to dose-expansion cohort
3-6	≥ 2	RP2D exceeded, dose de-escalate to one level down




Dose Expansion Stage
All CD4 counts
Maximally Tolerated Dose
(De-Escalation Stage MTD)
Cycles 1-4 every 21 days
Tumor measurement
CR/PR
PR/SD
Cycles 5 and 6
Follow-up: 5 years for recurrence and survival
Off treatment
Follow-up: 5 years for survival

Pathology Workflow Diagram



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LIST OF ABBREVIATIONS

ABC ..... activated B-cell (as determined by GEP)
ACSR ..... AIDS and Cancer Specimen Resource
AE ..... adverse event
AIDS ..... Acquired Immunodeficiency Syndrome
ALT ..... alanine aminotransferase
AMC ..... AIDS Malignancy Consortium
ANC ..... absolute neutrophil count
ART ..... antiretroviral therapy
ARL ..... AIDS-related lymphomas
ARV ..... antiretroviral
AST ..... aspartate transaminase
BCR ..... B-cell receptor
BTK ..... Bruton's tyrosine kinase
cART ..... combined antiretroviral therapy
CBC ..... complete blood count
CDC ..... Centers for Disease Control and Prevention
CDUS ..... Clinical Data Update System
CFR ..... Code of Federal Regulations
COO ..... cell-of-origin
CR ..... complete response
CRF ..... case report form
CT ..... computed tomography
CTA ..... clinical trial agreement
CTCAE ..... Common Terminology Criteria for Adverse Event reporting
CTEP ..... Cancer Therapy Evaluation Program
CTEP-AERS ..... CTEP Adverse Event Reporting System
CTMS ..... Clinical Trials Monitoring Service
DARF ..... investigational agent [drug] accountability record form
DHHS ..... Department of Health and Human Services
DLBCL ..... diffuse large B-Cell lymphoma
DLT ..... dose-limiting toxicity
DMC ..... data monitoring committee
EBER-ISH ..... Epstein-Barr encoding region (EBER) in situ hybridization
EBV ..... Epstein-Barr virus
ECOG PS ..... Eastern Cooperative Oncology Group Performance Status [Score]
FDA ..... Food and Drug Administration
GCB ..... germinal center B-cell (as determined by IHC)
GCSF ..... granulocyte colony-stimulating factor
GEP ..... gene expression profiling
HAART ..... highly active antiretroviral therapy
HHV-8 ..... human herpesvirus 8
HIV ..... human immunodeficiency virus
IDB ..... Investigational drug branch
IHC ..... immunohistochemistry
IRB ..... institutional review board

IND ..... investigational new drug [application]
ITK ..... inducible T-cell kinase
kg ..... kilogram
KSHV ..... Kaposi sarcoma-associated herpesvirus
LLN ..... lower limit of normal
MTD ..... maximum tolerated dose
mg ..... milligram
NCI ..... National Cancer Institute
NCT ..... National Clinical Trials [Registry]
NIH ..... National Institutes of Health
NHL ..... non-Hodgkin lymphoma
pBTK ..... phosphorylated Bruton's tyrosine kinase
PEL ..... primary effusion lymphoma
PI ..... principal investigator
PI ..... protease inhibitors
PIO ..... Protocol Information Office
PD ..... progressive disease
PO ..... per oral [by mouth]
PR ..... partial response
RP2D ..... recommended Phase II dose
RNA ..... ribose nucleic acid
SAE ..... serious adverse event
SD ..... stable disease
ULN ..... upper limit of normal

1.0 OBJECTIVES

1.1 Primary Objectives

To assess the safety and tolerability of ibrutinib and R-da-EPOCH in participants with ARL. This will define the recommended phase II dose (RP2D) of ibrutinib in combination with R-da-EPOCH in participants with ARL.

1.2 Secondary Objectives

1.2.1 To evaluate the complete response (CR) rates of ARL to ibrutinib and R-da-EPOCH.

1.2.2 To measure the 1-year and 2-year overall and progression-free survival of participants with ARL treated with combination ibrutinib and R-da-EPOCH, including preliminary comparison of non-GCB with historical controls treated with R-da-EPOCH.

1.2.3 To categorize and compare the cell-of-origin by GEP gene expression-based classification (GCB, activated B-cell-like, unclassifiable) to IHC classification (GCB, non-GCB), estimate the discordant classification, and correlate each biological classification (IHC and GEP) with treatment response rates and survival.

1.2.4 To calculate the percentage of participants who receive two or more cycles of R-da-EPOCH, and are able to continue on a minimum dose level of cyclophosphamide of -1 and above after dose adjustments for hematologic toxicities.

1.2.5 To determine the average number of days per cycle participants are able to stay on planned dose of ibrutinib at the RP2D.

1.2.6 To assess the effect of ibrutinib and R-da-EPOCH on levels of circulating tumor DNA.

1.2.7 To assess the effect and degree of ibrutinib and R-da-EPOCH on T-cell receptor signaling via ITK inhibition.

1.2.8 To assess the effect of ibrutinib and R-da-EPOCH on B-cell receptor signaling pathway including BTK activity in ARL.

1.2.9 To evaluate the soluble cytokine response to ibrutinib and R-da-EPOCH.

1.2.10 To characterize the pharmacokinetics of doxorubicin, etoposide, and vincristine in the presence of ibrutinib, and vice versa, and assess the clinical relevance of any drug-drug interaction and correlate with pharmacodynamics outcomes.

2.0 BACKGROUND

2.1 Study Disease

2.1.1 AIDS related lymphomas

Lymphomas are a significant complication of HIV infection. Epidemiologically, patients living with HIV/AIDS have a higher incidence of non-Hodgkin lymphoma (NHL).[1] For this reason, in 1985, the Centers for Disease Control (CDC) expanded the definition of AIDS to include NHL in this population.[2] Since the introduction of combined antiretroviral therapy (cART) in the mid-1990s, AIDS-related lymphomas (ARL) have decreased in incidence and improved in outcome, mostly due to better control of HIV and improved immune function. However, despite the three-fold increase in survival of patients with AIDS-related lymphomas, ARL continues to be one of the most common malignancies in the setting of HIV/AIDS. Given estimates of a minimum of 11-17-fold risk compared to the general population, the life time risk of lymphoma may be about 10%.[3] Consequently, many patients still die of disease refractory to standard therapy. While there are emerging data for treatment of non-ARL, ARL continues to be a rare disease with few clinical trials available, mainly due to the limited number of patients.

2.1.2 Classifications of ARL

The diagnostic category of ARL is heterogeneous and diverse in nature, not only clinically, but morphologically, genetically, and molecularly. As in HIV-negative NHL, a number of defined genetic abnormalities and subtypes exist in ARL. For instance, in HIV-negative diffuse large B-cell lymphoma (DLBCL), DLBCL can be classified according to its cellular origin of cell-of-origin (COO): germinal center B-cell (GCB)-like or non-germinal center B-cell (non-GCB)-like subtype. The germinal type typically expresses GCB-associated markers by immunohistochemistry (IHC), such as CD10 and BCL6. The non-GCB subtype is mainly CD10-negative, BCL-6 negative and MUM-1 positive, though lymphoma typing based on markers is a field in flux and best defined by genomic profiling. COO for DLBCL can also be distinguished by gene-expression profiling (GEP). The division of DLBCL into GCB and activated B-cell-like (ABC) subtypes based on GEP has proved to be important in understanding the pathogenesis of the disease. ARL can be divided into GCB and non-GCB variants; however, in contrast to immunocompetent patients, only a limited number of gene expression profiling studies exist of AIDS-related DLBCL and other ARL.

It is likely that ARLs are in some ways dissimilar to non-HIV related lymphomas. For example, many ARL are driven by Epstein-Barr virus (EBV) and human herpesvirus-8 (HHV-8), or Kaposi sarcoma-associated herpesvirus (KSHV). These lymphoma subtypes, typically ascertained by IHC, have in some studies been shown to predict both lymphoma-specific and overall survival in the general population. In the HIV-negative population, non-GCB DLBCL has inferior survival compared with GCB DLBCL.[4] Similarly, patients with HIV-associated non-GCB DLBCL have been shown to have inferior survival and increased rates of recurrent/refractory disease.[5,6] In a Phase II study of patients with HIV-associated DLBCL treated with R-EPOCH, tumor subtype by IHC was the only characteristic

associated with lymphoma-specific outcome. In the setting of planned short course (3 cycles of chemotherapy) patients with GCB subtype had a 95% 5-year PFS, while those with non-GCB had only a 44%.[6] In contrast, a retrospective analysis of several AMC clinical trials with full course R-EPOCH showed that subclassification of AIDS-associated DLBCLs into GCB or non-GCB type using IHC methods alone did not show any difference in survival.[7] This difference in these study results may be due to treatment factors as the AMC study had a more heterogeneous treatment program; alternatively, it may be explained by the finding that AIDS-related DLBCL expresses a unique immunophenotype compared to non AIDS-related DLBCL. A study by Madan et al. looking at protein expression of germinal center and activated B-cell markers between AIDS versus non AIDS-related DLBCL, found that non-AIDS DLBCL clustered into distinct GCB and ABC types, while AIDS-related DLBCL formed a single cluster with an intermediate germinal center ABC phenotype, suggesting a distinctive pathophysiology.[8] Therefore, at this time, traditional categories of non-GCB and GCB using IHC may not be accurately classifying ARL, as in HIV-negative lymphomas, and more studies looking into the gene expression profile of ARLs may be warranted.

2.1.3 Treatment of ARL

The treatment of ARL has changed over the last few decades. Better control of HIV and the improvement of overall immune status have allowed patients to be treated with combination chemotherapy similar to those used in the HIV-negative population. Treatments for ARL include regimens such as rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone (R-CHOP)[9] and rituximab with infusional etoposide, vincristine, and doxorubicin, with oral prednisone and bolus dose-adjusted cyclophosphamide (R-EPOCH).[10] Although R-EPOCH and R-CHOP were not compared in a randomized fashion, response and survival rates with R-EPOCH are improved compared with historical R-CHOP studies without increased toxicities.[10,11] In an AMC study comparing R-EPOCH to historical data on R-CHOP, patients with aggressive $CD20^+$ B-cell non-Hodgkin lymphoma (NHL), including DLBCL, Burkitt/Burkitt-like lymphoma, or other aggressive lymphomas associated with HIV infection, treated with R-EPOCH had a 73% complete response (CR) rate versus a ~50% CR rate with R-CHOP.[10] Currently, R-EPOCH and R-dose-adjusted (da)-EPOCH are accepted as the standard of care chemotherapy regimen in most cases of ARL. However, cancer research has entered a molecular age. Classifying tumors with respect to immunophenotype and genomic features is ever more essential to improving treatment. Improved therapy for ARL is needed and targeting inhibition in an active pathway of ARL may be the next approach to improving survival in this group of patients. Like in non-ARL, we seek to identify ways to continue to improve outcomes beyond current combination immunochemotherapy.

2.2 Study Agents

2.2.1 Ibrutinib

Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (BTK), an integral component of the B-cell receptor (BCR) and cytokine receptor pathways. Constitutive activation of B-cell receptor signaling is important for survival of malignant B-cells; BTK inhibition results in decreased malignant B-cell proliferation and survival. It is an oral drug approved as monotherapy in other B-cell lymphoproliferative diseases such as Waldenström macroglobulinemia, mantle cell lymphoma, chronic lymphocytic leukemia, and marginal zone lymphoma.

2.2.2 R-EPOCH

R-EPOCH consists of infusional rituximab, etoposide, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride, with oral prednisone, in combination with recombinant human granulocyte colony-stimulating factor (GCSF).

The components of EPOCH are at most weak inhibitors of CYP3A4 and unlikely to cause significant alterations to ibrutinib in the clinically relevant range utilized in this study.[12] However, ibrutinib may inhibit ABCB1, for which doxorubicin, etoposide, and vincristine are all substrates. Inhibition of ABCB1 may lead to increased concentrations of ABCB1 substrates, which may cause increased myelosuppression. Myelosuppression has been observed with other ABCB1 substrates, like paclitaxel[13] and sunitinib[14] in the presence of ABCB1 inhibitors or functional polymorphisms in ABCB1. Since drug interaction studies suggest that there is little chance of a clinically significant drug interaction via CYP450 between ibrutinib and EPOCH, a full pharmacokinetic profile to assess for the bi-directional pharmacokinetic interaction will not be performed in this study.

Rituximab

Rituximab is a chimeric mouse/human anti-CD 20 monoclonal antibody that binds human C1q, mediate complement-dependent cell lysis and lyse human target cells through antibody dependent cellular cytotoxicity. It has documented anti-tumor activity in CD20 positive lymphoma and FDA-approved for that indication. Please refer to the approved package insert for complete prescribing and toxicity information.

Etoposide

Etoposide, or VP-16, is an epipodophyllotoxin derived from the mandrake plant *Podophyllum peltatum (P. peltatum).* Etoposide is a substrate for CYP1A2, CYP2E1, CYP3A4/5, UGT1A1, ABCB1, ABCC1, and ABCC3 and a weak inhibitor of CYP2C9 and CYP3A4. It is a cell cycle phase specific agent that blocks topoisomerase II. It has a biphasic half-life and is eliminated by both renal clearance and metabolism. The major and dose-limiting toxicity of etoposide is myelosuppression. Constipation, diarrhea, dysphagia, aftertaste, abdominal pain, stomatitis, and anorexia have also been reported. Mucositis and hepatotoxicity are seen primarily with high doses. Transient hypotension and other anaphylactic-like

symptoms are associated with rapid infusion. Please refer to the approved package insert for complete prescribing and toxicity information.

Prednisone

Prednisone is a corticosteroid and its mechanism of action, as a cytotoxic agent is not clearly understood. Short-term use produces minimal side effects but prolonged use is associated with hypertension, hyperglycemia, myopathy, osteoporosis, pancreatitis, and immunosuppression. Alterations in mood and insomnia are common acute side effects. Please refer to the approved package insert for complete prescribing and toxicity information.

Vincristine sulfate

Vincristine sulfate is a vinca alkaloid from the plant *Cantharanthus roseus* (*C. roseus*). Vincristine is a substrate for CYP3A4/5, ABCB1, ABCC1, ABCC2, ABCC3, and ABCC10 and a weak inhibitor of CYP3A4. It acts by binding to or crystallizing microtubular proteins of the mitotic spindle. It is a cell cycle phase specific agent and can also affect DNA-directed RNA polymerase. It has a triphasic half-life and primary elimination is by the liver into the bile and feces. The major and dose-limiting side effect of vincristine is neurotoxicity. The main manifestation is a mixed sensorimotor peripheral neuropathy. Reduced or loss of deep tendon reflexes, paresthesias, weakness, myalgias and motor disturbances may occur. Autonomic toxicity also occurs which may cause constipation, obstipation, abdominal cramps and ileus. It has mild myelosuppressive effects and is a vesicant causing local necrosis at the site of injection if extravasation occurs. Please refer to the approved package insert for complete prescribing and toxicity information.

Cyclophosphamide

Cyclophosphamide is an alkylating agent and is cell cycle nonspecific. It causes cross-linking of DNA and is the most active single agent in the treatment of non-Hodgkin lymphoma. Cyclophosphamide is a substrate of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5. Cyclophosphamide is a weak-to-moderate inducer of CYP2B6, CYP2C8, and CYP2C9 and weak inhibitor of CYP3A4 and UGT (isozyme not specified). Side effects of cyclophosphamide include nausea, vomiting, myelosuppression and alopecia. Sterility and testicular atrophy are common in men and amenorrhea is seen in women. Hemorrhagic cystitis is caused by metabolites of cyclophosphamide excreted through the urine. Bladder irritation can be reduced by adequate hydration. Please refer to the approved package insert for complete prescribing and toxicity information.

Doxorubicin hydrochloride

Doxorubicin is an anthracycline antibiotic that binds tightly with DNA, inhibits nucleic acid synthesis and causes DNA strand breaks. Although active throughout the cell cycle, cells in S phase are most sensitive. Doxorubicin is a substrate for aldoketoreductase, NADPH-dependent cytochrome reductase, CYP2D6, CYP3A4, ABCB1, ABCC1, ABCC2, ABCG2, and SLC22A16. Doxorubicin also has been noted to be an inducer of ABCB1, a moderate inhibitor of CYP2B6, and a weak inhibitor of CYP2D6 and CYP3A4. Common side effects include

myelosuppression, alopecia, and stomatitis, which is dose related and may be severe. Drug-induced cardiomyopathy which may result in congestive heart failure is a cumulative dose dependent effect and risk becomes considerable at total doses exceeding 500 mg/m^2. Doxorubicin is given intravenously and is a vesicant causing severe local necrosis at the site of injection if extravasation occurs. Nausea and vomiting are frequent. Please refer to the approved package insert for complete prescribing and toxicity information.

2.3 Study Design and Rationale

2.3.1 Rationale

The activation of the B-cell receptor (BCR) signaling pathway plays a role in proliferation and survival in B-cell NHL. Chronic BCR signaling engages the adaptors CD79A and CD79B in a Syk-dependent mechanism. Downstream of CD79A/B, BTK is activated.[15] Although data are lacking regarding BTK inhibition in EBV or KSHV driven lymphomas, many NHL that occur in the setting of late stage AIDS are virally associated (EBV, KSHV), and these viruses are known to modulate BCR and subsequent signaling pathways to drive persistence and proliferation. Additionally, EBV latent membrane protein 2A (LMP2A) may initiate both BTK-dependent and BTK-independent pathways.[16]

Activation of the BCRB-cell receptor pathway is a new therapeutic target in B cell lymphoma, as BTK is an essential kinase for B cell survival.[17] An inhibitor to the BCR signaling pathway with BTK inhibitors like ibrutinib may improve response rates and survival.

Outside of AIDS-related DLBCLs, BTK inhibitors have been most promising in targeted inhibition of aberrant pathways in non-GCB DLBCL. Preclinical studies with BTK inhibitors showed inhibition of outgrowth of CD79 mutant non-GCB DLBCL cells.[15] A Phase II trial of single-agent ibrutinib in participants with relapsed or refractory DLBCL demonstrated an overall response rate (ORR) of 23% (16/70 participants) with a much higher response in the non-GCB subtype, (12/29, 41%) (five CR and seven PR) versus the GCB subtype, (1/20, 5%) (1PR).[18] In a phase I trial of R-CHOP and ibrutinib, all 18 participants with DLBCL who received the recommended Phase II dose had an overall response. For those subtyped and treated at the recommended phase II dose, five (71%) of seven participants with the GCB subtype and two (100%) participants with the non-GCB subtype had a complete response.[19] By contrast, for ARL, the division of oncogenic phenotypes of GCB and non-GCB has not been optimally determined.[8] While enrichment of patients for non-GCB seemingly would be ideal for a study with BTK inhibitors, exclusion of AIDS patients with GCB DLBCL based on IHC alone may be premature in this population as ARL may have a distinct molecular profile that is not best stratified by IHC alone.[8] More importantly, there are no current trials examining ibrutinib, a drug which has and continues to revolutionize the non-ARL arena, in ARL.

Given the activity demonstrated by ibrutinib in non-HIV DLBCL, we would like to evaluate the safety and feasibility of ibrutinib with chemotherapy in HIV patients with DLBCL. We propose a multi-center pilot study which will combine the BTK-

inhibitor ibrutinib with R-EPOCH chemotherapy in participants with treatment-naïve ARL. This pilot study will consist of a dose-finding cohort, and a dose-expansion cohort. The dose-finding portion of the study will be a dose de-escalation study beginning with ibrutinib 560 mg daily dose level. The minimum dose will be ibrutinib 280 mg daily as ibrutinib in combination with chemotherapy may require less than the FDA approved dose. The dose-expansion portion of the study will use ibrutinib at the recommended phase II dose (RP2D) in combination with chemotherapy.

The main reasons for this trial are to provide feasibility data for the combination of ibrutinib and R-EPOCH in DLBCL, and in particular, evaluate the safety and feasibility this combination in persons with HIV patients, specifically non-GCB or ABC subtypes.

There are several added benefits to this trial. In particular, this study builds on data provided by the ongoing Phase III trial using R-CHOP and ibrutinib in the front-line setting for non-GCB DLBCL,[19] which excludes HIV patients. Data from this trial will also allow the AMC to move forward to a larger efficacy study of ibrutinib and R-EPOCH in ARLs. An expanded cohort will enrich the population at the RP2D; accordingly, it will help gain insight into the proof-of-concept of ibrutinib and R-EPOCH, as well as improve the characterization and evaluation of the toxicity profile, interactions, tolerability, and pharmacology of ibrutinib in combination with R-da-EPOCH in ARL. More importantly, while we will not have power to distinguish non-GCB versus GCB, this trial will provide some information in the context of the current randomized Phase III R-CHOP and ibrutinib versus R-CHOP;[19] if the observed pattern seen in this trial fits with the Phase III outcomes, then it would support the use of ibrutinib in the ARL population, particularly for DLBCL. Finally, since assignment of COO is increasingly important with the emergence of novel therapies that have selective biological activity in GCB and non-GCB or ABC lymphomas, we will obtain a GEP on each tumor sample in addition to IHC for assessment of GCB and non-GCB classification. This may allow us to more accurately correlate ARL biology with treatment response and survival with ibrutinib at the end of treatment.

2.3.2 Study design

The proposed trial will be a multi-center pilot study studying of ibrutinib in combination with R-da-EPOCH. This pilot study will include a dose-finding cohort followed by a dose-expansion cohort at the MTD or RP2D.

Participants must not be on medications, including antiretroviral (ARV) regimens, with moderate or strong CYP3A4 inhibition; if on a moderate or strong CYP3A4 inhibitor regimen prior to study enrollment, participants must be switched to a qualifying regimen with the last dose of the moderate or strong CYP3A4 inhibitor taken at least one week before administration of protocol therapy due to effects on ibrutinib. Participants must have tissue (block, core or slides) available for submission available for mandatory central pathology review and additional correlative integral studies.

The pilot study aims to determine the MTD and RP2D of ibrutinib in combination

with R-EPOCH using a 3+3 dose de-escalation design. The decision to enroll participants in subsequent cohorts will be made after the available safety data at a given dose level of ibrutinib are reviewed, each participant in the current cohort must have completed at least cycle 1 (or 21 days) of ibrutinib and R-da-EPOCH before safety data will be reviewed. MTD will be the dose at which less than 2/6 of participants have a dose-limiting toxicity (DLT). **The protocol team reviewed the safety among the first 3 participants enrolled on 01MAY2018 and confirmed that dose level 1 was the MTD.**

R-da-EPOCH will be given on a 21-day cycle. EPOCH will be dose-adjusted based on nadir counts in the previous cycle (see below). Ibrutinib will be dosed daily on days 1-21. Participants with CD20 negative disease will receive the same treatment of EPOCH, but without rituximab. There will be no intra-participant dose escalation of ibrutinib in the dose-finding portion of the study. Given this is combination therapy, with the hypothesis that ibrutinib will have synergy with R-EPOCH, we have allowed ibrutinib de-escalation as needed for toxicity to a dose of 280 mg.

Once the RP2D or MTD dose is determined, additional participants will be enrolled into the dose-expansion cohort in order to better characterize the toxicity and safety profile, assess the pharmacokinetics, and identify early signs of efficacy within the GCB and non-GCB population. In the dose-expansion portion of the study, R-da-EPOCH will be given on a 21-day cycle. Ibrutinib and EPOCH will be dose-adjusted based on nadir counts in the previous cycle (see below). Ibrutinib, at the MTD, will be dosed daily on days 1-21 of each cycle except when held for toxicities as specified below.

Participants may receive treatment for a maximum of 6 cycles (21-day cycle length) total of chemotherapy in the dose-finding and dose-expansion cohort portion of the study. Participants will be allowed to enroll after one cycle of R-da-EPOCH or R-CHOP, as noted in the eligibility criteria; this cycle will count as Cycle 1 of therapy on study. A restaging diagnostic CT (chest/abdomen/pelvis, with PET/CT optional) will be performed after Cycle 4. Participants with CR after Cycle 4 will receive two additional cycles of chemotherapy. Given there is a range of what qualifies as PR (including participants with residual PET avidity which may represent CR with residual "healing tissue"), participants who achieve a PR after Cycle 4 may continue on protocol therapy or be removed from the study at the discretion of the physician (local investigator). PET/CT will be performed to document remaining active sites of lymphomatous disease 4-8 weeks after the beginning of Cycle 6, or within 4-8 weeks of treatment discontinuation if treatment was stopped after Cycle 4 and prior to Cycle 6 due to excessive toxicity.

Forty participants with adequate tissue for COO analysis (IHC and GEP) will be enrolled in the dose-finding and dose-expansion cohorts. A maximum of 54 participants will be allowed on the trial; for participants who do not have adequate tissue for GEP, tumor content of $\geq$ 60%, we will replace up to 14 participants (assuming 30-35% insufficient tissue for GEP) on trial. If we need to replace more than 14 participants, AMC and other involved parties will discuss a remediation plan. Therefore, the maximum number of participants is 54 participants (40 evaluable with 14 replacements, if needed).

2.3.3 Study Design Flow

The goal will be to obtain at least 40 participants with adequate tissue for COO and 15 participants with central pathology confirmed non-GCB (by IHC) subtype, and eventually ABC subtype (by GEP), for analysis. Given this is a multicenter trial and adequacy of tissue and IHC confirmation for COO will need to be reviewed and confirmed at the AMC Pathology Core Lab at Weill Cornell Medical College. In addition, given logistical and financial restraints, COO by GEP will be completed in batches. Therefore, IHC will be the only marker used for accrual and participant selection. To account for this logistical challenge inherent to a multicenter trial, the following method for adequacy of tissue for COO and IHC review will be implemented:

- COO (non-GCB or GCB) by IHC will be required and determined at each individual AMC site in which the participant is being treated. To compensate for the possible 30% misclassification rate, we will accrue a minimum of 22 participants with non-GCB histology via IHC as determined by the local pathologist.
- Diagnostic slides with IHC staining and the remaining tissue block will be sent within 1 month for central pathologic confirmation of IHC and central pathologic confirmation of adequacy of tissue for GEP analysis. Tissue, specifically formalin-fixed, paraffin-embedded specimens, will preferentially be used for COO biomarkers, GEP and IHC, in that order of priority.
- The AMC core laboratory will confirm COO by IHC on a case-by-case basis; the IHC determined at the AMC core lab will be used in the final analysis. Remaining tissue will be banked and batched at the AMC Biorepository for the GEP and other correlative studies. Given logistical and financial restraints, COO by GEP will be completed in batches. Note: because IHC will be used to determine the number of participants in each subgroup, COO by IHC will be an integral biomarker, while because COO by GEP will not change enrollment or treatment, COO by GEP will be an integrated marker. Remaining tissue will be used for the subsequent exploratory biomarkers and banked for additional studies for the future.
- In order to ensure for the minimum participant requirement for non-GCB ARL, if after enrollment of 20 and 30 participants on trial, there are <50% non-GCB, non-GCB COO (as determined at individual AMC site) will be the preferentially enrolled to meet the minimum number of participants required in the trial (22 non-GCB participants).

2.4 Correlative Studies

Integral Biomarker

2.4.1 IHC for COO

We hypothesize that COO by IHC and GEP will differ and help determine whether either or both could have identified those patients who might benefit from the addition of ibrutinib to their treatment regimen.

COO is traditionally defined by IHC. IHC for COO is also helpful for upfront analysis because it can be done rapidly in the context of a pathologic diagnosis. At this time, it is not known whether in HIV-positive patients there is a difference in BTK dependency among the DLBCL COO subtypes. In AIDS, GC DLBCL are more common, so COO assessment by IHC will provide rapid decision-making to make sure that sufficient patients with non-GC DLBCL are enrolled; IHC will be used to ensure a minimum number of non-GC cases (15 centrally confirmed non-GC DLBCL). In addition, this study will give us an opportunity to obtain GEP on each tumor sample, in addition to IHC, for assessment of GCB and non-GCB classification. GCB and non-GCB subgroups have different pathologies and treatment outcomes. By obtaining COO with GEP, this will allow us to assess the concordance among of GEP to IHC, and to correlate biology with treatment response rates and survival.

Ibrutinib may be an important factor in HIV-positive lymphomas. Retrospectively, after closure of the trial, the Lymph2Cx results on the pre-treatment biopsy will be compared to Hans IHC results. The Hans method for IHC classification for COO, which has been used as a surrogate for gene expression profiling in multiple studies, and is the most accepted immunohistochemical method for subclassification. This relies on assessing expression of CD10, BCL6 and MUM1/IRF4. Cases classified as GC will be those with CD10 expression in more than 30% of tumor cells and also those that are CD10-, BCL6+, MUM1/IRF4 -. All others will be classified as non-GC. While not as accurate as gene expression profiling (through microarray technology or RNA sequencing), it can be achieved within two days of receipt of the specimen, and requires standard diagnostic material. Nanostring (Lymph2CX) is an alternative classification method (Section 2.4.2), which has better concordance with gene expression data than immunohistochemistry.

IHC for COO (i.e., staining for CD10, BCL6 and IRF4) is used routinely in Dr. Cesarman's lab using standard FFPE sections. If there is a technical failure, the assay will be repeated. The main reason for repeated technical failure is poor preservation/fixation. Another source of possible failure is if the specimen received is not diagnostic, i.e., does not have DLBCL. If this occurs, it is unlikely that other methods would succeed, and a repeat biopsy will be recommended, and if not possible, participants would be replaced on the trial.

IHC is a highly reproducible method. The AMC Pathology Core Lab at Weill Cornell Medical College is approved to perform IHC by all major compliance agencies, including CLIA, NY State and CAP. Reproducibility and accuracy are parameters assessed by these agencies. There are in-built positive and negative controls in the specimens, as there are positive and negative normal infiltrating cells within the vast majority of diagnostic DLBCL specimens. In addition, the lab includes positive (lymphoma) and negative control (tonsil) sections with every antibody run. Scoring will be done by microscopic visualization by a hematopathologist.

Dr. Cesarman's laboratory is one of the largest in the country and among the first to perform immunohistochemistry for the diagnosis of lymphomas, back in the 80s. Currently six faculty members, which are board certified hematopathologists, are

part of this group. The lead hematopathologist evaluating the slides and reporting the results will be Dr. Amy Chadburn, who has approximately 30 years of experience with IHC for lymphoma diagnosis and classification.

The pathology laboratory at the specific site the participant is enrolled at will perform the IHC assays. The IHC will be reviewed and confirmed at the AMC Pathology Core Lab at Weill Cornell Medical College. When specific IHCs are not available, the IHC will be performed at the AMC Pathology Core Lab at Weill Cornell Medical College. If the study is done on site, slides will be sent to Weill Cornell for confirmation and centralized review.

Integrated Biomarkers

2.4.2 GEP for COO

We hypothesize that COO by IHC and GEP will differ and help determine whether either or both could have identified those patients who might benefit from the addition of ibrutinib to their treatment regimen.

This assay provides molecular COO subtyping of DLBCL into GCB, ABC, and unclassifiable subtypes, which have different biological features such as gene expression, mutation profiles, signal pathway activation, and prognosis. A phase II study of DLBCL in HIV-negative patients demonstrated improved outcome when ibrutinib (which targets the B cell receptor signaling pathway that is upregulated in the ABC subtype) was added to R-CHOP for treatment of patients with the non-GCB subtype.[19] Retrospectively, after closure of the proposed trial, the Lymph2Cx results on the pre-treatment biopsy will be compared to Hans IHC results.

In a phase I/II clinical trial performed at the NCI, N=80 patients with relapsed or refractory DLBCL, ibrutinib produced complete or partial responses in 37% (14/38) of those with ABC DLBCL, but in only 5% (1/20) of subjects with GCB DLBCL (P = 0.0106).[46] COO subtyping for this study was performed using Affymetrix platform and a data analysis algorithm that is no longer in research or clinical use. Lymph2Cx has been applied to 2 different population based patient cohorts of 119 and 344 patients respectively,[47] however, not yet reported in clinical trials. As of February 2017, a retrospective analysis of 221 patients treated on the GELA trial, LNH2003, is under review, but not yet published. The ECOG phase II 1412 trial and the Celgene ROBUST phase III trial, also using the Lymph2Cx assay, are not yet complete.

The Lymph2Cx assay that will be used in this clinical trial is exactly comparable to the published studies. Concordance studies with 30 cases showed 100% agreement between the original result from the publication and results in the Molecular Diagnostics of Arizona Laboratory.[47] We have standardized operating procedures, controls, and a completely locked algorithm. The original reports of the 2 subtypes of DLBCL were based on gene expression profiling of snap frozen tissues, which was a purely research methodology. Shortly thereafter, for practical reasons, an IHC assay was developed called the “Hans algorithm,”[48] which was approximately 83% accurate compared to the original gene expression method. Subsequently, numerous IHC and other molecular methods were developed. An

extensive meta-analysis and review concluded that the molecular methods were more accurate.[49] Subsequently, our research consortium undertook to test several molecular methods resulting in development of the Lymph2Cx assay on the nCounter platform by Nanostring, which uses formalin-fixed paraffin embedded tissues.[47] This assay is now going through commercial development to become an FDA-cleared test. "Lymph2Cx" is the original published, academic, name of the assay from the LLMPP research consortium. At this time, the commercial prototype of Lymph2Cx is under development by Nanostring and is generally referred to as the "Lymphoma Subtyping Test" or "LST" until such time as the product is officially through the FDA clearance process and formally named by the company. The Lymph2Cx is the only DLBCL cell-of-origin assay at such an advanced stage of development. Due to ease of implementation, IHC assays continue to be used in the clinical setting at this time. However, a recent study of 218 cases demonstrated that using 9 different popular IHC staining algorithms, only 4% of tumors were misclassified as GCB but 21% as ABC/non-GCB by all IHC methods.[50] This is compared to the 98% concordance between different laboratories using the Lymph2Cx assay.[47] For these reasons we chose the Lymph2Cx assay as the molecular method of choice.

Archived paraffin blocks were used for the initial development and publications of the Lymph2Cx assay, and were up to 20 years old. To avoid potentially degraded tissue, the protocol first requires cutting a 10-micron thick section off the surface of the block before cutting the deeper tissue sections used for analysis. Fresh versus 14-day old unstained tissue sections, at ambient temperature, were compared and yielded the same results on 5 samples indicating a 2-week time lag between cutting the samples and initiating testing is acceptable. The accuracy of the Lymph2Cx assay using paraffin embedded tissue biopsies and the nCounter instrument was first compared against the gold standard (frozen tissue, Affymetrix gene expression profiling) in the prior publication from our research consortium and demonstrated an accuracy of 98%.[47] Subsequently, we evaluated the performance of the Lymph2Cx assay in our own laboratory and showed a perfect 30/30 (100%) concordance with the prior results. Reproducibility between 2 different technical staff members, pathologists, and instruments was 100% for 9 samples repeated 2 weeks apart. Precision was assessed by repeating 5 cases on 3 different occasions, with 100% concordance. Dilutional studies demonstrated that 400ng was the minimal reliable input for the assay. The different substances, including all reagents used in the assay, were tested and demonstrated no interference.

An important pre-analytical variable is percentage of tumor, which should be a minimum of 60% based on a second dilutional study demonstrating that 60% and 50% gave reliable results, but that 40%, 30%, and 20% did not. To be conservative, 60% was chosen to allow for slight variability in tumor content estimates and different cuts off of the block. To address the tumor percent, an H&E stained section of each case will be assessed by Dr. Rimsza, who will estimate tumor purity. If needed, macro-dissection of the tissue sections will be performed to increase tumor content. Input is 1 x 10-micron thick section for a 1cmX1cm biopsy. For smaller biopsies, proportionally more sections will be taken, and if more than 2 sections are required, macrodissection will be utilized to remove excess paraffin.

Dr. Rimsza will measure the size of the tumor area and determined the number of needed sections at the same time that she determines the tumor content. A Pathology Quality Assurance form is used to document the tissue input specifics (size/number of needed sections and percent tumor). At this time, only formalin fixed biopsies (not other fixatives) have been assessed. The Pathology reports on the biopsies will be reviewed to determine whether formalin or another fixative was used. The average raw count of the housekeeping genes in the assay is used as a final quality control marker – samples with <20 counts for this metric are reported as "Poor Quality." The materials for this study will be analyzed in the exact same manner as the samples in the clinical laboratory that are tested for medical care. A positive and negative control and up to ten samples can be included in each 12-well cassette. Positive controls include a mixture of oligonucleotides which hybridize with all probes in the assay. These were pre-mixed by the manufacturer, lyophilized, and reconstituted into stock solutions. The negative control is a well in the cassette that includes all reagents and probes, but no RNA. Scoring is not applicable in this assay.

The lab performing this assay is Molecular Diagnostics – Arizona Laboratory, Mayo Clinic Arizona, CLIA #03D2113087; Medical Director: Dr. Lisa Rimsza; Performing technologist: Colleen Ramsower, MB(ASCP) and Tameson Yip, MB(ASCP). "MB" indicates these staff members are certified in molecular biology by the American Society of Clinical Pathologists. Testing for the proposed trial will follow the exact same procedures as are used for the samples in the clinical laboratory. Dr. Rimsza has extensive experience with the assay, which is actively testing Mayo Clinic patients for clinical use. She is the senior author on the initial publication, co-author on 2 additional publications, co-inventor on the assay patent, and is the Medical Director of a CAP-CLIA certified laboratory performing the assay. This is the first clinical laboratory in the country to offer the test for patient care. She both directs the laboratory and signs the medical results cases.

Circulating Tumor DNA

2.4.3 Circulating tumor DNA – cancer mutations

NextGen Sequencing of circulating tumor DNA to identify residual tumors on the basis of oncogene mutations will be performed at an AMC Core Laboratory.. This is a feasibility study that relies on commercial assays. This is an early study for ctDNA and is designed to test the logistics, infrastructure, and assay performance for potentially CD4 lymphocyte -depleted, HIV+ samples.

The statistical analysis will be descriptive in nature, describing the number of single nucleotide variations (SNV) identified at each sample collection time point and whether the type of mutation or frequency in blood changes over the course of treatment.

Circulating tumor DNA – B cell receptor clonality

NextGen Sequencing for BCR rearrangement using LymphoTrack technology will also be performed in an AMC Core Laboratory at Johns Hopkins. This study relies on newly developed procedures. The statistical analysis will also be descriptive in nature.

Exploratory Biomarkers

2.4.4 BTK IHC

It has been well documented that the primary target of ibrutinib is BTK, which is involved in B cell receptor signaling in lymphoma, so expression of BTK will be used to determine if the relevant drug target is expressed and if lack of response is due to lack of BTK expression. Currently, there are little data of BTK expression in ARL. We hypothesize that there will be more specimens lacking BTK expression in participants with poorer response to therapy. If this is the case, future treatment can be designed to use ibrutinib only participants whose ARL expresses BTK.

In addition to BTK IHC, we will also be performing phosphorylated expression of BTK in pre-treatment biopsies. In some experimental systems, it has been shown that phosphorylated BTK (pBTK) correlates with cytotoxic sensitivity to ibrutinib, though it has not been clearly shown that total or phosphorylated expression of BTK in pre-treatment biopsies predicts response to therapy. However, this has not been done in the context of ARLs, where there is evidence that some lymphomas, such as PEL lack BTK expression and cell lines are resistant to ibrutinib.[21] Preclinical and some clinical studies have used Western blotting or flow cytometry to study activation of BTK pre-and post-treatment. However, in the context of this trial, tumor material is only in the form of formalin-fixed, paraffin embedded tissue sections. Therefore, IHC is the only possible method to assess expression of BTK and pBTK in ARL. One recent study that used this method, reporting that approximately 65% of DLBCLs express BTK, and showed that BTK expression together with high expression of MYC or BCL2 is a poor prognostic indicator (Han et al Anticancer Res 2021). If BTK is not expressed, our expectation is that these tumors would not respond to Ibrutinib, but to our knowledge this has not been explored in the context of a clinical trial

Antibodies are available that have been shown to work in FFPE tissue sections for BTK and pBTK. Dr. Cesarman's laboratory has extensive experience in IHC. If interpretation by visual examination is difficult because of a range of intensities, image analysis will be used for quantitative analysis, as exemplified in other publication from our group.[22] The antibody validated for use in FFPE tissues (anti-BTK antibody ab25971) from Abcam and Anti-BTK Antibody (phospho-Tyr551) from Thermo-Fisher will be used. There is potential variability with regard to staining intensity based of tissue fixation and processing procedures, which will be done at different pathology departments from the various AMC sites, however problems scoring as positive or negative are not expected, in the context of good controls (tonsil tissue will be used, and this has positive and negative cells and a very specific cytoplasmic expression pattern can be seen with scattered bright positive cells in the germinal center, and a more diffuse but positive pattern in the mantle zones). If quantification is difficult in specific cases, these will be excluded from quantitative analyses.

Scoring will be done by microscopic visualization and interpretation by two hematopathologists and for quantification, slides scanning and image analysis using HALO. If difficulties with any given antibody, others commercially available (there

are several clones/vendors that carry BTK antibodies) will be tested. Dr. Chadburn and Dr. Cesarman will be interpreting the results and supervising the assay. They both have more than 20 years of experience with IHC of lymphoma. The laboratory conducting the assay is the Immunopathology Laboratory at Weill Cornell Medical College, which is a well-established, high volume laboratory. This laboratory is an AMC Central Lab.

2.4.5 EBER-ISH

Approximately 20% of ARL cases will be EBV positive. This method will be used to determine if the ARL is EBV positive. This will be important to assess if the presence of this virus affects response to therapy at the tumor level concurrently with the blood EBV levels. At this time, there is little information regarding BTK expression in a large series of EBV positive lymphomas, and their response to ibrutinib. We hypothesize that some EBV positive lymphomas will lack BTK expression and that in these, ibrutinib will not provide a therapeutic advantage.

There are numerous studies showing that EBV proteins LMP1 and LMP2 can activate NF-kB, and this signaling may bypass the need for BCR signaling. For example, many EBV-positive lymphoma cell lines are resistant to dasatinib.[23] There are no clinical studies assessing sensitivity of EBV positive ARL to ibrutinib. EBER ISH is a well-established method for EBV detection in FFPE sections. It is routinely used clinically, and has well known performance characteristics. We will use a known EBV positive lymphoma specimen as a positive control. The majority of cells are EBV negative, so a negative control is available in the same section. To score, there will be microscopic visualization and interpretation by two hematopathologists. Positive cases are those in which atypical lymphoma cells are EBER-positive. A few positive cells within a lymph node, which do not correspond to the lymphoma cells, will be interpreted as negative, since these are seen in many lymphoid specimens from individuals carrying latent EBV.

Dr. Chadburn and Dr. Cesarman will be interpreting the results and supervising the assay. They pathologists have more than 20 years of experience with IHC of lymphoma. The laboratory conducting the assay is the Immunopathology Laboratory at Weill Cornell Medical College, which is a well-established, high volume laboratory. This laboratory is an AMC Central Lab.

2.4.6 Blood cytokines

Elevated serum levels of these cytokines (IL-6, IL10, IP10/CXCL10, and BCA1/CXCL13) are known to be produced by T helper cells and/or activated B cells, and are elevated in those HIV+ persons who develop NHL.[24-27] Additionally, some of these cytokines were seen to predict response to treatment for persons with AIDS-NHL in the AMC-034 study.[28] Similarly, serum levels of the soluble receptors that will be quantified in serum (sIL2R, sCD30, sTNFR2, and sCD14) have been associated with the development of AIDS-NHL in recent preliminary studies (Hussain, Epeldegui and Martinez-Maza, unpublished results).[27,29] Therefore, defining the effect of ibrutinib treatment on the serum levels of these cytokines and soluble receptors is expected to be informative. We hypothesize that: 1) pre-treatment initiation serum levels of these molecules (IL-6, IL10, CXCL10,

CXCL13, sIL2R, sCD30, sTNFR2, and sCD14) will predict response to therapy, and 2) that treatment will lead to decreased levels of these molecules.

Several cohort-based studies of the molecular epidemiology of AIDS-NHL have shown that levels of these molecules are elevated prior to the development of these cancers.[24-27,29-32] Additionally, studies in a murine model of AIDS-NHL, using SCID mice implanted with an AIDS-Burkitt lymphoma line (2F7) showed that tumor growth was associated with a marked increase in CXCL13 levels.[33] In the same murine/human AIDS-NHL model, IL-6, CXCL10 and IL-10 also were seen to be elevated in animals bearing tumors, when compared to controls (Widney and Martinez-Maza, unpublished results).

A recently published study of cytokines and immune activation biomarkers in AIDS-related non-Hodgkin lymphoma treated with rituximab plus infusional EPOCH showed that CXCL13, IL-6 and IL-10 serum levels were associated with response to therapy.[28]

These molecules will be quantified using a multiplexed immunometric assay system (Luminex platform), using assay reagents that are commercially available from R&D Systems. These are the same assays that have been used in several recent published studies, in which it was seen that these molecules are detectable in the great majority of persons,[24,34-36] and also, that most of these molecules (sCD14, sIL-2R, sTNFR2, CXCL13, IL-6, IL-10) showed high temporal stability.[36]

The assay technology was chosen for several reasons: 1) The assays to be used are multiplexed immunometric assays, which are technically robust and repeatable, and require only a small serum/plasma volume, 2) The assays will be obtained from a highly-respected manufacturer (R&D Systems) and are commercially-available, so any investigator can utilize these same assays in future studies, enhancing the reproducibility of this work, and 3) These assays and molecules have been proven to be temporally stable over time in healthy populations,[36] and to be markedly-upregulated in persons who have AIDS-related lymphoma.[24-27] These markers have been studies in many studies by us in the past, and have always been readily detectable in frozen serum/plasma.[24-27,34] Additionally, we know from unpublished pilot studies that several of these molecules are stable and do not degrade rapidly (biochemical stability) when blood is collected under standard conditions, and is processed within a reasonable amount of time (Martinez-Maza, unpublished observations).

The technical performance characteristics of the assays to be used have been reported previously, in a publication aimed at defining these parameters, as well as temporal stability (how much these markers vary over an extended period of time in healthy persons).[36] The major sources of variability are driven by poor blood collection techniques and processing. Therefore, given that blood will be collected and processed using a standard protocol, these sources of variation should be minimized in this study. Positive and negative laboratory controls will be added to all assay plates. Positive controls will be archival human serum known to have elevated levels of these cytokines, as well as lower, but detectable levels, from prior work. Negative controls will include assay wells to which no human serum was

added. Results will be presented in picograms per milliliter – no scoring system will be used.

These studies will be done at the AMC Biomarkers Core Lab at UCLA (Martinez-Maza, PI). The laboratory that will do these assays has extensive published experience assessing cytokines and other immune activation biomarkers using the proposed immunometric assay technology.[24-45]

2.4.7 Chemotherapy pharmacokinetics

There is a potential for a drug interaction between ibrutinib and the components of EPOCH. Ibrutinib is primarily metabolized by CYP3A4 with additional contribution by CYP2D6.[51] Ibrutinib is a sensitive substrate whose exposure is altered when administered with CYP3A4 inhibitors (~24-29-fold increase in exposure) and inducers (~10-13 fold decrease in exposure).[51] In order to minimize variability in ibrutinib exposure, we have opted to only enroll participants on non-CYP3A4-interacting antiretroviral regimens rather than creating separate cohorts for the CYP3A4-inducers and inhibitors. Ibrutinib has a low propensity to inhibit CYP450s *in vivo* but has a potential to inhibit ABCB1, for which doxorubicin, etoposide, and vincristine are all substrates. Inhibition of ABCB1 may lead to increased concentrations of ABCB1 substrates which may cause myelosuppression. R-EPOCH consists of infusional rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin in combination with recombinant human granulocyte colony-stimulating factor (GCSF). The components of EPOCH are, at most, weak inhibitors of CYP3A4 and unlikely to cause significant alterations to ibrutinib in the clinically relevant range utilized in this study.[12] Since ibrutinib exposure is highly variable but proportional to dose over the dose range proposed in this study (% CV for AUC is ~75%), we will assess ibrutinib PK to correlate with other pharmacodynamics endpoints (laboratory, toxicity, and efficacy). Given that we do not anticipate a clinically significant drug-drug interaction via the CYP3A4 pathway, we will propose trough level monitoring to provide an assessment of exposure for ibrutinib as was performed by the company in their NDA to the FDA. Ibrutinib trough levels collected at Days 1, 8, 15, and 22 of Cycle 1 were utilized successfully for exposure-response analyses (section 2.2.4 of the FDA Clinical Pharmacology review; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf). We plan to incorporate the expansion to a full PK profile for ibrutinib if toxicities are frequent and severe with the combination. We will propose a limited sampling schema for doxorubicin, etoposide, and vincristine to assess whether ABCB1 inhibition by ibrutinib is clinically significant. We will obtain PKs only on participants at the MTD.

We hypothesize that no pharmacokinetic-based drug-drug interaction will occur between ibrutinib and R-EPOCH since the trial is only enrolling non-CYP3A4 modulating antiretrovirals. However, we hypothesize that ibrutinib will inhibit ABCB1, which will not alter the systemic pharmacokinetics of doxorubicin, etoposide, and vincristine but may cause increased myelosuppression.

In AMC-061, a lower sunitinib dose resulted in equivalent drug exposure but

increased neutropenia in the ritonavir-containing ARV cohort compared to other regimens.[14] Sunitinib is a CYP3A4 and ABCB1 substrate[52] while ritonavir is a potent inhibitor of both CYP3A4 and ABCB1.[53]

The resulting data will be able to be compared with existing data. Since the drug combination being explored in this clinical trial is different, one cannot predict if the same effect will be observed.

Liquid chromatography with tandem mass spectrometry is the gold-standard for drug quantitation. The Analytical Pharmacology Core Lab already has developed and validated separate analytical methods for doxorubicin, etoposide, and vincristine. For etoposide and vincristine, plasma containing EDTA is the matrix that has been validated in the Analytical Pharmacology Core Lab. For doxorubicin, heparinized plasma is the matrix that has been validated in the AMC Pharmacology Core Lab at Johns Hopkins University.

2.4.7.1 Bioanalytical method for determining vincristine sulfate

This is for an integrated assay aimed at assessing drug exposure in participants on the clinical trial. The bioanalytical method for determining vincristine in human plasma with the anticoagulant dipotassium ethylenediaminetetraacetic acid (K2EDTA), was developed utilizing liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) in the Analytical Pharmacology Core Laboratory the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, under the direction of Michelle A. Rudek, PharmD, PhD. The analytical method was validated as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (http://www.fda.gov.cder/-guidance/index.htm).

Plasma samples (1000 µL) were prepared for analysis by liquid-liquid extraction with 2 mL of extraction solution (2 ng/mL of internal standard in 100% MeOH). The mixture was vortex-mixed for 30 seconds then centrifuged (913 x g, 10 min). A 1.5 mL aliquot of the supernatant was collected and transferred into a borosilicate glass tube, and then 4 mL of n-Butyl chloride was added into it. The mixture was vortex-mixed for 10 seconds then centrifuged (1430 x g, 10 min). A 3.0 mL aliquot of the supernatant was collected and transferred into a borosilicate glass tube. The mixture was evaporated under a gentle nitrogen flow at 40°C until completely dry. To the residue, 100 µL of MeOH/water (40:60, v/v) was pipetted into each tube. The tubes were then vortex-mixed for 30 seconds, and then the final sample solution was transferred into autosampler vials. A 20 µL aliquot of the final sample solution was loaded onto a Waters Atlantis C18 HPLC column (100 mm x 2.1 mm i.d., 3 µm) and separated by isocratic elution using a pre-mixed mobile phase composed of 0.1% (v/v) formic acid in 2 mM of ammonium acetate in water: 100% MeOH (57:43, v/v), delivered at 0.25 mL/min. A triple quadrupole mass spectrometer with a positive electrospray ionization interface was operated in the selected-ion monitoring mode to detect the m/z 413.3→362.4 and m/z 397.3→376.2, transitions for vincristine and internal standard, respectively.

Summary information taken from the assay validation performed by the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins is detailed below. Carryover was effectively eliminated by washing the autosampler injection needle with a solution of MeOH/water (60:40, v/v) between injections. There was no cross interference between the analytes and internal standard. Peaks that interfered with the detection of the vincristine or the internal standard were not evident in extracted ion chromatograms of plasma from multiple anonymous normal human donors. Calibration curves were quadratic at concentrations ranging from the 0.2 ng/mL lower limit of quantitation to 50 ng/mL. The validation studies demonstrated acceptable within-day and between-day accuracy and precision. See details from Calibrator and QC assessment tables below. Samples with concentrations exceeding the upper limit of quantitation can be diluted up to 10-fold using drug-free human plasma while maintaining precision and accuracy. Based on the validation performed by Damen et. al., vincristine was stable in plasma for at least three freeze/thaw cycles at -20°C and -70°C. Furthermore, vincristine was stable up to 23 days in the final extract at nominally 2-8°C. Vincristine was stable in plasma up to 7 months at -20°C and -70°C. Stock solution of vincristine was stable up to 10 months when stored at -20°C.

Table 2-A: Calibrator assessment, vincristine sulfate

Analyte	Accuracy	Within-day Precision	Between-day Precision
Vincristine	92.53 –110.83%	1.58 – 13.52%	*** – 2.59%

***If Model Mean Square < Error Mean Square (Between-Run Precision with "No additional variation result of performing assay in different runs.")

Table 2-B: QC assessment, vincristine sulfate

Analyte	Accuracy	Within-day Precision	Between-day Precision
Vincristine	93.17 – 107.13%	2.72 – 6.98%	*** – 7.84%

***If Model Mean Square < Error Mean Square (Between-Run Precision with "No additional variation result of performing assay in different runs.")

2.4.7.2 Bioanalytical method for determining etoposide and its metabolite, 3'-O-desmethyl etoposide

This is for an integrated assay aimed at assessing drug exposure in participants on the clinical trial. The bioanalytical method for determining etoposide and its metabolite, 3'-O-desmethyl etoposide, in human plasma

with the anticoagulant dipotassium ethylenediaminetetraacetic acid (K2EDTA), was developed utilizing liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) in the Analytical Pharmacology Core Laboratory the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, under the direction of Michelle A. Rudek, Pharm.D., Ph.D. The analytical method was validated as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (http://www.fda.gov.cder/-guidance/index.htm).

Plasma samples (100 µL) are prepared for analysis by liquid-liquid extraction with a solution of 50 mM of L-Ascorbic Acid in water (40 µL), then 1 mL of extraction solution with (0.1 µg/mL of internal standard in 100% ethyl acetate). The mixture was vortex-mixed for 30 seconds, and then centrifuged (1430 x g, 10 min). A 950 µL aliquot of the supernatant was collected and transferred into a borosilicate glass tube. The mixture was evaporated under a gentle nitrogen flow at 35°C until completely dry. To the residue, 100 µL of acetonitrile/water (50:50, v/v) was pipetted into each tube. The tubes were vortex-mixed for 30 seconds, and then the final sample solution was transferred into autosampler vials. A 10 µL aliquot of the final sample solution was loaded onto a Waters Atlantis C18 HPLC column (100 mm x 2.1 mm i.d., 3 µm) and separated by isocratic elution using a binary mobile phase composed of 0.1% (v/v) formic acid in 100% of acetonitrile (A1) and 0.1% (v/v) formic acid in water (B1) (45% A1: 55% B1, v/v) delivered at 0.3 mL/min. A triple quadrupole mass spectrometer with a positive electrospray ionization interface was operated in the selected-ion monitoring mode to detect the m/z 589.6→228.9 and m/z 575.3→228.8, and m/z 657.2→383.0, transitions for etoposide, 3'-O-desmethyl etoposide and internal standard, respectively.

Summary information taken from the assay validation performed by the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins is detailed below. Carryover was effectively eliminated by washing the autosampler injection needle with a solution of acetonitrile/water (50:50, v/v) between injections. There was no cross interference between the analytes and internal standard. Peaks that interfered with the detection of the etoposide, 3'-O-desmethyl etoposide or the internal standard were not evident in extracted ion chromatograms of plasma from multiple anonymous normal human donors. Calibration curves were linear at concentrations ranging from the 5 ng/mL lower limit of quantitation to 5,000 ng/mL. The validation studies demonstrated acceptable within-day and between-day accuracy and precision. See details from Calibrator and QC assessment tables below. Samples with concentrations exceeding the upper limit of quantitation can be diluted up to 10-fold using drug-free human plasma while maintaining precision and accuracy. Long-term stability for etoposide and 3'-O-desmethyl etoposide in stock upon storage at -20°C was demonstrated for up to 80 days. Long-term stability for etoposide and 3'-O-desmethyl etoposide in human plasma upon storage at -70°C is ongoing.

Table 2-C: Calibrator assessment, etoposide

Analyte	Accuracy	Within-day Precision	Between-day Precision
Etoposide	91.47 –110.43%	1.67– 9.33%	*** – 1.81%
3'-O-desmethyl etoposide	95.82 – 105.87%	4.48 – 10.72%	*** for all

***If Model Mean Square < Error Mean Square (Between-Run Precision with "No additional variation result of performing assay in different runs.")

Table 2-D: QC assessment, etoposide

Analyte	Accuracy	Within-day Precision	Between-day Precision
Etoposide	98.43 – 114.83%	2.81– 7.40%	*** – 9.96%
3'-O-desmethyl etoposide	99.95 – 102.84%	4.03 – 8.20%	*** – 9.49%

***If Model Mean Square < Error Mean Square (Between-Run Precision with "No additional variation result of performing assay in different runs.")

2.4.7.3 Bioanalytical method for determining doxorubicin and its metabolite, doxorubicinol

This is for an integrated assay aimed at assessing drug exposure in participants on the clinical trial. The bioanalytical method for determining doxorubicin and doxorubicinol in human plasma with the anticoagulant heparin was developed utilizing liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) in the Analytical Pharmacology Core Laboratory the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, under the direction of Michelle A. Rudek, Pharm.D., Ph.D. The analytical method was validated as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (http://www.fda.gov.cder/-guidance/index.htm).

Plasma samples (100 µL) were prepared for analysis by liquid-liquid extraction with 4 mL of extraction solution (60 nM of internal standard in a solution of 2-Propanol: CHCl3 (20:80, v/v)). The mixture was shaken at high speed for 10 min, and then centrifuged (1430 x g, 10 min). The top layer was discarded, and the bottom layer was transferred into a borosilicate glass tube. The mixture was evaporated under a gentle nitrogen flow at 40°C until completely dry. To the residue, 100 µL of acetontrile/water (50:50, v/v) was added into each tube. The tubes were then vortex-mixed and sonicate for 5 min, and then the final sample solution was transferred into autosampler vials. A 5 µL aliquot of the final sample solution was loaded onto a Waters Atlantis RP18 HPLC column (150 mm x 2.1 mm i.d., 3.5 µm) and separated by isocratic elution using a binary mobile phase composed of 0.1% (v/v) formic acid in 100% of acetonitrile (A1) and 0.1% (v/v) formic

acid in water (B1) (60% A1: 40% B1, v/v) delivered at 0.20 mL/min. A triple quadrupole mass spectrometer with a positive electrospray ionization interface was operated in the selected-ion monitoring mode to detect the m/z 544.3→397.1, m/z 546.3→399.2, and m/z 854.5→286.3 transitions for doxorubicin, doxorubicinol and internal standard, respectively.

Summary information taken from the assay validation performed by the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins is detailed below. Carryover was effectively eliminated by washing the autosampler injection needle with a solution of acetonitrile/water (50:50, v/v) between injections. There was no cross interference between the analytes and internal standard. Peaks that interfered with the detection of the doxorubicin, doxorubicinol or the internal standard were not evident in extracted ion chromatograms of plasma from multiple anonymous normal human donors. Calibration curves were linear at concentrations ranging from the 10 nM lower limit of quantitation to 2000 nM. The validation studies demonstrated acceptable within-day and between-day accuracy and precision. See details from Calibrator and QC assessment tables below. Samples with concentrations exceeding the upper limit of quantitation can be diluted up to 10-fold using drug-free human plasma while maintaining precision and accuracy. Long-term stability for doxorubicin and doxorubicinol in stock upon storage at -20°C were demonstrated for up to 75 days.

Table 2-E: Calibrator assessment, doxorubicin and doxorubicinol

Analyte	Accuracy	Within-day Precision	Between-day Precision
Doxorubicin	96.73 –106.07%	4.15 – 10.26%	*** – 5.20%
Doxorubicinol	97.00 – 104.10%	6.36 – 11.29%	*** – 2.47%

Table 2-F: QC assessment, doxorubicin and doxorubicinol

Analyte	Accuracy	Within-day Precision	Between-day Precision
Doxorubicin	94.79 – 106.42%	3.98 – 5.36%	1.73 – 7.61%
Doxorubicinol	94.25 – 105.46%	3.30 – 5.88%	1.70 – 7.23%

***If Model Mean Square < Error Mean Square (Between-Run Precision with "No additional variation result of performing assay in different runs.")

2.4.8 EBV viral load

A distinctive feature of aggressive HIV-NHLs is their high association with gamma herpesviruses such as Epstein-Barr virus (EBV). These viruses play important oncogenic roles and their intrinsic presence in the tumors may represent potential therapeutic targets.[60,61] EBV-associated HIV-NHL includes the majority of immunoblastic DLBCL variants, primary effusion lymphoma (PEL), plasmablastic lymphoma (PBL), and about 30-60% of Burkitt lymphoma (BL). EBV DNA can be a tumor marker in these lymphomas. In post-transplant lymphoma, nasopharyngeal carcinoma, Hodgkin lymphoma, and nasal lymphoma there are data to suggest that clearance of viral DNA is associated with response to therapy.[62-65]

EBV-positive DLBCL has EBV-mediated oncogenic signaling pathway activation, and these multiple intracellular pathways can be potential therapeutic targets in this disorder. Thus, EBV-associated protein, LMP1 can induce the activation of various downstream pathway molecules such as PI3K/Akt and NF-kB activation. The activation of NF-kB is one of essential factors contributing to prolonged survival and aggressive phenotype of DLBCL. In a more aggressive subtype of diffuse large B-cell lymphoma, activated B-cell like type, chronic active B-cell receptor signaling and MYD88 mutation are known to stimulate NF-kB transcription and activation. As a result, a key molecule mediating B-cell receptor signaling pathway, BTK can have a critical role, and BTK has been emerging as a therapeutic target in DLBCL. Considering the close association between B-cell receptor signaling pathway and PI3K/Akt pathway in DLBCL targeting BTK might be helpful for improving treatment outcome of EBV-positive DLBCL. We hypothesize that the addition of ibrutinib with R-da-EPOCH will affect the EBV viral load and reactivation in positive tumors. We anticipate that participants who fail to clear EBV viral DNA will also fail to achieve sustained CR. Descriptive statistics such as frequencies and percentages will be used to aid in the evaluation of EBV gene expression patterns (associations) in positive tumors banked at baseline.

The PCR methods used for EBV DNA are all quite similar and involve use of a standard. Two standards are widely used and are comparable. One involves use of a Burkitt cell line (Namalwa) that is unusual in that the EBV is integrated and does not replicate as virus. The total amount of cell DNA thus yields an estimate of the total viral DNA. By targeting the large internal repeat region of the virus, the sensitivity of the assay is increased. Positive controls are DNA extracted from an EBV(+) Burkitt cell line. Negative controls are DNA from an EBV(-) cell line. Viral DNA is quantitated as copies/ml plasma. This PCR methodology was selected because this is a standard viral DNA assay. The particular method for this study has been used in many other cooperative group studies.[64] This PCR method has also been validated against a commercial B95.8 DNA standard.

Blood will be mailed at ambient temperature and separated into plasma and cells at the receiving lab. Variability is minimized by following a standard operating procedure. Technicians assaying specimens are supervised and certified before handling study specimens. GLP are followed.

The Ambinder laboratory at Johns Hopkins will be performing this particular correlative study. They have ample experience with this assay, and they have performed the same assay for other AMC studies. The assay has also been used in for the Eastern Cooperative Oncology Group (ECOG) Hodgkin studies, and the Children's Oncology Group Hodgkin studies.

2.4.9 Ibrutinib pharmacokinetics

Potential drug interactions will be taken into account in this study. In cancer patients, ibrutinib exposure is variable but proportional to dose over the dose range proposed in this LOI (% CV for AUC is ~75%).[51] Ibrutinib is primarily metabolized by CYP3A4 with additional contribution by CYP2D6.[51] Ibrutinib has a low propensity to inhibit CYP450s *in vivo,* but may inhibit ABCB1 at clinically relevant concentrations.[51] However, ibrutinib is a sensitive substrate whose exposure is altered when administered with CYP3A4 inhibitors (~24-29-fold increase in exposure) and inducers (~10-13 fold decrease in exposure).[51] For this study, we have opted to only enroll participants on non-CYP450-interacting antiretroviral regimens to minimize variability in ibrutinib exposure.

PK sampling studies are proposed for all participants on the study, with evaluations to be obtained prior to the initiation of treatment, and then pre-treatment on Cycle 1 Day 8. If significant toxicity (defined as a DLT, see Section 4.2) is observed, an expanded profile, Day 8 at 0.5, 1, 2, 4, 6, 8, and 24 hours (Day 9) after ibrutinib, will be obtained. In discussions with Pharmacyclics, the specific assay and assay methods, performance, and operating characteristics information for ibrutinib PK is proprietary information and has not been published. Therefore, this information is confidential. However, in general, the pharmacokinetics of ibrutinib will be performed at Frontage Laboratories and managed through Pharmacyclics.

2.4.10 BTK occupancy/ITK occupancy

BTK occupancy will be measured in this trial to determine the pharmacodynamics of ibrutinib in HIV patients with ARL. However, in conjunction with BTK occupancy, inducible T-cell kinase (ITK) occupancy will also be performed, which is the more interesting aspect to this specific HIV population.

Ibrutinib may have intriguing and provocative off targets effects, which may improve the control of HIV. Ibrutinib may have inhibitory effects on HIV viral replication and spread. In addition to inhibition of BTK, ibrutinib is known to inhibit ITK. ITK is a Tec family tyrosine kinase that regulates T cell receptor (TCR)-induced activation of PLC-1, Ca2+ mobilization and transcription factor activation, and actin rearrangement downstream of both TCR and chemokine receptors. ITK mediates T cell receptor signaling, which is highly relevant given productive HIV infection requires T cell activation.[66] Without active ITK protein, HIV cannot effectively take advantage of many signaling pathways within T cells, which in turn reduces or blocks the spread of the virus. We therefore propose to concurrently assess ITK inhibition and HIV viral loads in this study for evidence of possible anti-HIV activity resulting from ibrutinib. If identified, this could have broader implications regarding therapy of HIV with ibrutinib beyond ARL. We hypothesize that ITK will also be inhibited with ibrutinib and further suppress HIV

viral load replication. Currently, there are no data available for in-vivo or in-vitro models in for BTK or ITK occupancy in this specific population. However, there are data using these assays in other diseases such as CLL.[67,68]

Thus far, BTK and/or ITK occupancy is our only reliable PD measurement tool. Phosphorylation of BTK and ITK is theoretically possible, but in practice it is very difficult due to the logistics of blood collection and rapid isolation of cells. Furthermore, occupancy is the only validated assay currently available for ibrutinib.

The method for BTK and ITK occupancy Pharmacyclics will use will be by and large the same as the ones used in previous studies. They have made improvements recently (as of 2016), but the results are comparable and the improvements simply improve accuracy and precision. For BTK, the positive control is DOHH2 lysates (treated with ibrutinib) and the negative control is Jurkat lysates (treated with ibrutinib). For ITK, it is the reversal of BTK. No scoring is used in this study. The occupancy is a calculated based upon the pre-treatment dose measurements. Each sample is compared to the pre-treatment level for that specific patient reducing the impact of assay variability on the overall results.

Pharmacyclics® had the current form of the assay validated and it is now run, using our specific protocol, at Cambridge Biomedical. Samples will be sent to Cambridge Biomedical, who runs the assays on Pharmacyclics' behalf.

The proposed collection methods proposed in this study have no known impact on the stability of BTK or ITK occupancy. Experiments were conducted where ibrutinib was placed into freshly isolated human blood and the samples were either processed immediately or processed at 24 hours (as in this trial). The resulting occupancy readings were ostensibly the same and within validation parameters.

Both occupancy assays have been validated. In discussions with Pharmacyclics, the specific assay and assay methods, performance, and operating characteristics information for BTK and ITK occupancy is proprietary information and has not been published. Therefore, this information is confidential. However, in general, the pharmacokinetics of ibrutinib will be performed and managed this through Pharmacyclics.

3.0 PARTICIPANT SELECTION

A rostered AMC physician investigator must document that each protocol participant meets all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

NOTE: Institutions may use this section of the protocol as an eligibility checklist for source documentation if it has been reviewed, signed, and dated before registration/randomization by the study investigator. If used as source documentation, this checklist must be printed, the investigator must check each item to document their assessment that the participant meets each eligibility criterion, and the completed checklist must be maintained in the participant's chart.

Participant ID Number: 101 - ___ ___ ___ - ___ ___ ___ ___ ___

Patient's Initials (L, F, M *[optional]*): ___ ___ ___

NOTE: All questions regarding eligibility should be directed to the study chair.

3.1 Eligibility Criteria

___ 3.1.1 Participants must have histologically (via at least a core or ideally, incisional or excisional biopsy) documented CD20 positive or negative diffuse large B-cell lymphoma (DLBCL).

___ 3.1.2 Tissue available from the diagnostic biopsy in the form of blocks, tissue cores, or slides available for submission to central pathology is required for all participants enrolled to this study, for analysis of integral biomarkers. Formalin-fixed paraffin-embedded tissue from diagnostic tissue is acceptable and recommended. See Appendix IX for full details. Submission of the institutional diagnostic slides is also preferred for all participants enrolled in the study. Tissue and diagnostic slides are required to be submitted within 1 month of enrollment.

___ 3.1.3 Stage II-IV disease (See Appendix XVI, Ann Arbor Staging Criteria). Participant will need measurable disease by CT or PET scans if enrolled in the dose-expansion cohort.

___ 3.1.4 HIV positive. Documentation of HIV-1 infection by means of any one of the following:

- Documentation of HIV diagnosis in the medical record by a licensed health care provider;
- Documentation of receipt of ART (at least three different medications) by a licensed health care provider (documentation may be a record of an ART prescription in the participant's medical record, a written prescription in the name of the participant for ART, or pill bottles for ART with a label showing the participant's name);
- HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating >1000 RNA copies/mL;

- Any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed HIV assay such as a HIV-1 Western blot confirmation or HIV rapid multispot antibody differentiation assay.

NOTE: A "licensed" assay refers to a U.S. FDA-approved assay, which is required for all IND studies.

___ 3.1.5 For the **dose-finding cohort** participants lymphoma must be untreated.

For the **dose-expansion cohort** participants may have either untreated lymphoma or may have received prior therapy. Please see the exclusion criteria Section 3.2.2. for full details of chemotherapy participants may have received off study.

___ 3.1.6 Ages 18 – 64.

___ 3.1.7 ECOG performance status ≤ 2 (Karnofsky ≥ 50%, see Appendix III).

___ 3.1.8 For the **dose-finding cohort** participants must have a CD4 count ≥ 100 cells/mm^3

For the **dose-expansion cohort** participants may have any CD4 count, including a CD4 count <100 cells/mm^3.

___ 3.1.9 Participants must have organ and marrow function within the following parameters:

- Absolute neutrophil count: ≥ 1,000/mm^3, unless decreased due to bone marrow involvement with lymphoma.
- Platelets: ≥ 75,000/mm^3, unless decreased due to bone marrow involvement with lymphoma.
- Hepatic impairment:
  - Total bilirubin: ≤ 1.5 times the institutional ULN; if potentially due to lymphoma, in the dose-expansion cohort, the first cycle may be given without ibrutinib and if transaminitis and bilirubinemia improves to meet parameters, participant may be enrolled.
- AST (SGOT) / ALT (SGPT): < 2 times the institutional ULN; if potentially due to lymphoma, in the dose-expansion cohort, the first cycle may be given without ibrutinib and if transaminitis and bilirubinemia improves to meet parameters, participant may be enrolled.
- Creatinine:
  - Creatinine levels below the normal institutional upper limits; or,
  - Creatinine clearance ≥ 50 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal; unless decreased due to renal involvement by lymphoma.

___ 3.1.10 Participants must not be on medications, including ARV regimens such as cobicistat, indinavir, or ritonavir, or agents with moderate or strong CYP3A4 inhibition; if on a moderate or strong CYP3A4 inhibitor regimen prior to study enrollment, participants must be switched to a qualifying regimen with the last dose of the strong CYP3A4 inhibitor taken at least one week before administration of ibrutinib. See Appendix XV.

___ 3.1.11 Willingness of sexually active participants to use adequate contraception. Because the effects of ibrutinib on the developing human fetus are unknown, tyrosine kinases may be teratogenic, and rituximab crosses the placenta, both men and women of child-bearing potential treated or enrolled on this study must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) before study entry, for the duration of study participation, 90 days after completion of ibrutinib, and 12 months after the last dose of rituximab, whichever comes last. Men who only have sex with other men do not need to use contraception specifically for this study (Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately).

___ 3.1.12 All participants will be required to be screened for Hepatitis B. All participants who present with acute hepatitis B or show normal transaminases and are HBsAg+ and IgM+ for Hepatitis core antigen will not be eligible for trial enrollment. Per IDSA and AASD guidelines, those participants that show no immunity, defined by the lack of Hepatitis B surface antibody, and show evidence of chronic infection (i.e., HBsAg+, HBcore+, HBsAB-) will be required to be on anti-Hepatitis B therapy, during the study, in order to be eligible. The exact Hepatitis B therapy will be at the discretion of the infection disease specialist or investigator. If infected with Hepatitis B, participants will be permitted to enroll in the study provided liver function tests meet criteria listed above, there is no evidence of cirrhosis AND participants will be required to be on anti-Hepatitis B therapy.

___ 3.1.13 All participants will be required to be screened for Hepatitis C. If Hepatitis C antibody positive, with or without a positive Hepatitis C RNA level, participants will be permitted to enroll in the study provided liver function tests meet criteria listed, and have no evidence of cirrhosis. Participants diagnosed with Hepatitis C less than 6 months from trial enrollment will be considered to have acute Hepatitis C, and will be excluded from study UNLESS Hepatitis C viral load is undetectable.

___ 3.1.14 Adequate cardiac function defined as an ejection fraction on ECHO or MUGA that is at or above the institutional normal limits.

For the **dose-expansion cohort**, if the participant had a pre-treatment ECHO prior to pre-study therapy which reports adequate cardiac function defined as an ejection fraction on ECHO or MUGA that is at or above the institutional normal limits, a repeat ECHO will not need to be repeated prior to start of study treatment.

___ 3.1.15 Participants must be able to swallow oral pills.

___ 3.1.16 Ability to understand and willing to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who do not fulfill the criteria as listed in Section 3.1 above, are ineligible. Additionally**,** the presence of any of the following conditions will exclude a participant from study enrollment:

___ 3.2.1 Participants who have had chemotherapy other than R-EPOCH, R-CHOP or limited therapy as outlined in Section 3.2.2, or radiotherapy other than palliative radiation for medical emergencies (like cord compression), within the last 4 weeks.

___ 3.2.2 For the **dose-finding cohor**t prior cytotoxic chemotherapy or radiotherapy for this lymphoma is exclusionary.

For the **dose-expansion cohort** participants may have received:

- A maximum of one cycle of combination chemotherapy, including rituximab-containing regimens R-CHOP and R-EPOCH. The start of previous chemotherapy cycle must occur at least 21 days but no more than 28 days prior to beginning treatment under this protocol, and such cycle will count towards the maximum of 6 cycles under this study (i.e., cycle off study will count as Cycle 1).

  OR

- 1 prior cycle of limited therapy including cyclophosphamide and/or rituximab and/or glucocorticoids to improve hepatic or renal function impaired due to lymphoma involvement. The start of this therapy may occur up to 28 days prior to beginning treatment under this protocol; cyclophosphamide administration must have been completed at least 14 days prior to initiation of protocol therapy. Such treatment will not count towards the maximum of 6 cycles under this study (i.e., participants will receive 6 cycles on study).

___ 3.2.3 For the **dose-finding cohor**t rituximab within 12 months prior to study registration will be exclusionary; only exception will be if rituximab was given for indications other than the treatment of aggressive lymphoma.

For the **dose-expansion cohort** one cycle of rituximab as part of R-CHOP or R-EPOCH or limited therapy as outlined in Section 3.2.2 may be administered off study prior to enrollment; prior rituximab will also be allowed if rituximab was given for indications other than the treatment of aggressive lymphoma.

___ 3.2.4 Participants who are receiving any other investigational agents.

___ 3.2.5 Participants who have previously received ibrutinib for another indication.

___ 3.2.6 Expected survival < 2 months.

___ 3.2.7 Participants with a history of an opportunistic fungal infection or active fungal infection requiring, or at high risk of requiring, prophylactic or treatment with fluconazole, voriconazole or posaconazole.

___ 3.2.8 Participants with known brain metastases from solid tumors should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

___ 3.2.9 Presence of second active tumor, other than non-melanoma skin cancer, carcinoma in situ of the cervix, or Kaposi's sarcoma (KS) that requires systemic therapy.

___ 3.2.10 For the **dose-finding cohort** participants with known or suspected parenchymal brain, spinal cord, leptomeningeal disease prior to study enrollment will be excluded.

For the **dose-expansion cohort** participants with known or suspected parenchymal brain or spinal cord disease, or symptomatic leptomeningeal disease will be excluded. *Asymptomatic* leptomeningeal disease will be allowed.

___ 3.2.11 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib or other agents used in study.

___ 3.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.

___ 3.2.13 Pregnancy or breastfeeding. A pregnancy test must be performed within 7 days prior to ibrutinib initiation in women of childbearing potential. Pregnant women are excluded because ibrutinib is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Breastfeeding must be discontinued because of unknown but potential risks in the nursing infant.

___ 3.2.14 Unable to comply with the requirements of the protocol, or unable to provide adequate informed consent in the opinion of the Principal Investigator.

___ 3.2.15 Serious, ongoing, non-malignant disease or infection, which in the opinion of the investigator and/or the sponsor would compromise other protocol objectives. Participants with active opportunistic infections are ineligible.

___ 3.2.16 Major surgery, other than diagnostic surgery, occurring 4 weeks prior to study entry. Splenectomy will not be considered an exclusionary major surgery.

___ 3.2.17 History of cutaneous or mucocutaneous reactions, or diseases in the past, due to any cause, severe enough to cause hospitalization or an inability to eat or drink for > 2 days. This exclusion relates to the long-term possibility of severe cutaneous or mucocutaneous reactions to rituximab that might occur at increased frequency in participants who have had severe skin disease or reactions in the past.

___ 3.2.18 Myocardial infarction (MI) within 6 months prior to study entry, New York Heart Association (NYHA) Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities.

3.3 Number of Participants to be Enrolled

3.3.1 Proposed sample size

This study will enroll a minimum of 9 participants and a maximum of 54 participants.

The goal of the study is to accrue 40 participants with adequate tissue for COO analysis with minimum of 15 participants with non-GCB subtype DLBCL as confirmed by central pathology by IHC. To compensate for the possible 30% misclassification rate of COO, this study will accrue a minimum of 22 participants of non-GC DLBCL subtype by IHC, as performed by the local pathologist, to reach the accrual target of 15 participants with central pathology confirmed non-GC subtype. Assuming 30-35% insufficient tissue for GEP COO (tumor content of <60%), 14 participants will be allowed on study as replacement participants should the participant not have adequate tissue for COO analysis, for a maximum of 54 participants on study.

3.3.2 Accrual rate

Approximately 1 participant per month during the dose-finding portion, and 3 participants per month during the dose-expansion cohort.

Physician Signature: _____ Date: _____

(Optional unless this section is used as an eligibility checklist)

3.4 Participant Enrollment Procedures

Sites must have this protocol approved by their Institutional Review Boards (IRB) and be registered for study participation with the AMC Operations and Data Management Center (ODMC) before they may enroll participants.

All enrollment and data collection will occur via AMC Advantage eClinical[SM] Internet Data Entry System (Advantage eClinical). After the participant signs the informed consent form and a CTEP-registered AMC investigator has verified all eligibility criteria, the site will register the participant via Advantage eClinical by completing the protocol-specific eligibility checklist. Enrollment will occur no more than 1 week before treatment initiation (enrollment 1 day before or on the day of treatment is strongly encouraged). Once the eligibility checklist is successfully submitted, a system-generated confirmation email will be issued to the enrolling site. If the on-line system is inaccessible, the site must notify the AMC ODMC (via email at amcpm@emmes.com or via phone at 301-251-1161) for enrollment instructions.

3.4.1 Enrollment

After the screening evaluations have been obtained and the participant is determined to be eligible, the participating site will complete the protocol-specific eligibility checklist and enroll the participant into AMC-101 (on-line via Advantage eClinical). Enrollment should occur no more than 1 week prior to administration of the first dose of the protocol agent(s) (enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted, a system generated confirmation email will be sent to the enroller upon successful completion of the participant enrollment. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at amcpm@emmes.com or via phone at 301-251-1161) for further instructions.

Participants must be enrolled into AMC-101 prior to receiving the first dose of the protocol agent(s).

4.0 TREATMENT PLAN

4.1 Agent Administration

Protocol agents will be administered on an inpatient or outpatient basis. Reported adverse events and potential risks for ibrutinib and R-da-EPOCH are described in Section 6.0. Appropriate dose modifications for ibrutinib and R-da-EPOCH are described in Section 5.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Each cycle (21 days) of treatment will include R-da-EPOCH and ibrutinib (oral, daily) (see Sections 4.1.1 and 4.1.2). Adherence to the target treatment date is highly encouraged; however, delays of up to 3 days for subsequent cycles are permitted to accommodate site and participant schedules. If the next cycle is delayed no ibrutinib should be administered during the dose delay for R-da-EPOCH. For CD20 negative lymphomas, each cycle of treatment will include da-EPOCH.

NOTES: The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

The site will be required to document study agent return by the participant in the source documents. Non-compliance with study agent administration should be noted at the time of diary collection and the participant should be instructed again regarding dosing instructions.

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The participant should not take extra capsules on the next day to make up the missed dose.

4.1.1 Ibrutinib

Dosing cohorts of ibrutinib are shown Section 5.1. Given the RP2D of ibrutinib in combination with R-CHOP in HIV-negative participants is 560 mg, the starting dose level of ibrutinib in this trial will be 560 mg daily.

In the dose-finding portion of the study, ibrutinib will begin at dose level 1 (560 mg PO), and de-escalate to dose -1 and -2 if excessive toxicity is seen at dose levels 1 and -1, respectively.

Ibrutinib will be given on days 1-21 of each cycle. Each dose level of ibrutinib will be assessed to determine safety, tolerability, and RP2D in participants.

Table 4-A: Ibrutinib Dose Levels and Schedule

Dose Levels	Ibrutinib Dosing (daily)
1	560 mg
-1	420 mg
-2	280 mg

4.1.2 R-da-EPOCH-ibrutinib regimen (EPOCH-ibrutinib for CD20 negative disease)

- Rituximab 375 mg/m^2 IV, Day 1 (for CD20 positive lymphoma; biosimilar agents are permitted);
- Etoposide 50 mg/m^2/24 hours x 4 days (96 ±6 hours infusion), Days 1-4;
- Doxorubicin 10 mg/m^2/24 hours x 4 days (96 ±6 hours infusion), Days 1-4;
- Vincristine 0.4 mg/m^2/24 hours x 4 days (96 ±6 hours infusion), Days 1-4;
- Prednisone 60 mg/m^2 PO daily Days 1-5 (may be rounded to the nearest 10 mg);
- Cyclophosphamide dose at 750 mg/m^2 for baseline CD4 count ≥ 200 and 375 mg/m^2 for baseline CD4 count < 200, IV over 1 hour, Day 5; subsequent cycles adjusted as per Section 5.1 for dose modification instructions.
- Ibrutinib at cohort dose orally days 1-21.
- Pegfilgrastim 6 mg subcutaneously from one calendar day up until 48 hours after completion of chemotherapy; if pegfilgrastim is not available, then filgrastim (or biosimilar) 300 or 480 mg starting day 6 for a minimum 10 days and until ANC >5000 cells/mm^3.

4.1.3 Criteria for initiation of subsequent cycles

For cycles 2 – 6, repeat R-da-EPOCH with ibrutinib regimen every 21 days (maximum of 6 cycles) if the following criteria are met:

- ANC ≥ 1000/mm^3 and platelets ≥ 75,000/mm^3.
- Adequately recovered from treatment associated toxicity.
- See Appendix XVII for details of ibrutinib and EPOCH dose adjustments.

4.2 Definition of Dose-Limiting Toxicity

The dose de-escalation and schema, and definitions of dose limiting toxicities (DLTs) are as follows:

Table 4-B: Ibrutinib dose escalation and schema

Number of Participants at Dose Level	Number of Participants with Cycle 1 DLT	Action
3	0	RP2D, move on to dose-escalation cohort
3	1	Treat another 3 participants at the same dose
6	1	RP2D, move on to dose-escalation cohort
3-6	≥ 2	RP2D exceeded, dose de-escalate to one level down

Table 4-C: Dose limiting toxicities

Dose-limiting toxicity	Definition applies to cycle 1 of the dose-finding portion of the trial
Hematologic	ANC nadir < 500 cells/mm^3 on ≥ 3 nonconsecutive days at least 3 days apart (i.e., ANC <500 cells/mm^3 on days 9, 12, and 15). Febrile neutropenia (ANC < 500/mm^3) requiring critical care support (i.e., intubation OR pressor support). Platelet count < 25/mm^3 resulting in a life-threatening bleed OR treatment delay for following cycle of > 7 days.
Non-hematologic	Any Grade ≥ 3 toxicity that causes a dose delay of > 1 week for the next planned treatment cycle despite adequate treatment/ supportive care.

4.3 General Concomitant Medication and Supportive Care Guidelines

Participants MUST receive medically appropriate care and treatment for HIV infection, including antiretroviral medications.

4.3.1 Concomitant medication

4.3.1.1 **HAART therapy**: Participants must not be on medications, including ARV regimens, with moderate or strong CYP3A4 inhibition; if on a moderate or strong CYP3A4 inhibitor regimen prior to study enrollment, participants must be switched to a qualifying regimen with the last dose of the moderate or strong CYP3A4 inhibitor taken at least one week before administration of protocol therapy due to effects on ibrutinib. Antiretroviral naïve participants: It is recommended that participants who are not on HAART at study entry begin therapy at the discretion of the treating provider(s). Diagnosis of HIV should not delay the initiation of HAART. However, given potential drug interactions, it may be preferred that participants complete the infusional chemotherapy before initiation of HAART. Participants ***must not*** be started on regimens with moderate or strong CYP3A4 inhibition. For further standard of care HIV management guidelines, please refer to the U.S. Department of Health and Human Services guidelines at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Supportive care and prophylaxis must be followed and regimen will be determined based on CD4 count.

Only changes in antiretroviral therapy, receipt of any disallowed medications (e.g., medicines that inhibit CYP3A4), or any concurrent medications that are attributed to SAEs will be reported in the Concomitant Medications form in Advantage eClinical from study enrollment through the last day of the final cycle of treatment.

4.3.1.2 All participants who tested positive for Hepatitis B and C must initiate treatment and remain on treatment for the duration of the study. The exact therapy will be administered per the standard of care.

4.3.2 Supportive care guidelines

4.3.2.1 Prevention of tumor lysis syndrome (cycle 1 only)

It is recommended that participants with evidence of high numbers of circulating tumor cells (≥ 50,000/mL) or high tumor burden (bone marrow involvement, high lactate dehydrogenase [LDH]) receive allopurinol. Additional measures such as aggressive IV hydration and urinary alkalization will be used at the discretion of the Investigator.

4.3.2.2 Precautions for surgeries or procedures

The following guidance[69,70] should be applied during the peri-operative/peri-procedure period for participants who require surgical interventions or procedures while on treatment and receiving ibrutinib:

- For surgery or invasive procedures requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedures, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For procedures such as central line placement, needle biopsy, thoracentesis, or paracentesis, ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the participant is on ibrutinib, it is not necessary to hold ibrutinib. For intrathecal CNS prophylaxis, a short hold (up to 3 days, suggested 2 days prior and 1 day post) should be considered based on the clinical situation of the participant, including assessment of underlying lymphoma and bleeding risk.
- For emergency procedures, ibrutinib should be healed after the procedure until the surgical site is reasonably held, for at least 7 days after the urgent surgical procedure.

4.3.2.3 Central nervous system (CNS) work up

If lymphomatous CNS involvement (including parenchymal brain, spinal cord or leptomeningeal) is clinically suspected, or the participant is symptomatic from CNS involvement during screening, participants must complete a full diagnostic work-up for CNS involvement with imaging and lumbar puncture (LP), and results of these studies must be known PRIOR to registration.

In the dose-finding portion of the study, no participants with known or suspected parenchymal brain, spinal cord, or leptomeningeal disease will be allowed on study.

In the dose-expansion portion of the study, no participants with known or suspected parenchymal brain or spinal cord disease, or symptomatic leptomeningeal disease will be allowed on study. However, asymptomatic leptomeningeal disease will be allowed in the dose-expansion cohort. For asymptomatic participants, if the participant's screening CSF returns positive by flow cytometry or cytology AFTER registration, they may still remain on study but must receive treatment dose intrathecal chemotherapy per institutional standards (see 4.3.2.4).

4.3.2.4 CNS treatment for positive CSF

See Section 4.3.2.2 for recommendations regarding hold of ibrutinib while on treatment. In cases in which there may be a higher risk of bleeding (i.e., history of difficult LP access), it may be useful to perform the LP under fluoroscopy.

Placement of an Ommaya reservoir is strongly recommended for cases of leptomeningeal CNS lymphomatous involvement in order to maximize CNS distribution of intrathecally administered chemotherapy. Additionally, Ommaya reservoir access does not require ibrutinib to be held due to the lower risk of bleeding complications. Therefore, placement of an Ommaya reservoir in patients requiring treatment of leptomeningeal CNS lymphoma would minimize interruption of ibrutinib dosing.

Although the specific regimen may vary at each center, a suggested regimen is listed below:

- Cytarabine 50 mg
- Methotrexate 12 mg
- Hydrocortisone 50 mg

Intrathecally administer twice a week until CSF is negative, then weekly x 1 month and then monthly x 6 months

4.3.2.5 CNS prophylaxis for negative CSF

See Section 4.3.2.2 for recommendations regarding hold of ibrutinib while on treatment. In cases in which there may be a higher risk of bleeding (i.e., history of difficult LP access), it may be useful to perform the LP under fluoroscopy.

CNS prophylaxis will be required in participants who meet the following criteria: lymphomatous involvement of bone marrow, testes, sinuses, or epidural regions. One of the following regimens will be required: IT liposomal cytarabine (Depocyt®), IT cytarabine, or IT methotrexate. The specific dosing regimen will be at the discretion of the primary oncologist but should include 4-6 doses of therapy.

4.3.2.6 Growth Factor (GF) therapy with G-CSF, GM-CSF, or pegfilgrastim\ filgrastim (or biosimilar), beginning about 24-48 hours (1-2 days) after the administration of cyclophosphamide will be used in all participants until post nadir recovery of blood counts from each chemotherapy cycle.

4.3.2.7 Use of erythropoietic factors, as per drug package insert, is allowed at the discretion of the Investigator.

4.3.2.8 Prophylaxis against *Pneumocystis jirovecii (P. jirovecii)* is required, with the specific regimen at the discretion of the Investigator. Recommended options include trimethoprim/sulfamethoxazole (80-400 mg daily or 160-800 mg Mondays, Wednesdays, Fridays), dapsone 100 mg daily, or atovoquone 1500 mg with food once daily).

4.3.2.9 Prophylaxis against other common opportunistic infection (OI) is dependent upon the participant's medical history and CD4 cell count at study entry, and at the discretion of the Investigator. Fluconazole, voriconazole, and posaconazole are at least moderate CYP3A4 inhibitors, so may not be used for prophylaxis or treatment in combination with ibrutinib on this study. If fluconazole, voriconazole, or posaconazole is required, ibrutinib must be discontinued. Topical and/or antifungal agents are permitted. Prophylaxis against *Mycobacterium avium (M. avium)* is recommended if CD4 cells are $< 100/mm^3$. Antiherpetic prophylaxis is recommended in participants. Investigators may consider famciclovir when available as it is the least myelosuppressive option.

4.3.2.10 Investigators should be vigilant about detecting cases of suspected pulmonary and/or CNS fungal infections, specifically, aspergillosis which has been seen with other clinical trials with ibrutinib alone or in combination with chemotherapy.

4.3.2.11 **Quinolone antibacterial prophylaxis**: Participants with a CD4 count of $< 100/mm^3$ at baseline or whose CD4 count decreases below $100/mm^3$ during therapy are required to receive quinolone prophylaxis. Begin quinolone prophylaxis during each cycle no later than Day 8 of chemotherapy and continue until documented recovery from neutropenia (ANC $\geq 1000/mm^3$). If participants are allergic or intolerant of quinolones an alternative antibiotic will be used.

4.3.2.12 **Transfusions**: Participants will be allowed platelet and packed red blood cell transfusions while on treatment. Specifically, given hemostasis-related adverse effects of ibrutinib correlate with platelet dysfunction, platelet transfusions should be considered for serious bleeding regardless of the platelet count.

4.3.3 Reporting requirements for concomitant medications

All medications must be reported in the site's source documents at baseline. All medications will be reviewed and updated in the site's source documents at all visits where indicated in the schedule of evaluations (Appendix I). Only a subset of medications will be reported in the Concomitant Medications CRFs after study entry, as listed below:

- Anti-seizure medications
- Prophylactic medications
  - Antiviral
  - Antifungal
  - Quinolone/Antibiotic therapy (See Section 4.3.2.10)
  - Any other medications used for prophylaxis of opportunistic infections
- Hepatitis medications
- Growth colony stimulation factors (GCSF)
- Erythropoiesis Stimulating Agents (ESA)
- Anti-retroviral medications.
  - **Note**: Antiretroviral therapy will be collected in the On Study Form. If the participant remains on the same anti-retroviral medications throughout study participation that have already been reported in the On Study Form, then do not report them in the Concomitant Medications Form. If the participant changes or discontinues anti-retroviral therapy for any reason, then update the Concomitant Medication Form with the start and stop date of the discontinued medication(s) and start date of the new (if applicable) medication(s).
- Receipt of disallowed medications (CYP3A4 modulating) after study enrollment, as per Appendix XV.

4.4 Duration of Therapy and Criteria for Removal from Treatment

In the absence of treatment delays due to adverse event(s), treatment may continue for 6 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Other unacceptable adverse event(s)
- Participant decides to withdraw from treatment or all other further study participation
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator
- Pregnancy.

Participants will be removed from study treatment when any of the above criteria applies. The reason for study treatment removal and the date the participant was removed must be documented in the Off Protocol Treatment Form in Advantage eClinical.

4.5 Duration of Follow Up

Participants will be treated for a maximum of 6 cycles (21-day cycle length); treatment for ARL off study, as defined in Section 3.1.4, will count as Cycle 1. Participants with CR after Cycle 4 will receive two additional cycles of chemotherapy. Participants who achieve a PR after Cycle 4 may continue on protocol therapy or be removed from the study at the discretion of the local registered AMC investigator.

Participants who discontinue ibrutinib (due to toxicity, participant refusal, or any other reasons) but continue R-da-EPOCH are considered on study until protocol chemotherapy is completed, and should have efficacy, toxicity, and follow-up data reported. Participants who discontinue all protocol therapy after having a CR or PR are followed for up to 5 years after treatment for recurrence and survival. Participants who discontinue protocol therapy due to disease progression, cross over to non-protocol therapy (if PR or stable disease at physician discretion), or other reasons are followed for survival only for up to 5 years after treatment.

Participants will be followed for 5 years after completion of treatment, with follow-up visits every 3 months for years 1-2 post-treatment, and then every 6 months for 3-5 years post-treatment. See Section 8.6 for full details of requirements for follow up.

5.0 DOSING DELAYS/DOSE MODIFICATIONS

5.1 Dose Modifications for Ibrutinib and R-EPOCH

5.1.1 Dose de-escalation, dose-finding portion

Table 5-A: Ibrutinib dose levels and schedule

Dose Levels	Ibrutinib Dosing (daily)
1	560 mg PO, on day 1 – 21 of each cycle
-1	420 mg PO, on day 1 – 21 of each cycle
-2	280 mg PO, on day 1 – 21 of each cycle

Dose adjustment for R-da-EPOCH will be based on laboratory 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 the participant does not obtain twice weekly CBC counts (i.e., only obtains one or less CBC within a week), it will be assumed the counts that would have been obtained are the same as the nadir counts, but clinical evidence of severe neutropenia/thrombocytopenia in absence of lab availability may be discussed by investigator with protocol chairs to determine subsequent cycle dosing. CBCs may be stopped after absolute neutrophil count or platelet recovery after the final cycle of the study therapy.

After the initial cycle of therapy, dose adjustments for CD4 count should adhere to the instructions in Table 5B and Table 5C.

Table 5-B: EPOCH dose adjustment levels for baseline CD4 count ≥ 200

Drugs	-4	-3	-2	-1	1
Doxorubicin (mg/m^2/day) Continuous on days 1-4)	10	10	10	10	10
Etoposide (mg/m^2/day) Continuous on days 1-4)	50	50	50	50	50
Cyclophosphamide (mg/m^2/day) Bolus on day 5)	0	187.5	375	562.5	750 (maximum dose)
Vincristine (mg/m^2/day) Continuous days 1-4	0.4	0.4	0.4	0.4	0.4
Prednisone (mg/m^2) Daily, days 1-5	60	60	60	60	60

Table 5-C: EPOCH dose adjustment levels for baseline CD4 count < 200

Drugs	-2	-1	1	2	3
Doxorubicin (mg/m^2/day) Continuous on days 1-4	10	10	10	10	10
Etoposide (mg/m^2/day) Continuous on days 1-4	50	50	50	50	50
Cyclophosphamide (mg/m^2/day) Bolus on day 5	0	187.5	375	562.5	750 (maximum dose)
Vincristine (mg/m^2/day) Continuous days 1-4	0.4	0.4	0.4	0.4	0.4
Prednisone (mg/m^2) Daily, days 1-5	60	60	60	60	60

5.1.2 Dose adjustment for dose-expansion cohort participants

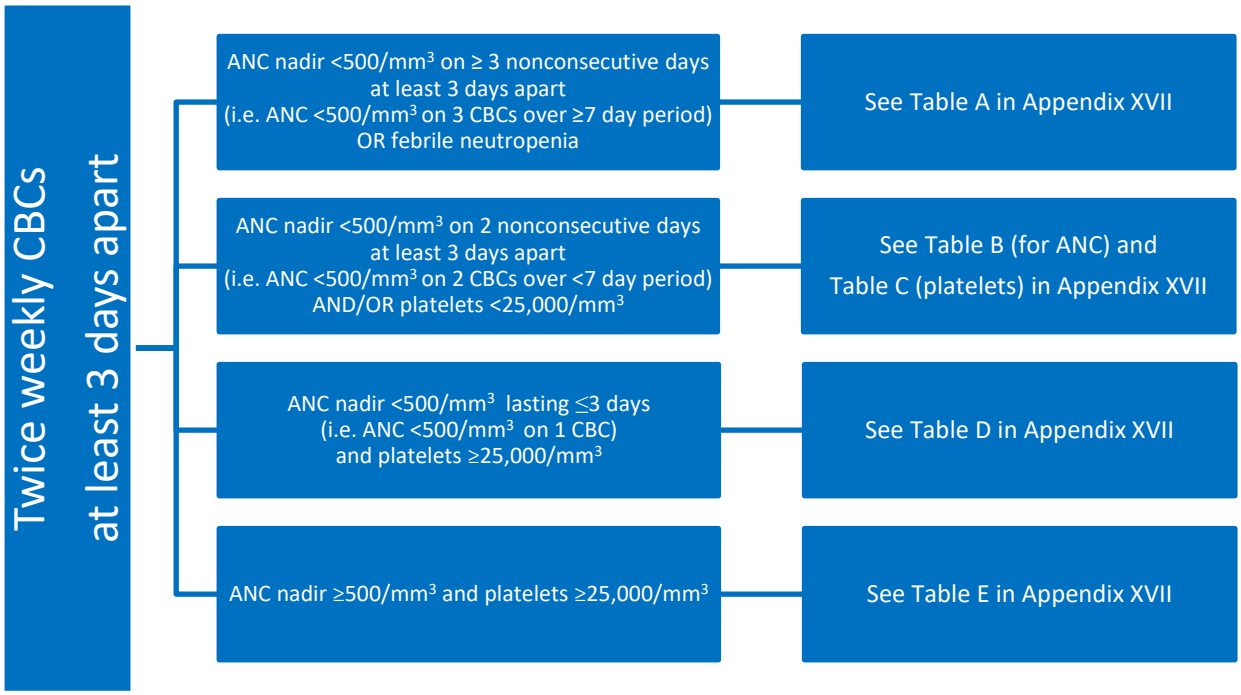
For the dose-expansion portion of the study, there will be intra-participant dose escalation and de-escalation of ibrutinib, in addition to dose-adjustment of R-da-EPOCH. Dose adjustment for R-da-EPOCH and/or ibrutinib will be based on laboratory measurements of the previous cycle ANC or platelet nadir, 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 the participant does not obtain twice weekly CBC counts (i.e., only obtains one or less CBC within a week), it will be assumed the counts that would have been obtained are the same as the prior, but clinical evidence of severe neutropenia/thrombocytopenia in absence of lab availability may be discussed by investigator with protocol chairs to determine subsequent cycle dosing. CBCs may be stopped after absolute neutrophil count or platelet recovery after the final cycle of study therapy. The dose adjustment for each cycle of ibrutinib and R-da-EPOCH will be based on the following criteria noted below. This schema was chosen to preferentially decrease cyclophosphamide initially, given that the most common grade 3 or 4 events in R-da-EPOCH in previous AMC trials were neutropenia: up to 42%.[10] Grade 3-4 neutropenia can also be seen with single agent ibrutinib,[27,28] but to a lesser degree.

5.1.3 Hematologic toxicity

Ibrutinib must be discontinued in participants who experience a DLT as defined in Section 4.2 during cycle 1 on dose-finding portion of the study. Dose adjustments for ibrutinib occur WITHIN the cycle, and dose adjustments for EPOCH occur PRIOR TO each cycle based on nadir counts of ANC <500 cells/mm^3 and platelet counts <25,000 cells/mm^3. Ibrutinib and/or chemotherapy drug adjustment based on nadir counts are as follows:

Dose Adjustment for EPOCH and Ibrutinib

Dose adjustment chart schema: See Appendix XVII for full details.



5.1.4 Non-hematologic toxicities

5.1.4.1 Nausea, vomiting, diarrhea

Ibrutinib has been associated with nausea, vomiting, and diarrhea.

Ibrutinib should be held if ≥ Grade 3 drug-related nausea, vomiting, diarrhea or dehydration as listed below occurs. Drug should be held until toxicity is Grade ≤ 1; at that time, ibrutinib may be re-started with a dose-reduction by 140mg to a minimum of 280mg. If ≥ Grade 3 toxicity recurs at the minimum dose of 280mg, ibrutinib must be discontinued permanently.

Nausea and Vomiting: Nausea and vomiting should be managed according to standard practice as outlined in the published American Society of Clinical Oncology (ASCO) guidance "Preventing and Treating Nausea and Vomiting Caused by Cancer Treatment." Briefly, antiemetic agents including, but not limited to, 5HT-3 antagonists, aprepitant, lorazepam, diphenhydramine, or phenothiazines may be considered. The use of empiric anti-emetic coverage is strongly encouraged, as is early and aggressive management of nausea, decreased oral intake and/or vomiting in participants treated with ibrutinib.

Diarrhea: Treat diarrhea promptly with supportive care. Encourage fluid intake. Loperamide anti-diarrhea therapy is permitted and should be recorded when used; recommendations include 4 mg at first onset of

diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Encourage participants to seek a nutritional consult. Treat diarrhea promptly with appropriate supportive care.

5.1.4.2 Neurologic toxicities

Table 5-D: Neurological toxicities

Toxicity	Dose
Moderate paresthesias (inability to button)	Vincristine: No change
Inability to walk on heels or obstipation	Vincristine: 25% dose reduction
Ambulation difficulties attributed to new neuropathy	Omit vincristine

5.1.4.3 Renal toxicities

Table 5-E: Renal toxicities

Toxicity	Dose
Creatinine Clearance <50cc/min	Etoposide: reduce 25% based on full dose cycle 1 or previous dose for cycles 2-6

5.1.4.4 Hepatic toxicities

Table 5-F: Hepatic toxicities

Toxicity	Dose
Direct bilirubin 1.2-3.0	Doxorubicin: reduce 50% based on full dose cycle 1 or previous dose for cycles 2-6
Direct bilirubin 3.1-5.0	Doxorubicin: reduce 75% based on full dose cycle 1 or previous dose for cycles 2-6 Vincristine: reduce 50% based on full dose initially or previous dose for cycles 2-6
Direct bilirubin >5.0	Omit doxorubicin and vincristine

5.1.4.5 Skin/mucositis

Participants who have evidence of clinically significant skin rash or oral/pharyngeal mucositis attributed to ibrutinib should have ibrutinib held until improvement to Grade ≤1. If rash/mucositis is attributed to ibrutinib, ibrutinib may be re-started with a dose-reduction by 140 mg to a minimum of 280 mg. If ≥ Grade 3 toxicity recurs at the minimum dose of 280 mg, ibrutinib must be discontinued permanently.

5.1.4.6 Aspergillosis

Several cases of invasive aspergillosis have been reported in patients who received ibrutinib alone or in combination with other therapies; it is possible that ibrutinib contributed to these adverse events. Therefore, investigators should be vigilant about detecting cases of suspected pulmonary and/or CNS fungal infections including aspergillosis. All suspected and confirmed cases of fungal infections should be reported to CTEP in 24 hours (expedited adverse event reporting). If a case of aspergillosis is suspected or observed, ibrutinib should be held until the infection has clinically improved and/or controlled on treatment. Ibrutinib may be restarted based on the investigator's discretion. Please note treatment with voriconazole and posaconazole may not be used in combination with ibrutinib given they are strong CYP3A4 inhibitors.

5.1.4.7 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 participants received rituximab 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 rituximab and have resulted in death.

5.1.4.8 Cardiac toxicity

Doxorubicin: If clinical findings suggesting congestive heart failure are present, doxorubicin will be discontinued and evaluation by MUGA should be performed.

Rituximab: The incidence of serious cardiovascular events in the double-blind part of the clinical trials was 1.7% and 1.3% in rituximab and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the rheumatoid arthritis (RA) studies, including all rituximab regimens (3/759=0.4%) as compared to none in the placebo treatment group (0/389). Since participants with RA are at increased risk for cardiovascular events compared with the general population, participants with RA should be monitored throughout the infusion and rituximab should be discontinued in the event of a serious or life-threatening cardiac event.

Ibrutinib: An increased risk of atrial fibrillation (AF) compared to the general population has been documented. The mechanism(s) by which ibrutinib may promote AF are unknown. Participants treated with ibrutinib should be closely monitored for the development of AF, which can be associated with a 5-fold increased risk of ischemic stroke, a leading cause of morbidity and mortality, unrelated to the underlying lymphoma. Anticoagulation should be used in cases of AF as clinically indicated.

5.1.4.9 Bowel obstruction and perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in participants receiving rituximab in combination with chemotherapy for DLBCL. In post-marketing reports, which include both participants with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1-77) in participants with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

5.1.4.10 Dehydration

Altered taste and decreased food and liquid intake are associated with ibrutinib administration. These toxicities can be actively managed with fluid management and nutritional consultation, as appropriate. To prevent dehydration, participants should consume at least 2 liters of fluid orally, on a daily basis, in particular during the days that they are being treated with ibrutinib. If participants are experiencing dysgeusia, popsicles or oral electrolyte fluid replacement may be recommended.

5.1.4.11 Hyperuricemia

Hyperuricemia has been observed with ibrutinib. Serum uric acid should be monitored, especially in participants with high tumor burden. Supportive care should be provided to all participants. Allopurinol and/or rasburicase should be administered based on the degree of hyperuricemia.

6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited (via CTEP-AERS) **in addition** to routine reporting (via Advantage eClinical).

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All appropriate treatment areas should have access to a copy of the CTEP Version 5.0 of CTCAE.

Monitoring will be performed by Emmes.

6.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) for Ibrutinib

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with **bold** and **italicized** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously via CTEP-AERS. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

6.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for ibrutinib (NSC 748645)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2082 patients.* Below is the CAEPR for ibrutinib.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Table 6-A: Ibrutinib CAEPR and SPEER

Version 2.8, November 4, 2024[1] Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (leukostasis)	
		Leukocytosis	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Ventricular arrhythmia	
		Ventricular fibrillation	
		Ventricular tachycardia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Mucositis oral		
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
	Fatigue		***Fatigue (Gr 3)***
	Fever		
		Sudden death NOS	
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (drug-induced liver Injury)	
		Hepatobiliary disorders - Other (hepatotoxicity)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	

Version 2.8, November 4, 2024[1] Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INFECTIONS AND INFESTATIONS			
		Hepatitis B reactivation	
	Infection[3]		***Infection[3] (Gr 3)***
		Infections and infestations - Other, specify (hepatitis E)	
		Infections and infestations - Other (bronchopulmonary and central nervous system infections)[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
INVESTIGATIONS			
	Lymphocyte count increased[2]		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
		Hyperuricemia	
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Muscle cramp		
	Myalgia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (benign neoplasm of skin)[5]		
		Treatment related secondary malignancy[5]	
NERVOUS SYSTEM DISORDERS			

Version 2.8, November 4, 2024[1] Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dizziness		
	Headache		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
		Pneumonitis[6]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Purpura		
		Skin and subcutaneous tissue disorders - Other (angioedema)[7]	
	Skin and subcutaneous tissue disorders - Other (rash)[8]		***Skin and subcutaneous tissue disorders - Other (rash)[8] (Gr 3)***
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
		Hypotension	
	Vascular disorders - Other (hemorrhage)[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Leukostasis and/or leukocytosis have been observed especially in patients with chronic lymphocytic leukemia (CLL) and mantle cell leukemia (MCL).

[3]Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[4]Fungal infections especially respiratory tract infections due to aspergillus and/or pneumocystis and central nervous system (CNS) infections due to aspergillus have been observed in clinical trials of ibrutinib. These reports may include incidents of presumptive fungal infections based on response to anti-fungal agents and/or radiographic evidence.

[5]Other malignant diseases have been observed in patients who have been treated with ibrutinib including solid tumors, skin cancer, and hematological malignancies.

[6]Pneumonitis is included in the group term Interstitial Lung Disease (ILD) which also includes lung infiltration, bronchiolitis, pulmonary fibrosis, eosinophilc pneumonia, pulmonary toxicity, and alveolitis allergic.

[7]Angioedema may be seen in association with the immune-related adverse event of anaphylaxis.

[8]Rash may include but is not limited to the terms dermatitis, erythema, rash generalized, rash maculo-papular, rash pustular, rash pruritic, and urticaria.

[9]It is possible that treatment with ibrutinib may increase the risk of hemorrhage which may occur anywhere in the body including CNS hemorrhage (including but not limitied to Intracranial hemorrhage, Intraventricular hemorrhage, and Subdural hematoma), Ecchymoses, Purpura (petechia), Gastrointestinal hemorrhage (including but not limited to Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage), Genitourinary tract hemorrhage (including but not limited to Hematuria and Vaginal hemorrhage), Respiratory tract hemorrhage (including but not limited to Epistaxis), and Spontaneous hemorrhage.

Adverse events reported on Ibrutinib (PCI-32765) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ibrutinib (PCI-32765) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hemorrhagic diathesis); Blood and lymphatic system disorders - Other (lymphadenitis); Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Atrial flutter; Atrioventricular block complete; Atrioventricular block first degree; Cardiac disorders - Other (bundle branch block left); Cardiac disorders - Other (extrasystoles); Chest pain - cardiac; Heart failure; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Sinus bradycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (eye discharge); Eye disorders - Other (macular edema); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (retinal hemorrhage); Eye pain; Floaters; Glaucoma; Keratitis; Periorbital edema; Photophobia; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Cheilitis; Colitis; Dyspepsia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gluteal intramuscular bleed); Gastrointestinal disorders - Other (irritable bowel syndrome); Gastrointestinal disorders - Other (tongue discoloration); Oral

dysesthesia; Oral pain; Pancreatitis; Periodontal disease; Small intestinal obstruction; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (early satiety); General disorders and administration site conditions - Other (multiple organ dysfunction syndrome); General disorders and administration site conditions - Other (sensation of foreign body); General disorders and administration site conditions - Other (temperature intolerance); Generalized edema; Injection site reaction; Localized edema; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction; Injury, poisoning and procedural complications - Other (excoriation)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (cardiac murmur); Investigations - Other (increase CRP); Lymphocyte count decreased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (cachexia); Metabolism and nutrition disorders - Other (hypoproteinemia); Metabolism and nutrition disorders - Other (lactose intolerance)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Flank pain; Generalized muscle weakness; Joint effusion; Joint range of motion decreased; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (muscle rigidity); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Neck pain; Pain in extremity
NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Dysgeusia; Encephalopathy; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (mental impairment); Nervous system disorders - Other (PML); Nervous system disorders - Other (parosmia); Paresthesia; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Somnolence; Stroke; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Insomnia; Restlessness
RENAL AND URINARY DISORDERS - Cystitis noninfective; Renal and urinary disorders - Other (calculus bladder); Renal and urinary disorders - Other (polyuria); Urine discoloration; Urinary frequency; Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dyspareunia; Reproductive system and breast disorders - Other (hematospermia); Vaginal dryness
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Hiccups; Laryngeal inflammation; Pleural effusion; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (alveolitis allergic); Respiratory, thoracic and mediastinal disorders - Other (nasal ulcer); Sinus disorder; Sinus pain; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Nail discoloration; Nail loss; Photosensitivity; Pruritus; Skin atrophy; Skin hyperpigmentation; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hot flashes; Thromboembolic event; Vascular disorders

- Other (peripheral coldness)

Note: Ibrutinib (PCI-32765) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.1.2 Potential risks for cyclophosphamide

Cyclophosphamide is an alkylating agent and is cell cycle nonspecific. It causes cross-linking of DNA and is the most active single agent in the treatment of non-Hodgkin lymphoma. Side effects of cyclophosphamide include nausea, vomiting, myelosuppression and alopecia. Sterility and testicular atrophy are common in men and amenorrhea is seen in women. Hemorrhagic cystitis is caused by metabolites of cyclophosphamide excreted through the urine. Bladder irritation can be reduced by adequate hydration. Please refer to the approved package insert for complete prescribing and toxicity information.

6.1.3 Potential risks for doxorubicin hydrochloride

Doxorubicin is an anthracycline antibiotic that binds tightly with DNA, inhibits nucleic acid synthesis and causes DNA strand breaks. Although active throughout the cell cycle, cells in S phase are most sensitive. Common side effects include myelosuppression, alopecia, and stomatitis, which is dose related and may be severe. Drug-induced cardiomyopathy which may result in congestive heart failure is a cumulative dose dependent effect and risk becomes considerable at total doses exceeding 500 mg/m^2. Doxorubicin is given intravenously and is a vesicant causing severe local necrosis at the site of injection if extravasation occurs. Nausea and vomiting are frequent. Please refer to the approved package insert for complete prescribing and toxicity information.

6.1.4 Potential risks for vincristine sulfate

Vincristine sulfate is a vinca alkaloid from the plant *C. roseus*. It acts by binding to or crystallizing microtubular proteins of the mitotic spindle. It is a cell cycle phase specific agent and can also affect DNA directed RNA polymerase. It has a triphasic half-life and primary elimination is by the liver into the bile and feces. The major and dose-limiting side effect of vincristine is neurotoxicity. The main manifestation is a mixed sensorimotor peripheral neuropathy. Reduced or loss of deep tendon reflexes, paresthesias, weakness, myalgias and motor disturbances may occur. Autonomic toxicity also occurs which may cause constipation, obstipation, abdominal cramps and ileus. It has mild myelosuppressive effects and is a vesicant causing local necrosis at the site of injection if extravasation occurs. Please refer to the approved package insert for complete prescribing and toxicity information.

6.1.5 Potential risks for etoposide

Etoposide, or VP-16, is an epipodophyllotoxin derived from the mandrake plant *P. peltatum*. It is a cell cycle phase specific agent that blocks topoisomerase II. It has a biphasic half-life and is eliminated by both renal clearance and metabolism. The major and dose-limiting toxicity of etoposide is myelosuppression. Constipation, diarrhea, dysphagia, aftertaste, abdominal pain, stomatitis, and anorexia have also

been reported. Mucositis and hepatotoxicity are seen primarily with high doses. Transient hypotension and other anaphylactic-like symptoms are associated with rapid infusion. Please refer to the approved package insert for complete prescribing and toxicity information.

6.1.6 Potential risks for prednisone

Prednisone is a corticosteroid and its mechanism of action, as a cytotoxic agent is not clearly understood. Short-term use produces minimal side effects but prolonged use is associated with hypertension, hyperglycemia, myopathy, osteoporosis, pancreatitis, and immunosuppression. Alterations in mood and insomnia are common acute side effects. Please refer to the approved package insert for complete prescribing and toxicity information.

6.1.7 Potential risks for rituximab

The Adverse Event and Potential Risks list provides a single list of reported and/or potential adverse events (AE) associated with rituximab.

Table 6-B: Adverse events and potential risks for rituximab

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rituximab, more than 20 and up to 100 may have:
• Nausea • Chills, fever • Reaction during or following infusion of the drug • Infection, especially when white blood cell count is low • Anemia which may require blood transfusions • Numbness and tingling of the arms and legs • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rituximab, from 4 to 20 may have:
• Bruising, bleeding • Abnormal heartbeat • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Sores in eye • A tear or a hole in the bowels that may require surgery • Diarrhea, vomiting • Pain • Swelling of the body • Hepatitis, or liver damage which may cause yellow eyes and skin • Dizziness, headache • Kidney damage which may require dialysis • Cough • Scarring of the lungs • Stuffy nose • Blockage of internal organs which may cause shortness of breath, wheezing, vomiting • Increased sweating • Itching, rash, blisters on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving Rituximab, 3 or fewer may have:
• Damage to the brain caused by a virus which may result in tiredness, weakness, changes in thinking, and disability. This is called progressive multifocal leukoencephalopathy (PML). • Heart stops beating

Also reported on rituximab trials but with the relationship to rituximab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Hemolysis

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (cyanosis); Left ventricular systolic dysfunction; Sinus bradycardia; Ventricular fibrillation

EYE DISORDERS - Conjunctivitis; Eye disorders - Other (ocular edema); Uveitis; Watering eyes

GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Dysphagia; Gastrointestinal obstruction[3]; Gastrointestinal perforation[4]; Mucositis oral

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=Grade 2 Lymphopenia)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture

INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Investigations - Other (hyperphosphatemia); Investigations - Other (LDH increased); Weight loss

METABOLISM AND NUTRITION DISORDERS - Anorexia; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoglycemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis

NERVOUS SYSTEM DISORDERS - Nervous system disorders - Other (Cranial Neuropathy NOS); Peripheral motor neuropathy; Peripheral sensory neuropathy; Pyramidal tract syndrome; Reversible posterior leukoencephalopathy syndrome; Syncope

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Depression; Insomnia

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Pharyngolaryngeal pain; Pleural effusion; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Skin and subcutaneous tissue disorders - Other (paraneoplastic pemphigus)

VASCULAR DISORDERS - Phlebitis; Thromboembolic event; Vasculitis

Note: Rituximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.2 Classification of AEs by Severity and Relationship to Study Drug Administration

6.2.1 Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

6.2.2 Life-threatening Adverse Event: Any AE that places the participant or participant, in view of the Investigator, at immediate risk of death from the reaction.

6.2.3 Serious Adverse Event (SAE): Any AE occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect.

6.2.4 Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction.

6.2.5 Toxicity: Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for AE reporting purposes. The CTCAE continues to use the term ‘toxicity’ because of familiarity.

6.2.6 Unexpected Adverse Event: Any AE that is not listed in available sources including the package insert, the Investigator’s Brochure, or the protocol.

6.2.7 CTEP Adverse Event Reporting System (CTEP-AERS): An electronic system for expedited submission of AE reports.

6.2.8 Attribution: The determination of whether an AE is related to a medical treatment or procedure. Attribution categories:

Definite – The AE is clearly related to the investigational agent.
Probable – The AE is likely related to the investigational agent.
Possible – The AE may be related to the investigational agent.
Unlikely – The AE is doubtfully related to the investigational agent.
Unrelated – The AE is clearly NOT related to the investigational agent.

6.3 Expedited Adverse Event Reporting

6.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page

(http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 6.3.3).

A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

6.3.2 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.

6.3.3 Expedited reporting guidelines

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

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions - Disease Progression."** 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.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

Table 6-C: FDA expedited reporting requirements

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

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 calendar days	24-Hour notification, 5 calendar days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

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

[1]SAEs 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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

6.4 Routine Adverse Event Reporting

All adverse events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

6.4.1 Additional protocol-specific routine adverse event reporting exclusions

All AEs, including clinically significant abnormal findings on laboratory

evaluations, regardless of severity, will be followed until satisfactory resolution. AEs will be reported up to 30 days following the last dose of R+daEPOCH or ibrutinib, whichever was administered last.

For this study, AEs will include ***clinically significant*** events reported by the participant, as well as ***clinically significant*** abnormal findings on physical examination or laboratory evaluation that the investigator feels was related to study drug. 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.

In assessing laboratory results, an abnormal laboratory value will be considered clinically significant if it is characterized by one or more of the following criteria:

1. Is judged by the investigator to have a causal relationship to the investigational agent
2. Requires clinical intervention or monitoring, such as: close observation, more frequent follow-up assessments, further diagnostic intervention, treatment/therapeutic intervention, or protocol therapy dose modification
3. Is associated with clinical signs or symptoms, which may suggest a disease and/or organ toxicity, or may represent a new condition or worsening of a baseline condition
4. Is associated with a serious adverse event, or is otherwise judged by the Investigator to be of significant clinical impact

Results proved erroneous result by repeat testing, if performed, will not be considered clinically significant laboratory abnormalities.

In general, a laboratory abnormality that is <u>not</u> clinically significant will be consistent with CTCAE grade 1 (mild) or 2 (moderate) severity, as categorized by the relevant severity description in the Investigations System Organ Class (SOC) or Metabolism and Nutrition Disorders SOC. Investigators may not designate laboratory abnormalities that are consistent with grade 3 or greater severity as not clinically significant.

All laboratory values deemed clinically significant will be subsequently reported as AEs unless the result is a sign of a clinical diagnosis that is reported as an AE.

6.4.2 Timeline for routine adverse event reporting

All adverse events will be assessed by the investigator in the study source from the first dose of protocol therapy through the treatment discontinuation visit, or until resolution, whichever is later. After this evaluation, assessment and reporting of AEs will only be required for all grade 5 AEs and any SAE that the investigator considers related to AMC-101 protocol therapy.

6.5 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 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 reported via the routine reporting mechanisms outlined in each protocol.

6.6 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** routine adverse event reporting.

7.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 6.1.

If required, commercial agents may be replaced with a suitable alternative formulation with approval from the protocol chairs.

7.1 Ibrutinib (NSC #748645)

Chemical Name: 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

Other Names: Ibrutinib

Classification: Selective, irreversible, small molecule inhibitor of Bruton's tyrosine kinase (Btk).

CAS Registry Number: 936563-96-1

M.W.: 440.5 g/mole

Mode of Action: Ibrutinib binds covalently to a cysteine residue in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity of B-cell receptors (BCR). B-cell maturation is mediated by BCR signal transduction and BTK is an essential part of the signaling pathway.

Description: White to off-white crystalline solid

How Supplied: Ibrutinib is supplied by Pharmacyclics, Inc., and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Ibrutinib is supplied as hard gelatin capsules containing micronized Ibrutinib and the following excipients: microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; may contain magnesium stearate. Capsules are manufactured as 140 mg in a size 0, gray, hard gelatin capsule. Capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle may contain either 120 capsules or 92 capsules. Ibrutinib capsules are to be dispensed in their original containers.

Storage: Ibrutinib Hard Gelatin Capsules should be stored at 15-25°C.

Stability: Shelf life surveillance of the intact bottles is ongoing.

Route of Administration: Ibrutinib 560 mg (4 x 140-mg capsules, or other dose level as assigned per Section 4.1) is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and participant should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix XV).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The participant should not take extra capsules to make up the missed dose.

Potential Interactions: Ibrutinib is primarily metabolized by CYP3A4. Any strong inhibitor or inducer of CYP3A4 (e.g., itraconazole, ketoconazole, clarithromycin, and rifampin) should be administered with caution and only after consultation with the Medical Monitor. Grapefruit and Seville orange juices should be avoided.

Availability: Ibrutinib is an investigational agent supplied by Pharmacyclics and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI.

Ibrutinib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix II).

7.1.1 Drug orders, transfers, and returns

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a participant is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

7.1.2 Agent inventory records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and final disposition of all agents received from the PMB using the Oral NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation, and ordering investigator on this protocol.

7.1.3 Useful links and contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov

- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: IBCoordinator@mail.nih.gov

  The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

7.2 Commercial Agents (EPOCH)

7.2.1 Rituximab

Product description: Rituximab is a chimeric mouse/human anti-CD 20 monoclonal antibody that binds human C1q, mediate complement-dependent cell lysis and lyse human target cells through antibody dependent cellular cytotoxicity. It has documented anti-tumor activity in CD20 positive lymphoma and FDA-approved for that indication. FDA-licensed biosimilars are permitted for use on this protocol. Please refer to the approved package insert for complete prescribing and toxicity information.

Solution preparation: Investigators may refer the reader to the package insert for standard preparation instructions, appropriate storage, and stability information.

Route of administration: 375 mg/m^2 IV, Day 1 (for CD20 positive lymphoma).

Agent ordering: Agent will be sourced by participating centers as commercially available.

7.2.2 Etoposide

Product description: Etoposide, or VP-16, is an epipodophyllotoxin derived from the mandrake plant *P. peltatum*. Etoposide is a substrate for CYP1A2, CYP2E1, CYP3A4/5, UGT1A1, ABCB1, ABCC1, and ABCC3 and a weak inhibitor of CYP2C9 and CYP3A4. It is a cell cycle phase specific agent that blocks topoisomerase II. It has a biphasic half-life and is eliminated by both renal clearance and metabolism. The major and dose-limiting toxicity of etoposide is myelosuppression. Constipation, diarrhea, dysphagia, aftertaste, abdominal pain, stomatitis, and anorexia have also been reported. Mucositis and hepatotoxicity are

seen primarily with high doses. Transient hypotension and other anaphylactic-like symptoms are associated with rapid infusion. Please refer to the approved package insert for complete prescribing and toxicity information.

Solution preparation: Investigators may refer the reader to the package insert for standard preparation instructions, appropriate storage, and stability information.

Route of administration: Etoposide 50 mg/m^2/24 hours x 4 days (~96-hour infusion), Days 1-4.

Agent ordering: Agent will be sourced by participating centers as commercially available.

7.2.3 Doxorubicin hydrochloride

Product description: Doxorubicin is an anthracycline antibiotic that binds tightly with DNA, inhibits nucleic acid synthesis and causes DNA strand breaks. Although active throughout the cell cycle, cells in S phase are most sensitive. Common side effects include myelosuppression, alopecia, and stomatitis, which is dose related and may be severe. Drug-induced cardiomyopathy, which may result in congestive heart failure, is a cumulative dose-dependent effect and risk becomes considerable at total doses exceeding 500 mg/m^2. Doxorubicin is given intravenously and is a vesicant causing severe local necrosis at the site of injection if extravasation occurs. Nausea and vomiting are frequent. Please refer to the approved package insert for complete prescribing and toxicity information.

Solution preparation: Investigators may refer the reader to the package insert for standard preparation instructions, appropriate storage, and stability information.

Route of administration: 10 mg/m^2/24 hours x 4 days (~96-hour infusion), Days 1-4.

Agent Ordering: Agent will be sourced by participating centers as commercially available.

7.2.4 Vincristine sulfate

Product description: Vincristine sulfate is a vinca alkaloid from the plant *C. roseus*. Vincristine is a substrate for CYP3A4/5, ABCB1, ABCC1, ABCC2, ABCC3, and ABCC10 and a weak inhibitor of CYP3A4. It acts by binding to or crystallizing microtubular proteins of the mitotic spindle. It is a cell cycle phase specific agent and can also affect DNA-directed RNA polymerase. It has a triphasic half-life and primary elimination is by the liver into the bile and feces. The major and dose-limiting side effect of vincristine is neurotoxicity. The main manifestation is a mixed sensorimotor peripheral neuropathy. Reduced or loss of deep tendon reflexes, paresthesias, weakness, myalgias and motor disturbances may occur. Autonomic toxicity also occurs which may cause constipation, obstipation, abdominal cramps and ileus. It has mild myelosuppressive effects and is a vesicant causing local necrosis at the site of injection if extravasation occurs. Please refer to the approved package insert for complete prescribing and toxicity information

Solution preparation: Investigators may refer the reader to the package insert for standard preparation instructions, appropriate storage, and stability information.

Route of administration: 0.4 mg/m^2/24 hours x4 days (~96-hour infusion), Days 1-4.

Agent ordering: Agent will be sourced by participating centers as commercially available.

7.2.5 Prednisone

Product description: Prednisone is a corticosteroid and its mechanism of action, as a cytotoxic agent is not clearly understood. Short-term use produces minimal side effects but prolonged use is associated with hypertension, hyperglycemia, myopathy, osteoporosis, pancreatitis, and immunosuppression. Alterations in mood and insomnia are common acute side effects. Please refer to the approved package insert for complete prescribing and toxicity information.

Solution preparation: Investigators may refer the reader to the package insert for standard preparation instructions, appropriate storage, and stability information.

Route of administration: 60 mg/m^2 PO daily Days 1-5 (may be rounded to the nearest 10 mg).

Agent ordering: Agent will be sourced by participating centers as commercially available.

7.2.6 Cyclophosphamide

Product description: Cyclophosphamide is an alkylating agent and is cell cycle nonspecific. It causes cross-linking of DNA and is the most active single agent in the treatment of non-Hodgkin lymphoma. Cyclophosphamide is a substrate of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5. Cyclophosphamide is a weak-to-moderate inducer of CYP2B6, CYP2C8, and CYP2C9 and weak inhibitor of CYP3A4 and UGT (isozyme not specified). Side effects of cyclophosphamide include nausea, vomiting, myelosuppression and alopecia. Sterility and testicular atrophy are common in men and amenorrhea is seen in women. Hemorrhagic cystitis is caused by metabolites of cyclophosphamide excreted through the urine. Bladder irritation can be reduced by adequate hydration. Please refer to the approved package insert for complete prescribing and toxicity information.

Solution preparation: Investigators may refer the reader to the package insert for standard preparation instructions, appropriate storage, and stability information.

Route of administration: Cyclophosphamide cycle 1 dose at 750 mg/m^2 for CD4 count $\geq$ 200 and 375 mg/m^2 for CD4 count < 200, IV over 1 hour, Day 5; subsequent cycles adjusted as per Section 4.1.

Agent ordering: Agent will be sourced by participating centers as commercially available.

8.0 CLINICAL AND LABORATORY EVALUATIONS

Schedules shown in the Study Calendar below are provided in Appendix I.

8.1 Screening/Baseline Evaluations

Unless otherwise specified, the following evaluations must be performed within 28 days prior to participant registration. For participants who are enrolled after receiving one cycle of chemotherapy off study, baseline assessments that were performed within the protocol timelines prior to the initiation of chemotherapy off study will be accepted at study enrollment. **All laboratory tests to document eligibility must be performed prior to enrollment.** Any other tests or evaluations for protocol requirements at baseline that were not performed prior to the initiation of chemotherapy (off study) **must be collected prior to initiation of treatment under protocol**.

NOTE: Research specimens that will be shipped to other institutions should not be collected before enrollment in Advantage eClinical, so that shipment through GT is possible upon collection.

8.1.1 Medical history; CDC HIV risk categories, and history of current and past anti-retroviral regimens, if available; and history of any prior AIDS-defining conditions. Date of initial lymphoma diagnosis is required, with a copy of the pathology report in the medical record. Presence of systemic "B" symptoms should be noted, as well as other symptoms of NHL. Current concomitant medication list, including all anti-retroviral, anti-viral, antibiotics, over the counter medications or dietary supplements, and opportunistic prophylaxis should be obtained.

8.1.2 Participants must not be on medications, including ARV regimens, with moderate or strong CYP3A4 inhibition; if on a moderate or strong CYP3A4 inhibitor regimen prior to study enrollment, participants must be switched to a qualifying regimen with the last dose of the moderate and/or strong CYP3A4 inhibitor taken at least one week before administration of ibrutinib.

8.1.3 Physical examination, including performance status (see Appendix III, Performance Status Scales), vital signs (weight, height, body surface area (BSA)), neurological examination, and if possible, two-dimensional measurement of all palpable, peripheral lymph nodes and measurement of other sites of disease present.

8.1.4 CT scan chest/abdomen/pelvis (+/- neck if involved) with contrast of diagnostic quality; if possible, measurement of sites of disease present. If PET/CT is feasible, a baseline PET/CT scan. If a PET/CT is not feasible, this will not be a protocol violation. MRI brain and/or spine as clinically indicated.

8.1.5 Electrocardiogram (EKG).

8.1.6 Laboratory tests, including:

- CBC with differential and platelet count (within 2 weeks prior to participant registration).
- Serum chemistries: magnesium, glucose, electrolytes (sodium, potassium, CO_2, chloride), blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT, and uric acid (within 2 weeks prior to participant registration).

- Serum pregnancy test for women of childbearing potential (within 7 days prior to first cycle of chemotherapy).
- Confirmation of HIV, as defined in Section 3.1.4.
- HIV-1 RNA viral load.
- CD4 and CD8 cell count.
- Quantitative serum immunoglobulin levels (IgG, IgA, IgM).
- Assessment for Hepatitis C antibody, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis B surface antigen (HBsAg). A baseline Hepatitis B or C viral load should be obtained on all participants who are Hepatitis B core antibody positive, Hepatitis B antigen positive, and/or Hepatitis C positive respectively.

8.1.7 Bone marrow biopsy or aspirate for histology and determination of percent bone marrow involvement is required within 6 weeks prior to participant registration only if PET/CT not performed and there was no prior documentation of bone marrow involvement by lymphoma. Based on the Lugano criteria, PET/CT scan indicating bone or marrow involvement is sufficient to designate advanced-stage disease, and a bone marrow biopsy is not required. If a bone marrow is necessary, unilateral bone marrow biopsy/aspirate is allowed, with an aggregate core length of 2 cm, either from one site or bilateral sites. If feasible, a portion of the bone marrow biopsy and aspirate will be sent for cytogenetic analysis. If bone marrow involvement by lymphoma has already been documented after bone marrow biopsy performed more than 6 weeks prior to registration the biopsy does not have to be repeated. Unilateral bone marrow biopsy/aspirate is allowed, with an aggregate core length of 2 cm, either from one site or bilateral sites. If feasible, a portion of the bone marrow biopsy and aspirate will be sent for cytogenetic analysis.

8.1.8 Determination of LVEF by MUGA scan or echocardiogram.

8.1.9 Lumbar puncture (LP) for dose-finding cohort: routine studies with cytology and flow cytometry.

8.1.10 LP for Dose-Expansion Cohort: Routine CSF studies including cytology and flow cytometry. Asymptomatic leptomeningeal disease will be allowed in the dose-expansion cohort.

8.1.11 Diagnostic slides and tissue block of biopsy submitted within **1 month** of enrollment in Advantage eClinical to the AMC Pathology Core Lab at Weill Cornell Medical Center and reviewed for adequacy for COO. Adequacy for COO is defined as adequate tissue for IHC determination of COO as well as tumor content of at least 60% for GEP analysis for COO.

8.1.12 Optional donation to the AIDS and Cancer Specimen Resource (ACSR). (See Appendix VI for ACSR Informed Consent Form and Appendix V for ACSR Specimen Preparation and Shipping Instructions).

8.1.13 Correlative studies

Note: For participants who are enrolled after receiving one cycle of chemotherapy off study, the following baseline studies must be collected after enrollment and prior to initiation of treatment under protocol. Subsequent studies will be collected at the specified times counting the off-study cycle as Cycle 1.

See Appendix X and Appendix XIV for full details on collection and shipping.

8.1.13.1 Blood samples for circulating tumor DNA

8.1.13.2 EBV viral load

8.1.13.3 Blood cytokines

8.1.14 Drug diaries provided to participant (Appendix VIII)

8.1.15 Letter to Physician provided to participant (Appendix XVIII)

8.2 Evaluations During Treatment

Evaluations are to occur in both Phases unless otherwise specified. For participants enrolled after receiving prior treatment, the off-study chemotherapy cycle treatment counts as Cycle 1 for the purpose of obtaining the following studies (except for correlative studies) and re-staging. Participants who discontinue ibrutinib (due to toxicity, participant refusal, or other reasons) but continue R-da-EPOCH are considered on study until protocol chemotherapy is completed, and should have efficacy, toxicity, and follow-up data reported.

8.2.1 Day 1 or within 3 days (day -3, -2 or -1) prior to each cycle of chemotherapy a physical examination, including weight/height/BSA, vitals, and performance status will be performed. Disease measurable by physical examination will be recorded in two dimensions, if possible.

8.2.2 Medical history, including concomitant medication changes and any signs and symptoms (Day 1 or within 3 days prior). Evaluate AEs and record those required in Advantage eClinical.

8.2.3 CBC with differential and platelet count

- CBC with differential will be repeated prior to beginning each cycle (Day 1 or within 3 days prior).
- For severely immune compromised participants (CD4 < 100 cell/mm^3) it is advisable that a CBC with differential be obtained on or about day 15 of each cycle in order to determine length of prophylactic antibiotic treatment.
- CBC and differential will be obtained on or about Days 9, 12 and 15 (± 3 days) after each cycle of chemotherapy in order to determine toxicity and cyclophosphamide dose adjustments. If by the second CBC, the nadir has been reached and the ANC is recovering, no further CBCs are necessary (i.e., 2 CBCs will suffice).

8.2.4 Serum chemistries to include magnesium, glucose, electrolytes, BUN, creatinine, total bilirubin, ALP, LDH, total protein, albumin, AST and ALT will be repeated on Day 1 (- 3 days) of each cycle with results obtained no more than 72 hours prior

to dosing. Rituximab may proceed in anticipation of chemotherapy while these results are pending provided there is no prior history of renal insufficiency or hepatotoxicity, and no evidence of jaundice on physical exam. Electrolytes and creatinine must be monitored while on ibrutinib and participants' potassium and magnesium should be corrected prior or during administration of ibrutinib.

8.2.5 CD4 and CD8 cell count within 7 days before the end of Cycle 2 (prior to the start of Cycle 3 or day 1 of Cycle 3).

8.2.6 Quantitative immunoglobulins (IgG, IgA, IgM) within 7 days before the end of Cycle 2 (prior to the start of Cycle 3).

8.2.7 HIV viral load will be done at the local institution within 7 days before the end of Cycle 2 (prior to the start of Cycle 3).

8.2.8 HBV and/or HCV viral load in participants who were HBV surface antigen positive, HBV core antibody positive, or HCV antibody positive with undetectable viral particles or viral load at baseline within 7 days before the end of cycles 2 and 4 (prior to the start of cycles 3 and 5) and within 4-8 weeks after Day 1 of cycle 6.

8.2.9 If Grade 3 or 4 hematologic toxicity occurs at any time, blood sampling for follow-up evaluation should be performed as clinically indicated until the abnormality resolves.

8.2.10 Collect participant Drug Diary and provide a new one (prior to Cycles 2-6); Appendix VIII.

8.2.11 Correlative Studies

See appendices and MOP for full details for specimen collection times, processing and shipping.

8.2.11.1 Pharmacokinetics for ibrutinib: only during cycle 1: See table "Ibrutinib Levels" in Appendix I for timing of collection and Appendix XIII for shipping information.

8.2.11.2 Pharmacokinetics for doxorubicin, vincristine and etoposide: only during cycle 1.

8.2.11.3 ITK and BTK occupancy: only during cycle 1, Monday-Thursday. If this is not planned for Monday-Thursday, the BTK/ITK occupancy will not be drawn. This will not be a protocol deviation.

8.2.11.4 Cytokines: after cycle 2 (between the last dose of ibrutinib in cycle 2 and before the next dose of EPOCH in cycle 3).

8.2.11.5 Circulating tumor DNA studies will be drawn at the end of cycle 2 and the end of cycle 4 after ibrutinib treatment is complete and before the next dose of EPOCH is infused.

8.3 Evaluation of Response

For those participants enrolled after prior treatment, the off-study chemotherapy cycle DOES COUNT towards re-staging. After Cycle 4 (between days 10-21) and 4-8 weeks after the beginning of Cycle 6, the following evaluations must be performed:

8.3.1 After Cycle 4 (between days 10-21), the following evaluations must be performed:

- Diagnostic CT scans of chest, abdomen, and pelvis +/- neck, if involved. If possible, measurement of sites of disease present.
- Participants with CR after Cycle 4 will receive two additional cycles of chemotherapy and complete a total of six cycles of chemotherapy. Participants who achieve a PR only after Cycle 4 may continue on protocol therapy or they may be removed from the study at the discretion of the physician (local Principal Investigator). Participants with stable disease after 4 cycles (i.e., who did not achieve at least a PR) or progressive disease at any time will be removed from protocol therapy and the examination and tests listed in Section 8.5 will be performed. These participants will be followed for survival only.

8.3.2 After Cycle 6 (4-8 weeks after the beginning of Cycle 6), or within 4-8 weeks of treatment discontinuation if treatment was stopped after cycle 4 and prior to cycle 6 due to excessive toxicity, the following evaluations must be performed:

- PET/CT scan.
- If diagnostic CT scans were performed at baseline and were abnormal before treatment, diagnostic CT scans should be repeated, including assessment of extranodal sites, at the end of therapy. If possible, measurement of sites of disease present. However, if the participant's insurance or third party will not cover the costs for these tests, omission of this exam will not be considered a protocol violation.

8.3.3 Participants with lymphomatous bone marrow involvement are required to have a repeat bone marrow exam only if all other evidence of disease has resolved (CR) and participant is unable to receive PET/CT scan restaging.

8.3.4 Repeat of any other test that demonstrated lymphomatous involvement at the baseline evaluation.

8.4 End of Treatment Evaluations

Evaluations should be performed 4-8 weeks after the beginning of Cycle 6. The following evaluations must be performed:

8.4.1 See Section 8.3 for response evaluations via imaging and marrow involvement.

8.4.2 History, physical examination, performance status will be performed. Disease measurable by physical examination will be recorded in two dimensions, if possible.

8.4.3 Adverse event evaluation.

8.4.4 CBC with differential and platelet count.

8.4.5 Serum chemistries to include magnesium, glucose, electrolytes, BUN, creatinine, total bilirubin, ALP, LDH, total protein, albumin, AST, and ALT.

8.4.6 CD4 and CD8 cell count.

8.4.7 Quantitative immunoglobulins (IgG, IgA, IgM). Once quantitative immunoglobulins are within normal limits, they no longer need to be collected.

8.4.8 HIV viral load at the local institution will be done 4-8 weeks.

8.4.9 HBV and/or HCV viral load in participants who were HBV core antibody positive or HCV antibody positive with undetectable viral load.

8.4.10 PET/CT scan to document remaining active sites of lymphomatous disease within 4-8 weeks after the beginning (day 1) of Cycle 6. If diagnostic CT scans were performed at baseline and were abnormal before treatment, diagnostic CT scans should be repeated, including assessment of extranodal sites, at the end of therapy. If possible, measurement of sites of disease present. However, if the participant's insurance or third party will not cover the costs for these tests, omission of this exam will not be considered a protocol violation.

8.4.11 Correlative Studies

See appendices for full details for specimen collection times, processing and shipping.

8.4.11.1 Blood samples for circulating tumor DNA

8.4.11.2 EBV viral load

8.4.11.3 Cytokines

8.4.12 Collect participant Drug Diary

8.5 Early Discontinuation Evaluations

Participants discontinuing therapy early (i.e., PD or stable disease, excessive toxicity, administrative reasons, participant non-compliance, etc.) will have a complete physical examination including performance status and blood drawn for the following studies within 1 month after treatment discontinuation, unless otherwise noted. Participants will be followed for survival only for up to 5 years after the last date of treatment.

8.5.1 CBC with differential and platelet count.

8.5.2 Serum chemistries to include magnesium, glucose, electrolytes, BUN, creatinine, total bilirubin, ALP, LDH, total protein, albumin, AST, and ALT.

8.5.3 HIV viral load (do not repeat if done within 1 month from removal from treatment).

8.5.4 CD4 and CD8 cell count (do not repeat if done within 1 month from removal from treatment).

8.5.5 Quantitative immunoglobulins (do not repeat if done within 1 month from removal from treatment).

8.5.6 HBV and/or HCV viral load in participants who were HBV surface antigen positive, HBV core antibody positive, or HCV antibody positive with undetectable viral load within 2 months after the completion of chemotherapy.

8.5.7 Follow-up of all ongoing, related AEs until resolved or determined to be permanent.

8.5.8 PET/CT scan is recommended to document remaining active sites of lymphomatous disease within 4-8 weeks of treatment discontinuation if treatment was stopped after cycle 4 and prior to cycle 6 due to excessive toxicity (do not repeat if it was already done after cycle 4, and if no further treatment was given after cycle 4). If diagnostic CT scans were performed at baseline and were abnormal before treatment, diagnostic CT scans should be repeated, including assessment of extranodal sites, at the end of therapy. If possible, measurement of sites of disease present. However, if the participant's insurance or third party will not cover the costs for these tests, omission of this exam will not be considered a protocol violation.

8.5.10 Correlative Studies

See appendices for full details for specimen collection times, processing and shipping.

8.5.10.1 Blood samples for circulating tumor DNA

8.5.10.2 EBV viral load

8.5.10.3 Cytokines.

8.6 Follow-up Evaluations

The studies listed below will be repeated post-therapy every 3 months (-2 weeks to +4 weeks for the first 3-month visit, then +/- 4 weeks for subsequent 3 month visits) counting from day 21 of the final cycle of chemotherapy for 2 years unless otherwise specified. Routine labs and imaging will be detailed below. All study participants should be followed for up to 5 years after treatment discontinuation or until death if occurring before 5 years of treatment discontinuation. During the third through the fifth years, *only* progression and survival should be reported every 6 months counting from day 21 of the final cycle of chemotherapy (+/- 4 weeks). Participants who discontinue ibrutinib (due to toxicity, participant refusal, or other reasons) but continue R-da-EPOCH are considered on study until protocol R-da-EPOCH is completed, and should have efficacy, toxicity, and follow-up data reported. Participants who discontinue all protocol therapy after having a CR or PR should be followed up for 2 years after treatment, as outlined below. During the third through the fifth years, only progression and survival should be reported every 6 months counting from day 21 of the final cycle of chemotherapy (+/- 4 weeks). For participants who cross over to non-protocol therapy (if PR or stable disease at physician discretion), or discontinue therapy other reasons (Section 4.4) are followed for survival for up to 2 years after treatment discontinuation as outlined below. During the third through the fifth years, only progression and survival should be reported every 6 months counting from day 21 of the final cycle of chemotherapy (+/- 4 weeks). No additional studies except follow up for survival are required after disease progression or study discontinuation for other reasons (Section 4.4). In those instances in which a third-party payer denies payment for some or all of these laboratory analyses, absence of these test results will not be considered a protocol violation.

Data to be collected and reported years 1-2 (every 3 months ±4 weeks)

8.6.1 History, physical examination, vital signs, performance status, review of adverse events will be performed. Disease measurable by physical examination will be recorded in two dimensions, if possible.

8.6.2 CBC with differential and platelet count.

8.6.3 Serum renal and liver functions tests to include BUN, creatinine, total bilirubin, ALP, AST, and ALT.

8.6.4 CD4 and CD8 cell count will be done 4-8 weeks, and at 6 and 12 months after the completion of chemotherapy.

8.6.5 Quantitative immunoglobulins (IgG, IgA, IgM) will be done 4-8 weeks, and at 6 and 12 months after the completion of chemotherapy. Once quantitative immunoglobulins are within normal limits, they no longer need to be collected.

8.6.6 HIV viral load at the local institution will be done 4-8 weeks, and at 6 and 12 months after the completion of chemotherapy.

8.6.7 HBV and/or HCV viral load in participants who were HBV core antibody positive or HCV antibody positive, respectively, with undetectable viral load will be measured 4-8 weeks post Day 1 of cycle 6.

8.6.8 PET/CT scan 4-8 weeks after the beginning (day 1) of Cycle 6 or the final cycle of protocol therapy, and then CT scans every 6 months (+/- 6 weeks) for 2 years.

8.6.9 Correlative studies

See appendices for full details for specimen collection times, processing and shipping.

8.6.9.1 Cytokines: 6 and 12 months after completion of treatment.

Data to be collected years 3-5 (every 6 months ±6 weeks)

8.6.10 Progression (as per participant or medical provider report)

8.6.11 Vital status

9.0 EVALUATION OF RESPONSE

All participants will be evaluated for clinical response by physical examination following each chemotherapy cycle and by imaging studies at the conclusion of the fourth and sixth cycles of chemotherapy and every 6 months thereafter for 2 years. For participants enrolled after prior treatment, the off-study chemotherapy cycle counts towards the 6 cycles requirement; in those participants, only 5 cycles of chemotherapy under protocol are required.

For those participants enrolled after prior treatment, the off-study chemotherapy cycle counts towards re-staging.

After Cycle 4 (between days 10-21), the following evaluation(s) must be performed:

- CT chest/abdomen/pelvis +/- neck if involved.
- PET/CT scan to document active sites of lymphomatous disease. However, if the participant's insurance or third party will not cover the costs for these tests, omission of this exam will not be considered a protocol violation.

Four to eight weeks after the beginning of Cycle 6 (or 4-8 weeks after treatment discontinuation if treatment was stopped after cycle 4 and prior to cycle 6 due to excessive toxicity), the following evaluation must be performed:

- PET/CT scan.
- If diagnostic CT scans were performed at baseline and were abnormal before treatment, diagnostic CT scans should be repeated at the end of therapy, including assessment of extranodal sites. However, if the participant's insurance or third party will not cover the costs for these tests, omission of this exam will not be considered a protocol violation.

9.1 Response Assessment

Response is currently assessed on the basis of clinical, radiologic, and pathologic (i.e., bone marrow) criteria.

Radiologic response will be based on the Lugano Classification.[71] A bone marrow aspirate and biopsy should only be performed after completion of therapy to confirm a CR if they were initially positive and participant is unable to receive PET/CT scan restaging, or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

9.2 Definition of Response

9.2.1 Revised Criteria for Response Assessment per Lugano classifications for PET/CT response[71]

Table 9-A: Definition of response for PET/CT

Response	Site(s)	PET/CT-Response
Complete Response (CR)	Lymph nodes and extralymphatic sites	Complete metabolic response with Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
	Nonmeasurable lesion	Not applicable
	Organ enlargement	Not applicable
	New lesions	None
	Bone marrow	No evidence of FDG-avid disease in marrow (see PET/CT response in extralymphatic sites above for exceptions to uptake in the marrow)
Partial Response (PR)	Lymph nodes and extralymphatic sites	Partial metabolic response with Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size
	Nonmeasurable lesion	Not applicable
	Organ enlargement	Not applicable
	New lesions	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan

Response	Site(s)	PET/CT-Response
No response or stable disease (SD)	Target nodes/nodal masses, extranodal lesions	No metabolic response with Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasurable lesion	Not applicable
	Organ enlargement	Not applicable
	New lesions	None
	Bone marrow	No change from baseline
Progressive disease (PD)	Individual target nodes/nodal masses	Progressive metabolic disease with Score 4 or 5 with an increase in intensity of uptake from baseline and/or
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment
	Nonmeasurable lesion	None
	Organ enlargement	Not applicable
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered
	Bone marrow	New or recurrent FDG-avid foci

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

9.2.2 Revised Criteria for Response Assessment for CT response[71]

Table 9-B: Criteria for response for CT

Response	Site(s)	CT-Response
Complete Response (CR)	Lymph nodes and extralymphatic sites	Complete radiologic response (all of the following) Target nodes/nodal masses must regress to 1.5 cm in longest diameter No extralymphatic sites of disease No new lesions
	Nonmeasurable lesion	Absent
	Organ enlargement	Regressed to normal
	New lesions	None
	Bone marrow	Bone marrow with normal morphology; if indeterminate, IHC negative
Partial Response (PR)	Lymph nodes and extralymphatic sites	Partial remission (all of the following) 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm 5 mm as the default value When no longer visible, 0 0 mm For a node 5 mm 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasurable lesion	Absent/normal, regressed, but no increase
	Organ enlargement	Spleen must have regressed by 50% in length beyond normal
	New lesions	None
	Bone marrow	N/A
No response or stable disease (SD)	Target nodes/nodal masses, extranodal lesions	50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Nonmeasurable lesion	No increase consistent with progression
	Organ enlargement	No increase consistent with progression
	New lesions	None
	Bone marrow	N/A

Response	Site(s)	CT-Response
Progressive disease (PD)	Individual target nodes/nodal masses Extranodal lesions	Progressive disease requires at least 1 of the following Perpendicular diameters: An individual node/lesion must be abnormal with: longest diameter 1.5 cm and Increase by 50% from perpendicular diameters nadir and An increase in longest diameter or shortest diameter from nadir 0.5 cm for lesions 2 cm 1.0 cm for lesions 2 cm In the setting of splenomegaly, the splenic length must increase by 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Nonmeasurable lesion	New or clear progression of preexisting nonmeasured lesions
	New lesions	Regrowth of previously resolved lesions A new node 1.5 cm in any axis A new extranodal site 1.0 cm in any axis; if ≥ 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent involvement

9.2.3 Recurrent disease is defined as the appearance of tumor following documentation of a complete remission.

9.2.4 Time to response is defined as time from the first dose of chemotherapy until documentation of first response.

9.2.5 Time to progression is defined as time from initiation of chemotherapy to documentation of first progression.

9.2.6 Response duration is defined as the time from first documentation of response to documentation of first progression.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

The primary aim is to determine the MTD and RP2D of ibrutinib in combination with R-da-EPOCH using a 3+3 dose de-escalation design. There will be no formal statistical testing for the dose-finding portion of the study.

Once the RP2D or MTD dose is determined, additional 36 participants will be enrolled into the dose-expansion cohort.

Secondary endpoints for safety, response, survival, COO and other biomarkers are being obtained to better characterize the toxicity and safety profile, assess the pharmacokinetics, and identify early signs of efficacy within the GCB and non-GCB population.

10.2 Sample Size/Accrual Rate

10.2.1 Sample size

The minimum sample size for this study is 9. The maximum sample size for the dose de-escalation dose-finding portion of the study will be 18 participants. The maximum number of participants on this study, including the dose-finding and dose-expansion portions, is 54.

10.2.2 Accrual rate

The accrual rate will be 1 participant per month during dose-finding and 3 per month during the dose-expansion phase.

In order to ensure for the minimum participant requirement for non-GCB ARL, if after enrollment of 20 and 30 participants on trial, there are <50% non-GCB, non-GCB COO (as determined at individual AMC site) will be preferentially enrolled to meet the minimum number of participants required in the trial (22 non-GCB participants by local pathology).

10.2.3 Replacement of inevaluable participants

For a participant who does not have adequate tissue for GEP, we will replace up to 14 participants (assuming 30-35% insufficient tissue for GEP) on trial. If we need to replace more than 14 participants, AMC and other involved parties will discuss a remediation plan. Therefore, the maximum number of participants is 54 participants (40 evaluable with 14 replacements, if needed).

For a participant who does not complete cycle 1, the participant can be replaced if, based on a review of the available safety for that dose level, the principal investigator agrees that the events leading to participant withdrawal are unlikely to constitute a safety risk for further participant enrollment and dose escalation. This means that as long as participant safety is not compromised, a participant who withdraws from the study for administrative reasons prior to experiencing DLT during cycle 1 of therapy can be replaced by another participant to complete the number of participants evaluable per dose level required by the protocol. Similarly, as long as participant safety is not compromised, if an eligibility criterion or protocol violation occurs that substantially impairs evaluation of DLT during cycle 1, another participant can enter the cohort to complete the number of

participants evaluable per dose level required by the protocol. Any replacement participant will be enrolled into the same dosing cohort as that for the participant who withdrew. Participants withdrawn because of ibrutinib-related DLT may not be replaced.

10.3 Stratification Factors

There will be no stratification of participants in this study.

10.4 Analysis of Primary Endpoint

Safety analyses in general will be descriptive and will be reported in tabular format with the appropriate summary statistics (count and percentage). In the dose-finding portion, the number of DLTs identified among the DLT-evaluable subjects will be listed and summarized by dose level. The safety variables will be listed and summarized for (1) subjects in the dose-finding portion, (2) subjects in the dose expansion cohort (DEC), and (3) all subjects in the study.

10.5 Analysis of Secondary Endpoints

Secondary aims (includes the dose-finding and dose-expansion cohort):

The dose-finding portion of the study is a dose de-escalation study of ibrutinib, and therefore, a small group of participants may potentially receive ibrutinib at a higher dose than the dose-expansion cohort. However, given this dose of ibrutinib may likely be efficacious, all participants in the pilot study will be analyzed for the secondary aims. However, the secondary aims will be analyzed and examined by dose level of ibrutinib.

Toxicity data will be presented by type and severity for each dose cohort. Incidence of toxicity related dose reductions and treatment discontinuations will be summarized for each dose group.

The complete response rates and their corresponding 95% confidence intervals will be calculated for participants with ARL treated with combination ibrutinib and R-da-EPOCH.

The Kaplan Meier method will be used to estimate the 1- and 2-year PFS and OS of participants with ARL treated with combination ibrutinib and R-da-EPOCH, as well as, their corresponding 95% confidence intervals. This pilot study will not be powered to detect changes survival from addition of ibrutinib to R-da-EPOCH.

The participant's lymphoma COO will be determined by GEP (GCB, ABC, unclassifiable) and IHC (GCB, non-GCB). The concordances and discordances between classifications will be estimated with binomial proportions and their 95% corresponding confidence intervals. The response rates and survival as categorized by GEP or IHC will be compared, to see which analysis of COO best correlates with treatment response. Chi-square tests will be used to test the associations between 1) GEP (GCB, ABC, unclassifiable) with response rates and 2) IHC (GCB, non-GCB) with responses rate. The Kaplan Meier method will be used to calculate estimates of OS and PFS within GEP (GCB, ABC, unclassifiable) and within IHC (GCB, non-GCB), as well as their 95% confidence intervals. The log-rank test will be used to test differences with respect to OS and PFS within GEP and within IHC.

The percentage of participants who receive two or more cycles of R-da-EPOCH, and are able to continue on a minimum dose level of cyclophosphamide of -1 and above after dose adjustments for hematologic toxicities will be calculated.

The average number of days per cycle participants are able to stay on planned dose of ibrutinib will be calculated.

Descriptive statistics will be used to evaluate the changes in levels of HIV-1 viral reservoirs and EBV viral loads from baseline (before initiation of treatment), compared with treatment completion. If there are sufficient data, the binomial test of proportions will be used to test if the long term viral reservoir is either undetectable or below baseline in at least half of the participants.

To assess the effect of ibrutinib and R-da-EPOCH on HIV latency reservoirs and correlate with degree of ITK inhibition, Pearson or Spearman correlation coefficients will be used, as appropriate.

Descriptive statistics will be used to assess the effect of ibrutinib and R-da-EPOCH on B-cell receptor signaling pathway including BTK activity.

Descriptive statistics will be used to evaluate the effect of ibrutinib and R-da-EPOCH on T-cell receptor signaling via ITK activity.

Descriptive statistics will be used to assess the soluble cytokine response to ibrutinib and R-da-EPOCH.

For ibrutinib, doxorubicin, etoposide, and vincristine: relevant individual PK parameters will be estimated using non-compartmental or compartmental PK methods with the software WinNonlin. The PK variables will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) and compared across dose levels (if applicable) using nonparametric statistical testing techniques. The PK variables will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation). Pharmacokinetic parameters (i.e., C_{ss}, Cl, and AUC) will be correlated with pharmacodynamics effects using nonparametric statistical testing techniques. Significance for comparisons will be at the $p<0.05$ level.

11.0 ROLE OF DATA MANAGEMENT

11.1 CRF Instructions

Access to the internet data entry system for this study, Advantage eClinical, and instructions for recording of study data on CRFs will be provided by the AMC ODMC at www.AIDSCancer.org. Participating institutions are responsible for submitting data and/or data forms via Advantage eClinical in accordance with the AMC Data Entry Guide and specific form instructions, within the timelines specified by the AMC's Standards of Procedure for Site Performance Measures.

11.2 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study (See Appendix VII, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study database.

11.3 Data Monitoring

This study will be monitored in compliance with AMC policies and by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and participant-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. 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).

The AMC ODMC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

11.4 Collaborative Agreements Language

The Collaborative Research Agreement is presented in Appendix II.

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 IRB Approval and Informed Consent

The principles of Institutional Review Board (IRB) approval and informed consent described in the Food and Drug Administration (FDA) regulations (21 CFR Part 50 and 56) and/or Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects regulations (45 CFR Part 46) must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IRB, which specifically approves the protocol and informed consent, before participant enrollment. The IRB must also approve any significant changes to the protocol and documentation of this approval must be sent to the AMC ODMC. The IRB must review the research project at least once every 365 days during the duration of the project. Continuing approval of the project must also be given in writing and provided to the AMC ODMC.

Records of all study review and approval documents must be kept on file by the Investigator and are participant to inspection during or after completion of the study. AEs must be reported to the IRB according to local procedures. The IRB should receive notification of completion of the study and final report within 3 months of study completion and termination. The Investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

Written informed consent will be obtained from the participant. The nature and significance of the risks associated with the study must be explained to the participant. The informed consent will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, all risks of the investigational agent(s) and/or study participation as listed in the model informed consent form, and all other elements of informed consent as required by regulation. A copy of the consent form will be given to the participant to keep.

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local and national laws and regulations governing the confidentiality and disclosure of health information.

12.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. All amendments require approval by the IRB/IEC of the treating institution. A copy of the written approval of the IRB/IEC must be sent to the ODMC.

12.3 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Consortium (AMC). As part of their contractual obligations, each participating site within the AMC and the AMC as a whole is required to assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

Table 12-A: Accrual targets

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	9	14	1	4	28
White	4	8	1	3	16
More Than One Race	1	3	2	1	7
Total	14	28	4	8	54

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APPENDIX I: SCHEDULE OF EVALUATIONS

The schedule of evaluations below applies to all participants on study. Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy unless otherwise specified. Scans and x-rays must be done 4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Labs, medical history, adverse event reporting, and physical exam (including vital signs, performance status, exam and weight) done prior to each cycle of treatment may be done on days -3, -2, -1, or 1 of each cycle.

	Screening/Baseline	Prior to Each Cycle	Day 8[14]	Days 9, 12, 15	End of Cycle 2	End of Cycle 4	End of Treatment Evaluations (4-8 Weeks Post Day 1 of Cycle 6)	Follow Up Evaluations	Early Discontinuation Evaluations
CTEP IND Agent ibrutinib		X							
Participant Drug Diary (provide for new cycle, collect/review for prior cycle)		X							
Informed consent	X								
Switch to non-moderate or strong CYP3A4 modulating antiretroviral (ARV) and medication regimen	X[10]								
Medical history	X	X[2]					X	X[8]	X
Physical exam (including node exam and measurement)/Height/Weight/BSA	X	X[2]					X	X[8]	X
Vital signs	X	X[2]							
Performance status	X	X[2]					X	X[8]	X
CBC w/differential, platelets	X[15]	X[2]		X[1]			X	X[8]	X
Serum chemistry	X[15]	X[2]					X	X[8, 21]	X
Serum magnesium	X[2]	X[2]					X		X
Serum pregnancy test	X[20]								
EKG	X								
Adverse event evaluation		X[2]					X	X	X[17]
Radiologic evaluation via CT chest/abdomen/pelvis +/- neck	X					X[4]	X[4]	X[18]	
Radiologic evaluation via PET/CT	X[12]						X[4]		X
Tumor measurement	X					X[4]	X[4]		X
MRI brain and spine (if clinically indicated)	X								

	Screening/Baseline	Prior to Each Cycle	Day 8[14]	Days 9, 12, 15	End of Cycle 2	End of Cycle 4	End of Treatment Evaluations (4-8 Weeks Post Day 1 of Cycle 6)	Follow Up Evaluations	Early Discontinuation Evaluations
B-HCG within 7 days prior to cycle 1	X								
Hepatitis B and C serologies	X				X[7]	X[7]	X[7]	X[7]	X[7]
Confirmation of HIV	X								
T cell subsets (CD4, CD8)	X				X[5]		X[5]	X[5]	X
HIV-1 RNA viral load	X				X[5]		X[5]	X[5]	X
Quant Immunoglobulins	X				X[5]		X[5]	X[5]	X
LVEF (MUGA or ECHO)	X								
Bone marrow biopsy and/or aspirate required if PET/CT is not performed	X[3]						X[6]		
Lumbar puncture[21]	X[15]								
Tissue (block, core, or slides) from at least a core, and ideally an incisional or excisional biopsy (FFPE tissue acceptable) AND IHC slides for central pathology review (Appendix IX)	X								
Pharmacokinetics (chemotherapy)		X[12]							
Pharmacokinetics (ibrutinib, pre-dose)		X[12]	X[12]						
Cytokines	X				X[9]		X[9]	X[9]	X[9]
EBV viral load	X						X		X
BTK/ITK		X[12, 18]							
ctDNA	X				X	X	X		
ACSR Donation (optional)	X[13]								

☐ Only if the participant has a normal hemoglobin or asymptomatic anemia, as determined by the investigator
■ Optional

NOTE: For participants enrolled after prior treatment, the off-study chemotherapy cycle counts towards the 6 cycles requirement. In these participants, only 5 cycles of chemotherapy under protocol are required. For these participants, baseline assessments that were performed within the protocol timelines prior to the initiation of chemotherapy off study as per Section 8.1 will be accepted at study enrollment as the pretreatment baseline values. All laboratory tests to document eligibility must be performed prior to enrollment. Any other tests or evaluations for protocol requirements at baseline that were not performed prior to the initiation of chemotherapy (off study) must be collected after enrollment and prior to initiation of treatment under protocol. The off-study chemotherapy cycle should be counted in the current number of cycles for the purpose of identifying the studies required in Section 8.2 (except pharmacokinetics), and re-staging.

1. Blood counts: CBC with differential will be obtained prior to beginning each cycle (Day -3, -2, -1 or Day 1). CBC with differential will be obtained on or about days 9, 12, and 15 (± 3 days) or more frequently if clinically indicated. If by the second CBC, the nadir has been reached and the ANC is recovering, no further CBCs are necessary (i.e., 2 CBCs will suffice). If the participant does not obtain two lab counts on 2 nonconsecutive days at least 3 days apart within a week but ANC nadir on any cycle < 500/mm^3, then we will assume the counts that would have been obtained are the same as the single nadir counts; however, clinical evidence of severe neutropenia/thrombocytopenia in absence of lab availability may be discussed by investigator with protocol chairs to determine subsequent cycle dosing. CBCs may be stopped after absolute neutrophil count or platelet recovery after the final cycle of study therapy. For severely immune compromised participants (CD4 < 100 cell/mm^3) it is advisable that a CBC with differential be obtained on or about day 15 of each cycle in order to determine length of prophylactic antibiotic treatment.
2. To be performed within 3 days prior to the start of each cycle of chemotherapy. Rituximab may proceed while these results are pending provided there is no prior history of renal insufficiency or hepatotoxicity, and no evidence of jaundice on physical exam.
3 Bone marrow biopsy or aspirate for histology and determination of percent bone marrow involvement is required within 6 weeks prior to participant registration only if PET/CT not performed and there was no prior documentation of bone marrow involvement by lymphoma. Based on the Lugano criteria, PET/CT scan indicating bone or marrow involvement is sufficient to designate advanced-stage disease, and a bone marrow biopsy is not required. If a bone marrow is necessary, unilateral bone marrow biopsy/aspirate is allowed, with an aggregate core length of 2 cm, either from one site or bilateral sites. If feasible, a portion of the bone marrow biopsy and aspirate will be sent for cytogenetic analysis.
4. Repeat imaging study and tumor measurement/evaluation at indicated times. Participants who achieve a CR after 4 cycles of treatment on all arms will receive 2 additional chemotherapy cycles to complete a total of 6 cycles. Participants with PR at the end of cycle 4 may continue on the protocol and complete a total of 6 cycles of chemotherapy or be removed from study at the discretion of the investigator. Participants who achieve a CR or PR at cycle 4 should have repeat imaging studies performed between 4-8 weeks after Day 1 of cycle 6 or the final cycle of chemotherapy in order to confirm response. PET/CT scan is recommended within 4-8 weeks of treatment discontinuation if treatment was stopped after cycle 4 and prior to cycle 6 due to excessive toxicity (do not repeat if it was already done after cycle 4, and if no further treatment was given after cycle 4). Diagnostic CT scans should be repeated, including assessment of extranodal sites, at the end of therapy. If possible, measurement of sites of disease present. However, if CT scans are not feasible, this will not be a protocol violation.
5. CD4, CD8 cell count, HIV viral load, quantitative immunoglobulins within 7 days prior to the end of cycle 2 (prior to start of cycle 3 OR day 1 of Cycle 3), and 4-8weeks, 6 and 12 months (+/- 4 weeks) after the completion of chemotherapy.
6. Participants with lymphomatous bone marrow involvement are required to have a repeat bone marrow exam only if all other evidence of disease has resolved (CR) and participant is unable to receive PET/CT scan restaging.
7. HBV and/or HCV viral load in participants who were HBV antigen or core antibody positive, or HCV antibody positive with undetectable viral particles or viral load at baseline, at the end of cycles 2; 4; and 4-8 weeks post Day 1 of cycle 6. If discontinuing treatment early, tests will be performed within 2 months following completion of chemotherapy.
8. Indicated study should be repeated post-therapy (after the completion of chemotherapy) every 3 months (-2 weeks to +4 weeks for the first 3-month visit, and +/- 4 weeks for the subsequent 3 month visits) for 2 years. These studies are required at these intervals until disease progression or death (whichever occurs first). Participants with stable disease after 4 cycles (i.e., who did not achieve at least a PR) or who have disease progression and are alive will be removed from protocol therapy and the examinations and tests listed in Section 8.5 performed.. During the third through the fifth years, *only* progression and survival should be reported every 6 months counting from day 21 of the final cycle of chemotherapy (+/- 4 weeks).
9. Cytokines will be obtained at baselines, after cycle 2; and 1, 6, 12 months after completion of therapy.

10. If on a strong or moderate CYP3A4 modulating medication(s), including ARV regimen, participant must be switched to an alternative non-strong or moderate CYP3A4 modulating ARV and medication regimens at least 1 week or 7 days before administration of protocol therapy due to effects on ibrutinib.
11. PET/CT, if feasible. If PET/CT is not feasible, this will not be a protocol violation.
12. Cycle 1 only. See tables "Overview of Biomarkers and Correlative Studies" and "Ibrutinib Levels" below for full details of timing of blood draws
13. Optional
14. Within 2 weeks
15. Lumbar puncture (LP) for Dose-Finding Cohort: Routine CSF studies including cytology and flow cytometry. No patients with known or suspected parenchymal brain, spinal cord disease, or leptomeningeal disease will be allowed on study.

    LP for Dose-Expansion Cohort: Routine CSF studies including cytology and flow cytometry. In the dose-expansion portion of the study, no patients with known or suspected parenchymal brain or spinal cord disease, or suspected/symptomatic leptomeningeal disease will be allowed on study. Asymptomatic leptomeningeal disease will be allowed in the dose-expansion cohort.
16. Continue evaluation until the adverse event(s) is resolved or until determined to be permanent.
17. CT scans every 6 months (+/- 6 weeks) for 2 years. Frequency or length of follow up imaging otherwise as clinically indicated.
18. BTK/ITK occupancy pre-ibrutinib and 4-hours post-ibrutinib may ONLY be drawn on Monday-Thursday. If Cycle 1 is started on Friday-Sunday, this exploratory lab is deferred; this will not be a protocol deviation.
19. Within 7 days of cycle 1
20. During the first two years of follow up, only serum renal and liver functions tests including BUN, creatinine, total bilirubin, ALKP, AST, and ALT are required.
21. If a lumbar puncture with or without intrathecal chemotherapy is planned on study, consider the timing of the lumbar puncture relative to anticipated neutrophil and platelet nadirs. For a lumbar puncture, a short hold (up to 3 days, suggested 2 days prior and 1 day post) should be considered based on the clinical situation of the subject, including assessment of underlying lymphoma and bleeding risk. In cases in which there may be a higher risk of bleeding (i.e., history of difficult LP access), it may be useful to perform the LP under fluoroscopy. Ommaya reservoir access will not require ibrutinib to be held due to low risk of bleeding complications. CNS prophylaxis will be required in participants who meet the following criteria: lymphomatous involvement of bone marrow, testes, sinuses, or epidural regions.

Overview of Biomarkers and Correlative Studies

Sample	Collection	Baseline/ Pretreatment	Cycle 1	Subsequent Cycles	Treatment Discontinuation	Handling and Shipping
EBV viral load	Whole blood (separate PBMC and plasma)	X			4 weeks after completion of therapy	Appendix X
BTK	Whole blood (separate PBMC)	X	Post-treatment 4 hours after first dose of ibrutinib in Cycle 1 only, Mon-Thurs ONLY			Appendix XIV
ITK	Whole blood (separate PBMC)	X	Post-treatment 4 hours after first dose of ibrutinib in Cycle 1 only, Mon-Thurs ONLY			Appendix XIV
Ibrutinib pharmacokinetics	Plasma (heparin)		See "Ibrutinib Levels" table below for timing			Appendix XIII
Etoposide and vincristine pharmacokinetics	Plasma (EDTA)		Collect between 24-48, and 72-96 hours after the start of the infusion on Cycle 1 only			Appendix IX
Doxorubicin pharmacokinetics	Plasma (heparin)		Collect between 24-48, and 72-96 hours after the start of the infusion on Cycle 1 only			Appendix IX
Cytokines	Whole blood (separate plasma)	X		After cycle 2	1, 6, 12 months after completion of therapy	Appendix XII
Circulating Tumor DNA	Whole Blood	X		After Cycle 2, and 4	Within 4 weeks of treatment discontinuation	Appendix XIV

Ibrutinib Levels

Sample	Collection	Cycle 1		Handling and Shipping
		Pre-Dose	Pre-Dose Day 8	
Ibrutinib Peripheral Blood	Plasma (Heparin)	X	X	See Appendix XIII

Ibrutinib Levels (if significant toxicities are seen in the first week)

If a DLT (as defined by Section 4.2) is observed, an expanded PK profile will be obtained on Day 8, 0.5, 1, 2, 4, 6, 8, and 24 hr (Day 9) after ibrutinib is administered.

Sample	Collection	Cycle 1 Day 8*								Handling and Shipping
		Pre-Dose	0.5 hour post-dose	1 hour post-dose	2 hour post-dose	4 hour post-dose	6 hour post-dose	8 hour post-dose	24 hour post-dose (Day 9)	
Ibrutinib Peripheral Blood	Plasma (Heparin)		X	X	X	X	X	X	X	See Appendix XIII

*Each time point for the Day 8 expanded PK profile should be taken within a ± 10 minute window.

APPENDIX II: COLLABORATIVE RESEARCH AGREEMENT

The agent, ibrutinib (hereinafter referred to as "Agent(s)"), supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between Pharmacyclics, Inc. (hereinafter referred to as Collaborator(s)) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the participant of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.):

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

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

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

Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
Fax: 301-402-1584
Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX III: PERFORMANCE STATUS SCALES

Karnofsky Performance Scale		ECOG Performance Status Scale	
Percent	**Description**	**Grade**	**Description**
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some 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).
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.	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.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

APPENDIX IV: INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.]

The patient _____ is enrolled on a clinical trial using the experimental agent **ibrutinib**. *This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient but includes important information for others who care for this patient.*

Ibrutinib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Ibrutinib interacts with a certain specific enzyme in your liver.

- This enzyme is called **CYP3A4**. This enzyme breaks down ibrutinib, gradually reducing the level of the active drug in your system.
- Other medicines may affect the activity of the enzyme. Ibrutinib must be used very carefully with these medicines, or you may need to switch to alternate medications.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects. This includes some drugs including antifungal medications.
    - Some HIV therapies include medications which are CYP3A4 inducers (e.g., efavirenz or etravirine) or inhibitors (e.g., ritonavir or cobicistat). This study will carefully evaluate the safety and tolerability of ibrutinib in patients taking these specific medications.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category. Your prescribers should look at this web site https://crediblemeds.org/healthcare-providers/ or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- In vitro studies indicated that ibrutinib is not a substrate of P-gp (p-glycoprotein) or BCRP (breast cancer resistance protein) transporters but is an in vitro inhibitor of P-gp and BCRP. Systemic ibrutinib is unlikely to be an inhibitor of P-gp at clinical doses ([I]1/Ki < 0.1) but may inhibit BCRP. Ibrutinib may have an effect on P-gp or BCRP substrates in the GI tract due to higher local concentrations after an oral dose. Co-administration of oral narrow

therapeutic index P-gp or BCRP substrates (e.g., digoxin, methotrexate) with ibrutinib may increase their blood concentration.

- Before you begin the study, your study doctor will work with your regular prescriber to switch any other medicines that are considered "**moderate or strong inhibitors or inducers of CYP3A4**." It is vitally important that you provide your study doctor with a complete list of your medications. Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
  - If you take acetaminophen (Tylenol) regularly: You should not take more than 3 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
  - If you drink grapefruit juice or eat grapefruit, or if you drink Seville orange juice or eat Seville oranges: Avoid these until the study is over.
  - If you take herbal medicine regularly: You should not take St. John's wort while you are taking ibrutinib.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

  _____

  and he or she can be contacted at

  _____

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent **ibrutinib.** This clinical trial is sponsored by the NCI. **Ibrutinib** interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Ibrutinib** interacts with a specific liver enzyme called **CYP3A4/5**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered strong inducers or inhibitors of **CYP3A4/5**. ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX V: AIDS AND CANCER SPECIMEN RESOURCE (ACSR) SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS

GENERAL

To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website: www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED **Mondays** through **Thursdays** as an OVERNIGHT PRIORITY shipment. Specimens are **NOT ACCEPTED ON SATURDAYS OR SUNDAYS** in the ACSR.

A. SPECIMEN PREPARATION, PACKAGING, AND SHIPMENT

BLOOD SPECIMENS

Draw two 8.5 cc (mL) yellow top [acid citrate dextrose (ACD)] tubes from study participant. With a black, water resistant, sharpie pen, label each specimen with the following information:

- AMC Protocol # 101
- AMC Participant ID#
- Date and time of collection
- Specimen type, i.e., WB=Whole Blood, P=Plasma, S=Serum, or Tissue
- Specimen purpose: Donation

Specimen shipment

- Seal the tops of the two 8.5 cc (mL) yellow tops with parafilm.
- Place the two sealed tubes into bubble wrap (provided in STP-210 kit).
- Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
- Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and “self-seal”.
- Place poly-bag containing tubes into the white TYVEK bag and seal.
- Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.
- Please refer to the Manual of Procedures and AMC Operations website’s (www.AIDSCancer.org) Shipping tab for more information and the FedEx account details.

Blood specimens should be shipped by overnight express at room temperature to:

Sylvia Silver, DA
AMC Biorepository
George Washington University Medical Center
Ross Hall, Room 118
2300 Eye St, NW
Washington, DC 20037
Phone: 202-994-2945
Fax: 202-994-5056
Email: ssilver@gwu.edu

- Make certain that shipper is already either pre-labeled with 'UN#3373' stamp, or make a paper label with 'UN#3373" and affix it to the shipper.
- Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in mL and affix to the shipper.
- Affix airbill to shipper so that the 'UN' and 'VOLUME' labels are visible.
- RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
- Place the box in the FedEx pickup area at your site or call to request a package pickup.

Please Note: The shippers will be mailed back to each AMC site.

INSTRUCTIONS FOR BLOOD SPECIMENS COLLECTED ON FRIDAY, SATURDAY OR SUNDAY

Preparation of plasma and mononuclear cells

Refer to the ACSR's SOP on Separation of Plasma and Mononuclear Cells on the AMC Operations web site for instructions on preparing plasma and PBMC aliquots. It is preferable that separation occurs as soon as possible. If necessary, whole blood in ACD (yellow top tubes) can be held at room temperature for no more than 24 hours.

Freeze the cell suspension in 0.5 mL aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

*****PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.**

PREPARATION OF TISSUE SAMPLES

Tissue specimens to be fresh frozen should be placed in OCT and then on dry ice immediately. The specimens may stay on dry ice until being transferred to a -80ºC freezer.

Tissue specimens for donation may be batched for shipping after storage in -80ºC freezer.

*NOTE: Specimens can only be accepted Monday through **Thursday**. Therefore, specimens can only be shipped **Sunday-Thursday** for delivery the next day. Shipping frozen tissue requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

TISSUE specimens should be shipped by overnight express to:

Sylvia Silver, DA
George Washington University Medical Center
Ross Hall, Room 118
2300 Eye St, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

C. RECORD OF SPECIMENS

This study will track specimens via GlobalTrace^{SM}, a component of the AMC Advantage eClinical system. The GlobalTrace^{SM} shipment manifest must accompany all specimen shipments.

APPENDIX VI: ACSR INFORMED CONSENT

Study Title for Study Participants:	Collecting Blood and Tissue Sample Donations for Research for HIV/AIDS-Related Cancers
Official Study Title:	Biospecimen Collection and Donation to the AIDS and Cancer Specimen Resource (ACSR)

What is the usual approach to donate blood and/or tissue to the ACSR?

You are being asked to donate blood and/or tissue for future research. You are being asked to donate your blood and/or tissue samples to the ACSR because you have HIV infection and are being considered for participation in an AIDS Malignancy Consortium (AMC) clinical trial. The AMC works with the ACSR to collect donated samples from persons with HIV infection for research studies. People who do not take part in an AMC clinical trial can also donate samples to the ACSR.

What are my other choices if I do not take part in this study?

It is your choice to donate or not donate your blood and/or tissue samples. You may still take part in the AMC clinical study if you choose not to donate blood or biopsy samples to the ACSR.

You may also choose to donate:

- Blood but not tissue, or
- Tissue but not blood.

What is the AIDS and Cancer Specimen Resource (ACSR)?

The ACSR is a biorepository (biobank) that collects human biological specimens (samples) from persons who have HIV or cancers related to HIV/AIDS. The ACSR stores the samples and some of the donor's medical information for use by researchers in future research studies. The National Cancer Institute (NCI) has set up the ACSR to assist researchers locate samples needed for their studies.

The ACSR has an independent research panel that approves researchers' requests to use the ACSR's stored samples for research studies. The ACSR only gives samples and medical information to researchers after their projects have been approved. Researchers may use the samples to study cancers and other diseases associated with HIV disease. This information may help us learn more about the causes of HIV-related diseases and cancers and to develop better ways to screen, diagnose, and treat them.

Why is this study being done?

The purpose of this study is to collect samples for the ACSR for future research studies. Researchers may study samples from the ACSR in combination with hundreds or thousands of other samples to explore how biologic or genetic factors may be related to HIV-related diseases and cancer. The information might help doctors in the future to identify who will or will not benefit from treatment. The samples may be used to learn more about how HIV-related diseases and cancers develop. The samples may also lead to new tests or discoveries. Finally, researchers may use the samples to study the genetic material from your cancer tissue and compare it to the material from your normal tissue (blood) to try to find the differences that exist. These studies could make it possible to identify many of the changes that are associated with diseases such as cancers. It may

also help us tailor treatments to a patient's unique genetic make-up and/or to the genetic markers of the tumors.

What extra tests and procedures will I have if I take part in this study?

1) If you agree to donate blood, the medical team will draw about 2 tablespoons of blood to give to the ACSR. This takes about 10 minutes.
2) If you agree to donate tissue, your leftover tissue biopsy material will be donated to and stored by the ACSR.
3) Some of your clinical information will be released to the ACSR and entered into their database. The information given to the ACSR will not include your name or any information that could personally identify you.

We will only give the ACSR tissue that is left over after making decisions about your treatment or diagnosis. The study doctor will not take any extra biopsies just for the ACSR.

We cannot tell you right now what future research these samples would be used for. Instead, we are asking that you give approval to give your samples for future testing without contacting you again. The results of whatever research is done on your samples will *not* be told to you or your doctor. The results of the tests will *not* be placed in your study records.

How long will ACSR keep my samples?

Your blood and/or tissue sample will be stored until it is used for research. The samples may be stored indefinitely.

What possible risks can I expect from taking part in this study?

- Blood Draw: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and, rarely, infection.
- Confidentiality: The ACSR will receive study samples with code numbers. There will be no personal identifiers on the samples. Then the samples will be re-labeled with a barcode and stored for future testing. While the ACSR and researchers who study ACSR samples will have no information that could identify you, there is a risk that someone could use information from genetic studies to trace your samples back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

Let your study doctor know of any questions you have about these possible risks. You can ask the study doctor questions about side effects at any time.

What possible benefits can I expect from taking part in this study?

This study is unlikely to help you. This study may help us learn things that may help people in the future.

The information may help to identify those who are at increased risk and those who may benefit from targeted treatment and screening. In turn, these studies could help find ways to prevent or improve treatments for HIV-related diseases and AIDS-related cancers.

Can I stop taking part in this study?

Yes, you may withdraw your samples from the ACSR at any time. You may contact your AMC study coordinator if you would like to withdraw your samples. The coordinator can ask in writing that your sample be removed from research use and that any identifiable sample and information still in their possession be destroyed. However, if any research has already been done using some of your samples, the data will be kept and analyzed as part of those studies.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

There will be no cost to you for donating your samples to the ACSR. You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The AMC will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to seek payment for injury even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The AIDS Malignancy Consortium (AMC)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Office for Human Research Protections and the National Cancer Institute in the U.S.

To protect your privacy, the AMC does not keep identifying information that links study participants to specific samples. As a result, the AMC and ACSR will not be able to link the results from studies that use your samples back to you. Thus, information, including genetic information, that researchers may obtain in studies that use your samples may not be directly linked to you and will not be placed in your medical record. However, some clinical and basic information obtained confidentially from the AMC will be attached with these data. It is possible that findings may one day help, for example, people of the same race or sex as you. It also is possible that genetic factors might come to be associated with people who have HIV and cancer through these kinds of studies.

Where can I get more information?

You may visit the NCI Web site at **http://cancer.gov/** for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at 1-800-4-CANCER (1-800-422-6237).

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

Please circle your answer to show whether or not you would like to take part in each option:

1) I agree to donate my blood to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

2) I agree to donate my blood to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

3) I agree to donate some of my tissue biopsy material that is not required for my treatment or diagnosis to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

4) I agree to donate some of my tissue biopsy material to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

My Signature Agreeing to Take Part in the Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the optional study.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

APPENDIX VII: AMC DATA AND SAFETY MONITORING PLAN

(Version 8.0 • 16JULY2020)

Introduction

The AIDS Malignancy Consortium (AMC) Data and Safety Monitoring Plan (DSMP) outlines the measures employed by the group to monitor the safety of participants and ensure the data validity and integrity for all clinical trials it conducts. This includes methods to: 1) monitor the progress of trials and the safety of participants; 2) comply with regulatory requirements for adverse event (AE) reporting; 3) processes for trial termination or temporary suspension and major modifications; and 4) plans for ensuring data accuracy and protocol compliance. As the AMC conducts protocols of varying research phase, region of conduct, IND sponsor (AMC investigator, CTEP, or industry-sponsored) and clinical data entry system use, this plan addresses broad processes applying to the range of trial designs and requirements. Refer to the individual AMC protocol to identify the applicable study characteristics for the relevant requirements described in this plan.

Monitoring the Progress of Trials and the Safety of Participants

Routine and expedited AE reporting

All AMC protocols that collect safety data adhere to the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm), as applicable to the clinical protocol. AEs are to be recorded in the source documents, assessed by a clinical investigator for the AE reporting criteria, and promptly reported in the clinical data entry system as required by each protocol. For AMC trials conducted under a CTEP IND and AMC trials conducted within the U.S., all AEs that meet the NCI's expedited reporting requirements are reported to the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application, either directly or through integration with Medidata Rave where this system is employed for AMC protocols. Use of this system ensures notification to the protocol chair and Investigational Drug Branch (IDB) at CTEP, as required for trials conducted under a CTEP IND, and a uniform expedited reporting and safety review process for AMC domestic trials. The system may also be programmed to include sponsor notification as required for trials with industry support. Alternate process for expedited AE reporting to the AMC protocol chairs and AMC Operations and Data Management Center (ODMC) within the clinical data entry system (AdvantageEDC or Advantage eClinical only) may be defined in the protocol for select trials (international studies and The ANCHOR Study).

All serious adverse events (SAEs) received by the AMC ODMC will be reviewed by the AMC medical monitor at the AMC ODMC for consideration of individual participant safety, safe trial conduct, data reporting quality for AE term selection, and appropriate application of the regulatory criteria for seriousness, expectedness, and relatedness to the investigational therapy. If alternate procedures are followed for SAE review, the process for adequate medical monitoring will be defined in the AMC protocol and the Transfer of Regulatory Obligations (TORO) with the sponsor. AMC medical monitor review includes review of the CTEP-AERS report before CTEP submission for IDB review (if applicable), or review of the SAE report in the data entry system for trials not using CTEP-AERS for expedited reporting. The IND sponsor or its designee will issue the determination as to whether the AE requires IND safety reporting to FDA as a serious and unexpected suspected adverse drug reaction (SUSAR). For protocols not conducted under an IND,

in the event of disagreement between the reporting physician and the AMC medical monitor regarding the relationship of the AE to the investigational agent(s) (i.e., determination of whether the attribution is unrelated or unlikely, or possible, probable, or definite), the AMC medical monitor will provide the final determination of the relationship. IND safety reporting to FDA is performed by CTEP for trials conducted under a CTEP IND; IND safety reporting is performed by the sponsor or sponsor's designee (AMC ODMC or other party defined in the study agreement or TORO) for IND studies sponsored by AMC investigators or industry sponsors.

Expedited reporting to the Institutional Review Board (IRB)

For trials subject to local IRB review, the site principal investigator is responsible for ensuring that expedited AE reports for its trial participants and any unanticipated problems that affect the local institution only are submitted to the local IRB of the reporting institution, per the local IRB's requirements for such reporting. For studies reviewed by the NCI CIRB, the protocol chair will render a determination as to whether a SAE or other problem constitutes a trial-wide unanticipated problem that requires reporting to the NCI CIRB; reporting will occur per the NCI CIRB's standards of procedure.

To comply with investigator notification requirements for IND studies under 21 CFR 312.32 and 312.55, IND safety reports from all trials the AMC conducts and reports from external sponsors investigating the same agents are made available to all investigators upon receipt from the sponsor or its designee, either via the password-protected section of the AMC Operations web site (AMC trials subject to local IRB review only) or the CTSU website (trials subject to CIRB review/CTEP IND agents). The site clinical investigator responsible for the applicable AMC protocol(s) is responsible for reviewing any IND safety reports received and documenting submission to the IRB of record (if required by local policy) within the timeline defined by the Clinical Trials Monitoring Branch (CTMB) audit guidelines.

Procedures for monitoring trial progress and pharmacovigilance

For trials using AdvantageEDC or Advantage eClinical for clinical data entry, the AMC ODMC provides on demand tabular listings of all reported AEs and SAEs on a participant level to the protocol chair and co-chair(s) for review via the password-protected section of the AMC Operations web site, www.AIDScancer.org. For trials using OPEN and Medidata Rave for clinical data collection, data listing will be made available using that system. Summary reports of AEs by frequency and relationship to the investigational agent(s) are provided to all AMC investigators and their staff It is the responsibility of each site to provide trial-specific AE listings to their respective IRB, if required by its policies. For blinded studies, the AE and SAE listings are reviewed and tabulated without treatment assignment.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the protocol chair and also by the appropriate Scientific Working Group (SWG) during scheduled conference calls (monthly SWG calls and as required, protocol-specific monitoring conference calls). Summary accrual, summary AE, and individual SAE reports are provided to SWG leadership and protocol chairs to monitor participant safety during these monthly calls.

The AMC medical monitor reviews listings of all reported AEs on a quarterly basis for assuring compliance with the protocol requirements for AE reporting and the identification of any safety concerns (individual AE or increased frequency/severity of expected AEs) for the agents under

investigation. Findings from these reviews are communicated to the protocol chairs and all AMC investigators, and posted to the AMC Operations web site.

Data and Safety Monitoring Board Review (DSMB) review

The AMC has formed an independent Data and Safety Monitoring Board (DSMB) for AMC trials and for the ANCHOR Study. As required by NCI policy, the AMC requires DSMB review for all phase III randomized trials. All other clinical trials that the AMC initiates will be reviewed by the AMC ODMC and AMC Statistical Center during protocol development to issue a recommendation as to whether the study requires DSMB oversight, which will require the approval of the AMC Executive Committee. This determination will be based on the phase of the study, experimental design, risk posed by the investigational approach, extent of data available on the safety of an investigational agent, risk posed by the natural course of the health condition under research, and the categories of vulnerable populations involved. The involvement of a DSMB in reviewing an AMC protocol will be identified in each clinical protocol as approved CTEP and, as applicable, the NCI CIRB.

Regarding the composition of the AMC DSMB, voting members usually include physicians, statisticians, an ethicist, and a patient advocate. All voting members have no other affiliation to the AMC, and are appointed by the AMC Executive Committee with the approval of the OHAM Director. Nonvoting members are the AMC group statistician, the protocol statistician, an AMC ODMC staff member, two representatives (normally a clinician or statistician) from CTEP, and the grant program directors from the NCI Office of HIV and AIDS Malignancy (OHAM).

The DSMB reviews all applicable AMC studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all trials under review are prepared by the AMC group statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the DSMB charter. This report addresses specific toxicity issues and any other concerns about the conduct of the trial, as defined by the protocol plan for DSMB review. The report may contain information for the DSMB to render determinations for participant safety, early trial termination, results reporting, or continuing accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB chair to the AMC group chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The group chair or designee is then responsible for notifying the protocol chair and relevant SWG chair before the recommendations of the DSMB are carried out. In the unlikely event that the protocol chair does not concur with the DSMB, then the OHAM program directors and the NCI division director or designee must be informed of the reason for the disagreement. The protocol chair, relevant SWG chair, group chair, DSMB chair, and NCI division director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a protocol amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, the DSMB's recommendations are provided to all AMC investigators and staff. It is each site principal investigator's responsibility for conveying this information to its local IRB as relevant for its protocol participation. For trials reviewed by the NCI CIRB, the AMC

ODMC will support notification to the CIRB as required per its procedures.

Cohort trial reviews not subject to DSMB review

For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met based on a review of all safety data for the protocol-defined evaluation period. If applicable for phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met.

Plans for Assuring Compliance with Requirements Regarding AE Reporting

The protocol chair, AMC group chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with applicable regulatory and protocol requirements for AE reporting. The AMC site principal investigator certifies compliance with NCI and FDA requirements for trial conduct by signing the site subaward agreement for the grant and the AMC Adherence Statement for site membership; clinical investigators also certify compliance in completing the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration, and also for AMC IND studies sponsored by AMC investigators or industry sponsors. Protocol compliance with AE identification, assessment and reporting requirements is assessed by the AMC ODMC using several methods: 1) programmed system checks and messages to instruct the site to complete routine and/or expedited reporting when certain criteria are reported in the clinical data entry system; 2) programmed data reports provided to the protocol chairs that identify reports requiring expedited AE reporting; 3) remote review of data entry or data reports to ensure compliance with protocol and NCI AE reporting requirements; 4) AMC medical monitor review described in the section above; and, 5) routine site audits by reviewing the site's source documentation.

The clinical data entry systems used for AMC studies include the Oncology Patient Enrollment Network, OPEN for enrollment, and Medidata Rave for clinical data entry for enrolled participants; trials activated before September 1, 2020 or that involve only AMC international sites may be reported in AdvantageEDC/Advantage eClinical, a web-based data entry and enrollment system. These data entry systems are programmed to notify the site investigator, protocol chair, AMC medical monitor, and AMC ODMC via email in the event that a site reports an AE that meets expedited reporting criteria to NCI and/or FDA. Additional reporting conditions may be programmed depending on the sponsor reporting requirements of a given protocol (e.g., adverse events of special interest [AESI]). If the site does not follow with an expedited report, the AMC ODMC contacts sites to request compliance with reporting requirements. Additionally, the protocol chair, AMC ODMC, and the AMC medical monitor review reported AEs on a routine basis to identify AEs reported by sites that require expedited reporting. The protocol chair, AMC SWG chairs, AMC group chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

For studies monitored by CTEP using the Data Mapping Utility (DMU), cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. For trials monitored by the NCI's Clinical Data Update System (CDUS), AE information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), AE information is transmitted electronically to NCI every two weeks.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that temporary or permanent suspension of a trial, or major modification to the protocol is under consideration, the protocol chair will convene the AMC ODMC, AMC Statistical Center, and SWG chair by conference call to discuss the options. Suspension actions will also be reviewed by the AMC Executive Committee for program oversight and direct communication of the action with the OHAM program directors. For phase III trials, closure decisions are typically rendered by the AMC DSMB; if the trial in question is under AMC DSMB oversight but rendered by the AMC investigators, the AMC DSMB will be notified of the suspension and the reason. For phase I and II trials, the protocol chair also has the option of asking the DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO), with copy to OHAM Directors, when studies are temporarily or permanently closed. In the event of major trial modification, CTEP must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC clinical site staff into the applicable clinical data entry system for the trial. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. Submitted data entry forms are reviewed for compliance with the protocol and data entry instructions according to the AMC ODMC's standards for data quality processes. AMC ODMC staff routinely interacts with site staff to resolve any data submission problems.

In accordance with NCI guidelines, the AMC ODMC conducts audits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site principal investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a written corrective and preventative action plan to correct deficiencies. If needed, a repeat site audit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option to implement remedial action(s) for the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX VIII: PARTICIPANT DRUG DIARY

YOU MUST KEEP THIS DIARY AND BRING IT TO EVERY APPOINTMENT.

Participant ID #: _____

Cycle #____

Taken once each day in the morning. One cycle (round) is 21 days.

INSTRUCTIONS TO THE PARTICIPANT:

1. Please record in the chart below the date and time each **Ibrutinib** dose was taken. Be sure to record the dose when you take it, and avoid writing entries for several days at once. In the "Comments" section write any problems you are having with the medicines, indicate why if you missed a dose, or if you only took part of the medicine, or you threw up within 2 hours of taking the pills.
2. You should take **Ibrutinib** in the morning, with an 8-ounce glass of water. Do not open, break, or chew the capsule. If your dose needs more than one capsule of Ibrutinib, take the capsules at the same time.
3. If you miss an **Ibrutinib** dose for any reason, take it as soon as you remember on the same day. On the next day, take your next ibrutinib dose at your regular time. Do not take extra doses of ibrutinib on the same day to make up for a missed dose.
4. **YOU MUST KEEP THIS DIARY. PLEASE BRING IT TO EVERY STUDY APPOINTMENT.** Please bring your pill bottle including any unused capsules with you.

Day of Cycle	Date Ibrutinib Taken	Time Ibrutinib Taken	# of Capsules Taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Day of Cycle	Date Ibrutinib Taken	Time Ibrutinib Taken	# of Capsules Taken	Comments
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

Physician's office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of capsules taken this cycle_____
5. Total number of capsules returned _____
6. Physician/Nurse/Data Manager's Signature _____ Date _____

Participant ID #: _____

Cycle #____

Taken once each day in the morning, for days 1-5 of each cycle.

Instructions to the Participant: Please fill out this diary for oral prednisone given as part of the EPOCH chemotherapeutic mixture. If receiving EPOCH as an outpatient, please fill in the full diary on all days prednisone is taken. If receiving EPOCH as an inpatient, your dose will be documented in your hospital record in which you need only check "In Hospital" box on the chart below.

YOU MUST KEEP THIS DIARY. PLEASE BRING IT TO EVERY STUDY APPOINTMENT. Please bring unused capsules with you.

Day of Cycle	Date Prednisone Taken	Time Prednisone Taken	Dose Taken	At home or in hospital	Comments
1				☐ At Home ☐ In Hospital	
2				☐ At Home ☐ In Hospital	
3				☐ At Home ☐ In Hospital	
4				☐ At Home ☐ In Hospital	
5				☐ At Home ☐ In Hospital	

Physician's office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this cycle_____
5. Total number of tablets returned _____
6. Physician/Nurse/Data Manager's Signature _____ Date _____

Filgrastim/Pegfilgrastim

Participant ID #: _____

Cycle #____

Please check the box below for the medication you were given, and if filgrastim circle (doses **bolded** below) the correct dose.

☐ Pegfilgrastim (Neulasta) – 6 mg taken once, 24-48 hours after chemotherapy, subcutaneously.

☐ Filgrastim (Neupogen, G-CSF or biosimilar) - **300 mcg** or **480 mcg** starting day 6 for a minimum 10 days (please speak to your physician about when to discontinue use), subcutaneously

Were you trained on the self-administration of the medication subcutaneously? Yes or No (please circle one)

Day of Cycle	Date Peg/filgrastim Administered	Time Peg/filgrastim Administered	Dose Administered	Comments
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				

Day of Cycle	Date Peg/filgrastim Administered	Time Peg/filgrastim Administered	Dose Administered	Comments
19				
20				
21				

Physician's office will complete this section:

1. Date patient started supportive treatment_____
2. Date patient ended supportive treatment_____
3. Patient's planned daily dose_____
4. Physician/Nurse/Data Manager's Signature _____ Date _____

APPENDIX IX: CENTRAL PATHOLOGY REVIEW

Handling of Tissues:

Tissues should be submitted to the following address:

Julio Cordero
Research Coordinator
Laboratory of Hematopathology
Department of Pathology and Laboratory Medicine
Weill Cornell Medical College/The New York Presbyterian Hospital
Starr-702
525 East 68th Street
New York, New York, 10065
Phone: (212) 746-6357
Fax: (212) 746- 8173
Email: juc9045@med.cornell.edu

Sample collection and processing for mandatory histopathology review by immunohistochemistry (IHC) and gene expression profiling (GEP)

Diagnosis confirmation and quality assessment are mandatory for all patients pre-registered to this study. Submission of the institutional diagnostic slides is preferred for all participants enrolled in the study. Submission of tissue from the diagnostic biopsy in the form of paraffin blocks, tissue cores, or slides (see below) is required for all patients enrolled to this study. Incisional or excisional biopsy is strongly preferred over a core needle biopsy. Diagnosis by fine needle aspirate (FNA) only is NOT acceptable for enrollment.

Pathology reports must also be included.

REQUIRED SPECIMEN SUBMISSION

Option A (Highly encouraged): Tissue block (formalin fixed, paraffin embedded). If requested, the block can be returned to the originating pathology lab.

Option B: Tissue sections. We require submission of one H&E stained slide and 17 tissue sections (or 18 if H&E is not available). These should be 4-5 µm in thickness and mounted onto positively charged slides. If slides of a different section thickness (4-10 µm) are the only available option, then submit the unstained slides and note the thickness on a submission form so that the appropriate number of slides can be processed (NOTE: The H&E must be standard thickness).

Quality assessment and IHC for COO will not be performed until it is clear that there is enough tissue for GEP.

Tissue will be distributed as follows:

i. The central pathology lab will confirm diagnosis, assess the COO using IHC and the Hans algorithm, estimate the % tumor cells to provide for GEP, and mark areas of involvement by lymphoma in the H&E slide.

ii. The marked H&E slide will be sent with 2-8 blank tissue sections (see table below) for GEP.

iii. The remaining slides will be used for complete central pathology review (see below).

Tissue Requirements for GEP Assay

Tumor Surface Area	Number of Slides (5 µm thickness)*	
	Minimum Number of Slides	Recommended Input
2 mm^2	4	8 or more as available
3 mm^2	3	8
4-7 mm^2	2	5-7
8-15 mm^2	1	3-4
≥ 16 mm^2	1	2

* Slide mounted tissue sections with 4-10 µm thickness also are acceptable. The minimum number of slides should be adjusted to obtain a total tissue volume of 0.04 mm^3

Specimen Accessioning: Upon receipt, each specimen from AMC will be logged into GlobalTrace and receive an Immunopathology Laboratory accession number which will be sequential with the other specimens received for various clinical trials, and will be entered into Copath. This will avoid delays in processing. Specimens belonging to AMC will be so stated under "Clinical Information", and therefore can be easily identified and tracked. A report will be issued within one week that includes review of H&E-stained section, diagnosis and immunohistochemistry for COO. A verbal preliminary diagnosis of the H&E, or if IHC stains are provided, can be given in two days if requested. This will be followed by additional reports describing the results of additional immunohistochemistry, in situ hybridization (EBER) and molecular analysis (if requested or considered informative for final diagnosis). All the reports will be sent by FAX to the Operations Center as well as to the submitting physician, and hard copies to both will follow.

Pathology Review: Specimens received will undergo histopathologic diagnosis and classification, immunostaining and molecular analysis. Specifically, cases will be processed as follows:

1. Histopathology- Process tissue, pathologist review of H&E and classification.
2. Immunohistochemistry for lymphoid, proliferation and COO, including as needed: CD20, CD3, BCL-6, CD10, MUM1, Ki67. Additional markers will be considered, if the COO is not clear using these markers.
3. In situ hybridization for EBER will be done. In addition, when indicated for accurate classification, FISH for BCL6, BCL3, and/or MYC will be performed.

Tumor block/tissue slides for GEP: Given the tissue for GEP will be done in batches, the tissue block/slides will be kept at central pathology until GEP is completed. The tissue slides will be shipped in batches of 10 to Dr. Lisa Rimsza.

Record of Specimens: This study will track specimens via GlobalTrace, a component of the AMC Advantage eClinical system. The GlobalTrace shipment manifest must accompany all specimen shipments.

APPENDIX X: EBV COPY NUMBER SPECIMEN PREPARATION & SHIPPING INSTRUCTIONS

Virus Quantitation (EBV and KSHV)

To ship blood for viral quantitation, place two 8.5 mL yellow top (ACD) tubes into a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended Each sample tube should be labeled using a Sharpie pen with the following information:

- Protocol #: AMC-101
- 9-digit Participant #
- Date and time of collection
- Specimen type: Whole Blood
- Specimen purpose: EBV, KSHV

Please refer to the Manual of Procedures and AMC Operations website's (www.AIDSCancer.org) Shipping tab for more information and the FedEx account details.

Specimen Shipment

Specimens are accepted MONDAY through THURSDAY. All specimens should be shipped **OVERNIGHT** to the AMC Biorepository at GWU.

Sylvia Silver, DA
George Washington University Medical Center
Ross Hall, Room 118
2300 Eye St, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

- It is the responsibility of the Primary Investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations (IATA Packing Instruction 650) relating to the handling and shipping of hazardous goods. (IATA Packing Instruction 650 is located on the AMC web site.)
- Use a federally approved shipper for biological substance shipment (Category B). Label the shipper with the "Infectious substance" diamond shaped label. On one side, in black marker write "Biological Substance, Category B, UN 3373", your name or name of responsible person, date of collection and phone number of the person responsible for the package. Package and label the shipment in accordance with the instructions provided for that specific shipper.
- A Shipper's Declaration for Dangerous Goods is not required. However, for all dry ice shipments, the following information must be shown in sequence on the airway bill in the "Nature and Quality of Goods" box: Dry Ice, 9, UN1845, number of boxes being shipped, net weight of dry ice per box.

Please Note: The shipper will be mailed back to the AMC site. The STP-210 SAF-T-PAK shipper is a complete kit (bubble wrap, absorbent paper, labels, etc.) for specimen shipment. To reuse the shipper, you will need new labels, wrap, etc.

Instructions below for bloods collected on Friday-Sunday:

In the event that blood samples are drawn on Friday, the samples must be processed into plasma and peripheral blood mononuclear cells (PBMC) immediately to maintain their viability for analysis, frozen over the weekend, and shipped to the lab on Monday. Preparation of Plasma and Peripheral Blood Mononuclear Cells (PBMCs)

It is preferable that separation occur as soon as possible. If necessary, whole blood in ACD (yellow top tubes) can be held at room temperature for no more than 24 hours.

Materials

- Lymphocyte Separation Medium (LSM Solution, Ficoll-Hypaque - sterile)
- 15 mL conical centrifuge tubes (sterile)
- PBS (sterile)
- 1, 5 mL and 10 mL serologic pipettes (sterile)
- 1.5 mL NUNC tubes
- Alcohol-saturated, control rate freezer container
- DMSO freezing media
- 50% Cryoprotective Medium, Cambrex (catalog no.:12-132A)
- 50% Heat Inactivated Fetal Bovine Serum

Plasma Separation and Freezing Procedures

1. The 8.5 mL tubes of whole blood in acid citrate dextrose should be rotated gently two or three times before being centrifuged. Do not transfer before centrifugation.
2. Separate the cells by centrifugation at 500 g for 10 minutes.
3. Remove 0.5 mL aliquots of plasma and put into separate 1.5 mL NUNC tubes and transfer to liquid nitrogen storage.

PBMC Separation and Freezing Procedures

1. The cells and plasma remaining from the previous step are transferred into a 15 mL conical tube or 50 mL centrifuge tube depending on volume.
2. Sterile PBS should be added to the suspended whole blood cells in an equal volume and pipetted up and down to mix (1:1).
3. The whole blood-PBS mixture should be carefully overlaid onto 4-5 mL of room temperature LSM or Ficoll-Hypaque solution in a sterile 15 mL conical centrifuge tube. A sharp interface should exist between the LSM and the whole blood mixture. (If the layer of LSM gets mixed with the blood-PBS, the tube should be gently rotated to mix the blood, PBS, and LSM, and transfer to a 50 mL sterile conical tube. An equal volume of PBS is added, and the cells are separated at 600 g for 15 minutes. After removal of LSM-PBS supernatant, return to Step 2).
4. Centrifuge the 15 mL conical tube for 30 minutes at 900 g at room temperature. The mononuclear leukocytes (principally lymphocytes and monocytes) will band at plasma/LSM interface.
5. The fluffy white layer just below the plasma layer should be aspirated off and transferred to an appropriately labeled 15 mL sterile conical centrifuge tube. Be careful to remove only the interface and a minimum amount of the LSM or Ficoll-Hypaque.
6. Add three volumes of PBS to the cell suspension and or enough to fill conical and mix by pipetting up and down.
7. Centrifuge at 500 g for 10 minutes.
8. Aspirate off and discard supernatant, taking care not to disturb pellet.
9. Resuspend in 12 mL of PBS. Take 10 µl of suspension for cell counting (dilute accordingly whether using a hemocytometer or automated cell counter). Centrifuge again for 10 minutes at 500g to wash cells.
10. Using a 1 mL pipette, the *DMSO freezing mixture should be added dropwise to the cell pellet suspension. Gently finger-tap between drops to resuspend cells. If the cell pellet is small, only 0.5 mL of freezing media is added (and only one aliquot of cells is frozen). If the cell pellet is large, up to 2 mL of freezing media can be added in a drop wise fashion. (Cell densities of 1 - 10 million PBMC/ml are best for cryopreservation. If a hemocytometer is available, the optimal concentration is 5 x 10^6 PBMC/ml).

    ***Important: Do not put the DMSO containing media on the cell button all at once.**

11. Freeze the cell suspension in 0.5 mL aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

Billing

Please refer to the Manual of Procedures and AMC Operations website's (www.AIDSCancer.org) Shipping tab for more information and the FedEx account details. It is only to be used for billing shipment of specimens to the lab where the sample is processed and/or stored.

Record of Specimens

This study will track specimens via GlobalTrace[SM], a component of the AMC Advantage eClinical[SM] system. The GlobalTrace[SM] shipment manifest must accompany all specimen shipments.

Technical Questions

Sylvia Silver, DA
George Washington University Medical Center
Ross Hall, Room 118
2300 Eye St, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

APPENDIX XI: PHARMACOKINETICS (PLASMA LEVELS OF DOXORUBICIN, VINCRISTINE, AND ETOPOSIDE)

All pharmacokinetic blood samples should be processed into plasma and aliquoted (equal volume into multiple tubes (NUNC cryotubes 1.8 mL with feet and inside threading [product #377267] are preferred). Plasma should be stored at -80º C or lower until shipped in batch.

1. Two tubes will be collected at each of the following time points: between 24-48, and 72-96 hours after the start of the infusion. For doxorubicin, collect ~6 cc of blood in **green-top vacutainer tubes** containing sodium heparin. For etoposide and vincristine, collect one ~10 cc of blood in **lavender-top vacutainer tubes** containing EDTA, for both drugs together. Ensure that the actual time of blood collection and the nominal time of blood collection (e.g., 24-48 time point) are documented with each specimen collected and in the data fields associated with the specimen in GlobalTrace[SM].
2. Specimens should be processed within 30 minutes and in no more than one hour following collection. Centrifuge blood sample at 2500 RPMs for 10 minutes to obtain plasma.
3. The number of aliquots will differ for each tube type. For the green top tube, transfer ~1.5 mL aliquots of plasma into multiple labeled 2 mL cryovials (~2-3 tubes anticipated per blood draw). For the purple top tube, transfer ~1.5 mL aliquots of plasma into multiple labeled 2 mL cryovials (~3-5 tubes anticipated per blood draw). Do not discard any plasma but place in another cryovial. Ensure that the green-top aliquots are labeled as doxorubicin and the purple-tops as etoposide or vincristine.
4. Label each tube with the following information:
   - AMC Protocol # AMC-101
   - 9-digit AMC Participant ID#
   - Date and time of blood collection
   - Specimen type - “Plasma”
   - Specimen purpose: “Doxorubicin PK” (for the green-top tube) or “Etoposide or Vincristine PK” (for the purple-top tube) and collection time (i.e., 24-48, and 72-96 hours)
5. Freeze the NUNC cryogenic tubes immediately and maintain frozen at -80º C.

If there were samples <u>not</u> obtained at the required time points, please inform the Analytical Pharmacology Core (APC) Laboratory prior to shipping.

Shipment

Samples will be kept at the study site and periodically during the study shipped to the APC Laboratory. Unless otherwise stated, samples will be shipped to the APC Laboratory under the direction of Michelle A. Rudek, Pharm.D., Ph.D. Specimens should be stored through the duration of the PK study (through 72-96 hr sample) and shipped as a batch by participant (more than one participant/shipment is acceptable if the site has >1 participant on-study). A participant's samples should be shipped to the APC lab within 1 month of the last sample's collection date. (i.e., if the 72-96 hr sample is collected on 1/1/2018, all of that participant's samples should be at the APC lab by 2/1/2018). If a second set of participant samples can be batched by waiting up to 2 weeks (i.e., 1.5 months), this deviation is allowed.

Please ship 2 aliquots (for both green top and purple top) to the APC laboratory. Once receipt is confirmed, the third/back-up aliquot may be shipped.

Overnight shipments should occur on **Monday** through **Wednesday** (**Tuesday** is the preferred day) except when the following day is a holiday. A fax or call should be place to the Analytical Pharmacology Core Laboratory prior to shipment providing the shipment tracking information. Samples should be shipped on dry ice to:

Analytical Pharmacology Core Laboratory*
Attn: AMC101 Study Samples
1650 Orleans St. CRB1 Rm 184
Baltimore, MD 21231-1000
Phone: 410-502-7192 or 410-955-1129
Fax: 410-502-0895

Technical Questions

Michelle Rudek (mrudek2@jhmi.edu) for questions for questions regarding the PK. Linping Xu (lxu11@jhmi.edu) or India Hinton (ihinton1@jhmi.edu) for questions regarding processing or shipments.

Please refer to the Manual of Procedures and AMC Operations website's (www.AIDSCancer.org) Shipping tab for more information and the FedEx account details.

Record of Specimens

This study will track specimens via GlobalTrace^{SM}, a component of the AMC Advantage eClinical^{SM} system. The GlobalTrace^{SM} shipment manifest must accompany all specimen shipments.

APPENDIX XII: ASSESSMENT OF CIRCULATING LEVELS OF PRO-INFLAMMATORY CYTOKINES

SHIPPING INSTRUCTIONS AND SAMPLE PROCESSING

A. General

To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED Monday through Thursday as an OVERNIGHT PRIORITY shipment. Specimens are NOT ACCEPTED ON SATURDAYS or SUNDAYS in the AMC BIOREPOSITORY.

Should the site collect specimens on Friday through Saturday, samples should be processed for plasma according to the AMC Biorepository's SOP on Separation of Plasma and Mononuclear Cells, available on the AMC Operations web site. At least four 0.5 mL aliquots of serum are required. Aliquots should be frozen at specimens at -80°C and shipped on dry ice to the AMC Biorepository the following week.

B. Specimen preparation, packaging, and shipment

Draw two 6 cc (mL) red top [no additive] tubes from study participant. Seal the tops of the tubes with parafilm. Place the two sealed tubes into bubble wrap (provided in STP-210 kit). Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break. Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and "self-seal." Place poly-bag containing tubes into the white TYVEK bag and seal. Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.

Affix the FED-EX airbill on blank side of the shipper making sure that it is marked "FED-EX PRIORITY OVERNIGHT." Mark "OTHER" in the airbill under "Packaging." Under airbill section "Special Handling," indicate "YES-SHIPPERS DECLARATION NOT REQUIRED." Place "From/To" information onto areas provided on the shipper.

Blood specimens should be shipped by overnight express at room temperature to:

Sylvia Silver, DA
George Washington University Medical Center
Ross Hall, Room 118
2300 Eye St, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

Specimen Labeling

Each sample tube should be labeled using a fine-tipped Sharpie pen with the following information:

- Protocol #: AMC-101
- 9-digit Participant ID #
- Visit #
- Date and time of specimen collection
- Specimen Type: "Serum"
- Purpose: "Cytokine Assays"

Make certain that shipper is already either pre-labeled with 'UN#3373' stamp. Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in mL and affix to the shipper. Affix airbill to shipper so that the 'UN' and 'VOLUME' labels are visible. RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS. Place the box in the FedEx pickup area at your site or call to request a package pickup.

Billing

Please refer to the Manual of Procedures and AMC Operations website's (www.AIDSCancer.org) Shipping tab for more information and the FedEx account details.

Contact for site questions (9AM-5PM Pacific Time)

Lab Manager: Larry Magpantay (lmagpantay@mednet.ucla.edu)
Lab phone: 310-206-6846
Marta Epeldegui office phone: 310-206-6846

AMC BIOREPOSITORY INSTRUCTIONS ONLY

The AMC Biorepository will separate serum, aliquot the serum into as many 0.5 mL aliquots until the sample is used as per AMC Biorepository SOPs, and store at -80°C. Specimens should be sent in batch at the end of the study to UCLA's Martinez-Maza laboratory per SOP.

APPENDIX XIII: PK PLASMA COLLECTION FOR IBRUTINIB

Collect the ibrutinib PK blood samples according to the time points described in the protocol (see "Ibrutinib Levels" table in Appendix I).

USE 1 x 2-mL **GREEN TOP SODIUM HEPARIN TUBE** FOR EACH PK COLLECTION.

1. Allow tube to fill COMPLETELY, as far as the vacuum will allow.
2. Mix the tube immediately upon completion to avoid clotting by inverting gently 5 times.

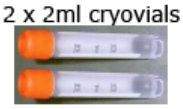
   DO NOT SHAKE.
3. Place the blood samples on melting ice until centrifugation
4. Place the sample in a refrigerated centrifuge (0-4°C).

NOTE: Use a refrigerated centrifuge bucket in cases where a refrigerated centrifuge is not available. Maintain cold temperature during the plasma preparation process.

5. Centrifuge tube within 60 minutes of collection at 4°C for 15 minutes at 2500 rpm.
6. Transfer plasma with pipette equally into two 2-mL cryovials (approximately 0.5 mL of plasma in each tube).
7. Enter the Subject ID number on the sample labels.
8. Store plasma samples in a freezer at -70°C or below, within approximately 60 minutes of blood collection.
9. Ship samples FROZEN in batches (after collection from each subject is completed) to Central Labs.

NOTE: Every effort should be made to collect the full 2 mL blood sample at each time point. In the event that less than 1 mL of blood is collected, the sample will be processed as described above except that the plasma will not be divided into two tubes. This single plasma sample should be frozen, stored and shipped with the primary set of samples.

All PK Timepoints

TEST	COLLECT	PREPARE	CONTAINER	SHIP TEMP
PK	1 x 2ml Green Sodium Heparin 	Centrifuge & Transfer Plasma	2 x 2ml cryovials 	**Frozen**

PK Sample Shipping Instructions

PK SPECIMENS to be batch shipped (FROZEN) from each subject. Please include:

- One primary set of samples for each subject
- One back-up set of samples for each subject (in a separate shipment unless only single plasma sample available)

Samples should be shipped on dry ice **Monday through Thursday** only.

As much as possible, a complete set of primary samples (all time points) for a subject should be batched and shipped together in the same shipment, to the Biorepository at George Washington University.

Please refer to the Manual of Procedures and AMC Operations website's (www.AIDSCancer.org) Shipping tab for more information and the FedEx account details.

The address is:

Sylvia Silver, DA
George Washington University Medical Center
Ross Hall, Room 118
2300 Eye St, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

Instructions for the Biorepository only.

Samples will be shipped in batches annually, after confirmation from the AMC ODMC.

Ship the **back-up** set after the confirmation of receipt of the primary set by Frontage Labs.

Do NOT ship back-up aliquots of plasma in the same shipment as the primary samples from the same subject.

To avoid sample mix-ups or misidentification, place the samples in the shipment by subject number and sample time using zip-lock bags or segmented cartons. There should be **adequate amount of dry ice** included in the shipment **to last for three days of shipping**. Please ship the samples to the following address:

Notify Frontage Laboratories at least 1 day prior to the arrival of the sample, providing shipping details and tracking numbers for the shipment. E-mail Joseph Falcone at samplemanagement@frontagelab.com. The e-mail must specify the study number, the number of pharmacokinetic samples, the time of shipment pick-up and include an electronic sample inventory. This is in addition to entering samples in GT.

Prior to shipment, prepare a sample shipment list (or Inventory list) containing the details of each sample / label identification included in the shipment. All of the sample details on this list must correspond with the details included on the individual sample labels, as each sample label will be checked against the list by Frontage sample coordination personnel. Any discrepancies between information on the sample tubes and information on the e-rosters will be verified and noted in the e-rosters prior to shipping. All sample correspondence must contain the Study Number, Study Drug, and Site references (including emergency contact details and responsible shipment coordinator).

APPENDIX XIV: BTK/ITK OCCUPANCY SPECIMEN PREPARATION & SHIPPING INSTRUCTIONS

A. General

This lab may only be drawn and sent OVERNIGHT EXPRESS Monday-Thursday. If this blood is planned for Friday-Sunday, then the patient's blood for this particular study will be deferred.

Each sample tube should be labeled using a Sharpie pen with the following information:

- Protocol #: AMC-101
- 9-digit Participant #
- Date and time of collection
- Specimen type: Whole Blood
- Specimen purpose: BTK/ITK occupancy

To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED Monday through Thursday as an OVERNIGHT PRIORITY shipment. Specimens are NOT ACCEPTED ON SATURDAYS or SUNDAYS in the AMC BIOREPOSITORY.

Should the site collect specimens on Friday through Sunday, samples will be discarded.

B. Specimen preparation, packaging, and shipment

Draw two 6 cc (mL) yellow top Acid Citrate Dextrose (ACD) tubes from study participant. Seal the tops of the tubes with parafilm. Place the two sealed tubes into bubble wrap (provided in STP-210 kit). Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break. Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and "self-seal." Place poly-bag containing tubes into the white TYVEK bag and seal. Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.

Affix the FED-EX airbill on blank side of the shipper making sure that it is marked "FED-EX PRIORITY OVERNIGHT." Mark "OTHER" in the airbill under "Packaging." Under airbill section "Special Handling," indicate "YES-SHIPPERS DECLARATION NOT REQUIRED." Place "From/To" information onto areas provided on the shipper.

Please refer to the Manual of Procedures and AMC Operations website's (www.AIDSCancer.org) Shipping tab for more information and the FedEx account details.

Blood specimens should be shipped by overnight express at room temperature to:

Sylvia Silver, DA
George Washington University Medical Center
Ross Hall, Room 118
2300 Eye St, NW
Washington, DC 20037
Phone: (202) 994-2945
Fax: (202) 994-5056

APPENDIX XV: DRUGS KNOWN TO BE METABOLIZED BY SELECTED CYP3A4 ISOENZYMES

Some inhibitors and inducers of CYP3A enzymes are listed below. Because lists of such agents are frequently changing, the study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 4.3 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

Inhibitors of CYP3A	**Inducers of CYP3A**
Strong inhibitors:	Carbamazepine
COBICISTAT	Efavirenz
INDINAVIR	Etravirine
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
SUBOXONE	Pioglitazone
TELITHROMYCIN	Rifabutin
Moderate inhibitors:	Rifampin
Amprenavir	St. John's Wort
Aprepitant	Troglitazone
Atazanivir	
Erythromycin	
diltiazem	
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	

Inhibitors of CYP3A	Inducers of CYP3A
NOT azithromycin	
Chloramphenicol	
Ciprofloxacin	
Boceprevir	
Ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
Dronedarone	
Fosamprenavir	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
Posaconazole	
star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

Source: https://crediblemeds.org/healthcare-providers/. Please refer to a constantly-updated resource for the most recent list of agents.

APPENDIX XVI: ANN ARBOR STAGING CRITERIA

STAGE	DESCRIPTION
STAGE I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE).
STAGE II	Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of extralymphatic organ or site and of one or more lymph node region on the same side of the diaphragm (IIE).
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS), or both (IIISE).
STAGE IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.
A	Absence of systemic symptoms
B	Presence of one or more general symptoms: (1) unexplained weight loss of more than 10% of the body weight in the 6 months before admission; (2) unexplained fever with temperatures above 38C; (3) night sweats.

Notes:

1. The lymphatic structures are defined as the lymph nodes (N), spleen (S), thymus, Waldeyer's ring, appendix and Peyer's patches.
2. The reasons for classifying the patient as stage IV is defined further by defining sites by symbols:

   H - Liver L - Lung

   M - Marrow O - Bone

   P - Pleura D - Skin

3. Liver involvement is always considered Stage IV disease, as is bone marrow involvement away from a site of an involved lymph node.

APPENDIX XVII: DOSE ADJUSTMENTS FOR IBRUTINIB AND/OR EPOCH

Dose adjustments for ibrutinib occur WITHIN the cycle, and dose adjustments for EPOCH occur PRIOR TO each cycle based on nadir counts of ANC <500/mm^3 and platelet counts <25,000/mm^3.

Please note for tables A-E, for those who had one cycle of CHOP/EPOCH +/- Rituximab prior to enrollment in the dose-expansion cohort, the first cycle on study will be "Cycle 2."

Reminder: Ensure the participant received pegfilgrastim or filgrastim (or biosimilar) as directed. If the participant is on filgrastim, continue filgrastim (or biosimilar) for a minimum of 10 days and until ANC >5000/mm^3.

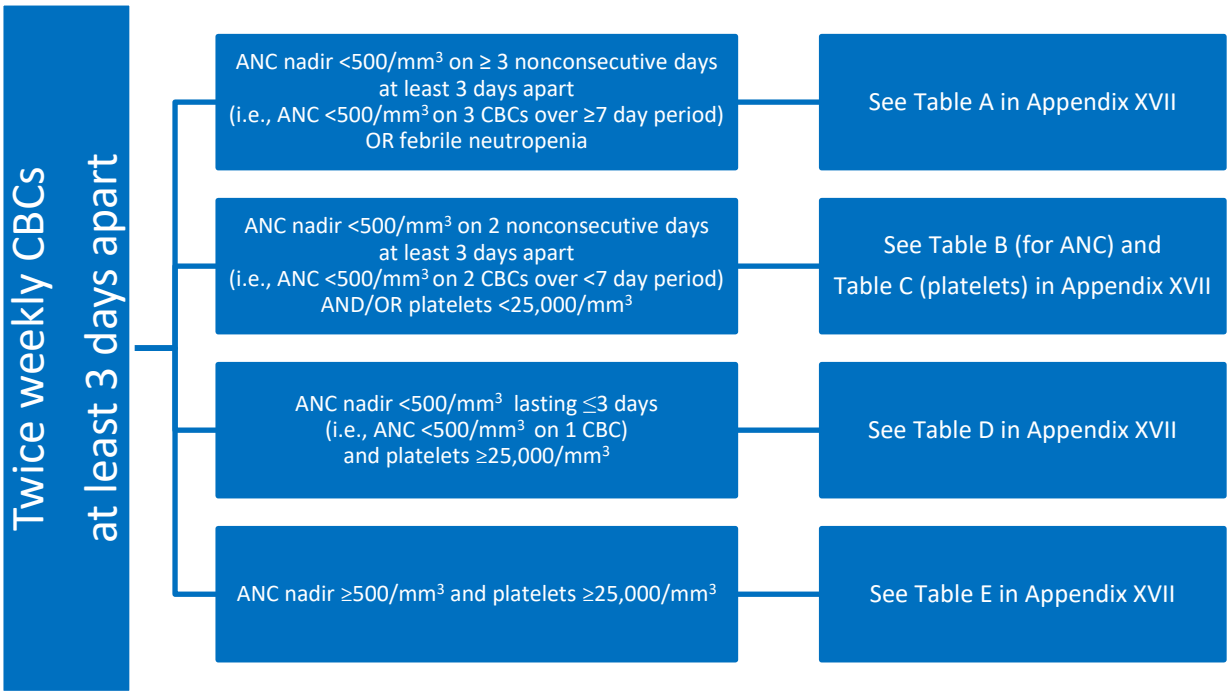


Table A

Event	Cycle of Event	Action (Ibrutinib)	Action (EPOCH)
ANC nadir < 500/mm^3 on ≥ 3 nonconsecutive days at least 3 days apart (i.e., ANC <500/mm^3 on 3 CBCs over ≥ 7-day period) OR febrile neutropenia	1 – 6	For the dose-expansion cohort, if this is the first cycle on study (after Cycle 1 off study), start ibrutinib at the MTD dose reduced by 140mg Hold ibrutinib until ANC recovers ≥1000, then resume daily ibrutinib at dose reduced by 140 mg for current and next cycle	Reduce cyclophosphamide by 187.5 mg/m^2 for the next cycle

Table B

Event	Cycle of Event	Action (Ibrutinib)	Action (EPOCH)
ANC nadir < 500/mm^3 on 2 nonconsecutive days at least 3 days apart (i.e., ANC <500/mm^3 on 2 CBCs over <7-day period)	1	Hold ibrutinib until ANC recovers ≥ 1000, then resume daily ibrutinib at the same dose for current and next cycle. After restart of ibrutinib, if ANC again drops <500 within the same cycle or ANC is <1000 at day 1 of the next cycle, hold ibrutinib until ANC recovers ≥ 1000, then resume daily ibrutinib at dose reduced by 140 mg	Reduce cyclophosphamide by 187.5 mg/m^2 for the next cycle
	2 – 6 when patient has NOT yet had a dose reduction in either cyclophosphamide OR ibrutinib	For the dose-expansion cohort, if this is the first cycle on study (after Cycle 1 off study), start ibrutinib at the MTD Hold ibrutinib until ANC recovers ≥1000, then resume daily ibrutinib at the same dose for current and next cycle After restart of ibrutinib, if ANC again drops <500 within the same cycle or ANC is <1000 at day 1 of the next cycle, hold ibrutinib until ANC recovers ≥ 1000, then resume daily ibrutinib at dose reduced by 140 mg	Reduce cyclophosphamide by 187.5 mg/m^2 for the next cycle
	2 – 6 when patient has previously required a dose reduction in cyclophosphamide but NOT ibrutinib	Hold ibrutinib until ANC recovers ≥ 1000, then resume daily ibrutinib at dose reduced by 140 mg for current and next cycle	Same dose level of EPOCH as previous cycle

Event	Cycle of Event	Action (Ibrutinib)	Action (EPOCH)
	2 – 6 when patient has previously required a dose reduction in BOTH cyclophosphamide AND ibrutinib	Hold ibrutinib until ANC recovers ≥1000, then resume daily ibrutinib at dose reduced by 140 mg for current and next cycle. If the event recurs after a minimum ibrutinib dose of 280 mg, discontinue ibrutinib permanently	Same dose level of EPOCH as previous cycle
	2 – 6 when patient has previously required a dose reduction in cyclophosphamide AND ibrutinib has been permanently discontinued	N/A	Dose-adjust cyclophosphamide one level down (by 187.5 mg/m^2)

Table C

Event	Cycle of Event	Action (Ibrutinib)	Action (EPOCH)
Platelets < 25,000/mm^3	1	Hold ibrutinib until platelets ≥50,000/mm^3, then resume daily ibrutinib at the same dose for current and next cycle. After restart of ibrutinib, if platelets again drop <25,000/mm^3 within the same cycle, hold ibrutinib until platelets recover ≥50,000/mm^3, then resume daily ibrutinib at dose reduced by 140 mg. Similarly, after restart of ibrutinib, if platelets are <75,000/mm^3 at day 1 of the next cycle, then decrease daily ibrutinib by 140 mg.	Reduce cyclophosphamide by 187.5 mg/m^2 for the next cycle
	2 – 6 when patient has NOT yet had a dose reduction in either cyclophosphamide OR ibrutinib	For the dose-expansion cohort, if this is the first cycle on study (after Cycle 1 off study), start ibrutinib at the MTD Hold ibrutinib until platelets >50,000/mm^3, then resume daily ibrutinib at the same dose for current and next cycle After restart of ibrutinib, if platelets again drop <25,000/mm^3 within the same cycle, hold ibrutinib until platelets recover ≥50,000/mm^3, then resume daily ibrutinib at dose reduced by 140 mg. Similarly, after restart of ibrutinib, if platelets are <75,000/mm^3 at day 1 of the next cycle, then decrease daily ibrutinib by 140 mg.	Reduce cyclophosphamide by 187.5 mg/m^2 for the next cycle
	2 – 6 when patient has previously required a dose reduction in cyclophosphamide but NOT ibrutinib	Hold ibrutinib until platelets ≥50,000/mm^3, then resume daily ibrutinib at dose reduced by 140 mg for current and next cycle	Same dose level of EPOCH as previous cycle

Event	Cycle of Event	Action (Ibrutinib)	Action (EPOCH)
	2 – 6 when patient has previously required a dose reduction in BOTH cyclophosphamide AND ibrutinib	Hold ibrutinib until platelets ≥50,000/mm^3, then resume daily ibrutinib at dose reduced by 140 mg for current and next cycle. If the event recurs after a minimum ibrutinib dose of 280 mg, discontinue ibrutinib permanently	Same dose level of EPOCH as previous cycle
	2 – 6 when patient has previously required a dose reduction in cyclophosphamide AND ibrutinib has been permanently discontinued	N/A	Reduce cyclophosphamide by 187.5 mg/m^2 for the next cycle

Table D

Event	Cycle of Event	Action (Ibrutinib)	Action (EPOCH)
ANC nadir < 500/mm^3 lasting ≤3 days (i.e., ANC <500/mm^3 on 1 CBC), and platelet nadir ≥25,000/mm^3	1 – 6	For the dose-expansion cohort, if this is the first cycle on study (after Cycle 1 off study), start ibrutinib at the MTD Hold ibrutinib until ANC ≥ 1000, then resume daily ibrutinib at the same dose for current and next cycle After restart of ibrutinib, if ANC again drops <500 within the same cycle or ANC is <1000 by day 1 of the next cycle, hold ibrutinib until ANC recovers ≥ 1000, then resume daily ibrutinib at dose reduced by 140 mg	Same dose level of EPOCH as previous cycle.

Table E

Event	Cycle of Event	Action (Ibrutinib)	Action (EPOCH)
ANC nadir ≥ 500/mm^3 and platelets ≥ 25,000/mm^3	1	Continue the same dose of ibrutinib for the current and next cycle	Increase cyclophosphamide by 187.5 mg/m^2 the next cycle up to maximum dose of 750 mg/m^2
	2 – 6	For the dose-expansion cohort, if this is the first cycle on study (after Cycle 1 off study), start ibrutinib at the MTD IF the current cycle cyclophosphamide is 750 mg/m^2, THEN ibrutinib may be increased by 140 mg to a maximum dose of 560 mg. Otherwise, continue the same dose of ibrutinib for the current and next cycle	Increase cyclophosphamide by 187.5 mg/m^2 the next cycle up to maximum dose of 750 mg/m^2

* Management of missing labs: If the participant does not obtain two lab counts on 2 nonconsecutive days at least 3 days apart within a week but ANC nadir on any cycle <500/mm^3, then we will assume the counts that would have been obtained are the same as the single nadir counts; however, clinical evidence of severe neutropenia/thrombocytopenia in absence of lab availability may be discussed by investigator with protocol chairs to determine subsequent cycle dosing.

** For the participants in the dose-expansion cohort who come in after cycle 1 OFF study, the first cycle on study will be counted as cycle 2. The same cycle 1 dose-adjustment rules will be applied for participants who received EPOCH and have documented twice weekly labs documenting a true nadir. If the participant received R-CHOP or there are insufficient records of nadir, the participant will start at dose level +1 of cyclophosphamide based on CD4 count and ibrutinib at the MTD dosing.

*** Note: these dose reductions do not apply to participants with baseline cytopenias attributable to bone marrow involvement with lymphoma, or to the period of time participants are receiving EPOCH infusions. Reductions on these participants will be discussed with the PI or protocol chair on an individual basis.

APPENDIX XVIII: LETTER TO THE PHYSICIAN

Model letter to be provided to the treating HIV physician of the participant.

(Date)

RE: AIDS Malignancy Consortium (AMC) Protocol-101 and Avoidance of Exclusionary Medications

Dear Dr. ***(Provider Name)***,

We are reaching out to you as your patient, (***Patient Name***), is receiving therapy at ***Institution Name*** for diffuse large B-cell lymphoma (DLBCL). (***Patient Name***) has enrolled in a clinical trial, AMC-101, for the upfront treatment of DLBCL. The therapy involves an oral drug named ibrutinib, in combination with more traditional therapy EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin).

We are writing this letter because potential harmful interactions have been identified with medications which are moderate and strong inhibitors of cytochrome 3A4 (CYP 3A4). Specifically, CYP 3A4 is responsible for ibrutinib metabolism. Therefore, to avoid excess toxicity of ibrutinib, we are avoiding these particular drug-drug interactions.

Patients need to be changed to a non- strong or moderate CYP 3A4 inhibitor HAART regimen at least one week prior to starting therapy for DLBCL. HAART drugs used frequently, such as both ritonavir (Norvir, also in Kaletra) and cobicistat (Tybost, also in Stribild), are included in the list of strong CYP 3A4 inhibitors. In addition, we are excluding the use of all moderate and strong CYP3A4 inhibitors one week prior to starting therapy for DLBCL and during therapy. For ease of review, we are including **a table on page 2** with all restricted medications.

We are asking for your assistance with this protocol requirement for your patient's HAART regimen and other prohibited medication.

Your patient enrolled on this study on (***Enrollment Date***). Please notify us in advance of any planned medication change. If you would like to discuss the trial, please feel free to call me at ***(Phone Number)***. Information on this clinical trial is also available online at https://clinicaltrials.gov/ct2/show/NCT01771107.

Thank you in advance,

Printed Name
Title
Site Name
Phone
Pager

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	Carbamazepine
COBICISTAT	Efavirenz
INDINAVIR	Etravirine
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
SUBOXONE	Pioglitazone
TELITHROMYCIN	Rifabutin
Moderate inhibitors:	Rifampin
Amprenavir	St. John's Wort
Aprepitant	Troglitazone
Atazanivir	
Erythromycin	
diltiazem	
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	
NOT azithromycin	
Chloramphenicol	
Ciprofloxacin	
Boceprevir	

Inhibitors of CYP3A	Inducers of CYP3A
Ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
Dronedarone	
Fosamprenavir	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
Posaconazole	
star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

Source: https://crediblemeds.org/healthcare-providers/. Please refer to a constantly-updated resource for the most recent list of agents.

APPENDIX XIV: CIRCULATING TUMOR DNA (CTDNA)

Background

Testing for circulating tumor DNA can include both NextGen sequencing for BCR rearrangement and NextGen sequencing to identify residual tumors on the basis of oncogene mutations. These are feasibility studies, possibly using commercial assays.

Collection of Specimen(s)

Collect three 10 mL Streck Cell-Free DNA BCT® tubes at baseline, after cycle 2, after cycle 4, and at the end of treatment. It is critical to mix tubes thoroughly by inverting the tube 8-10 times end-over-end immediately after collection. One inversion is a complete turn of the wrist, 180 degrees and back.

Handling of Specimens(s)

To ship blood for circulating tumor DNA, place the three 10 ml Streck Cell-Free DNA BCT® tubes into a canister of a STP-100 SAF-T-PAK shipper (VWR# 11217-163), wrapping each tube in bubble wrap and using the absorbent paper at the bottom of the canister. Each sample tube should be labeled using a Sharpie pen with the following information:

1. Protocol #: AMC-101
2. 11-digit Participant #
3. Date and time of collection
4. Specimen type: Whole Blood
5. Specimen purpose: circulating tumor DNA (ctDNA)

Place the lid on the canister and place it inside of the ambient SAF-T-PAK shipper indicating on packaging "**AMC Study - Call AMC Biorepository (**202)-994-3422 **for pick-up**. Seal the ambient shipper with cellophane shipping tape.

Shipping of Specimen(s)

Specimens are accepted MONDAY through THURSDAY. All specimens should be shipped overnight to:

Sylvia Silver, DA
George Washington Medical Center
Ross Hall, Room 118
2300 Eye Street, NW
Washington, DC 20037
Tel: (202) 994-3422
Fax: (202) 994-5056

1. It is the responsibility of the Primary Investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations (IATA Packing Instruction 650) relating to the handling and shipping of hazardous goods. (IATA Packing Instruction 650 is located on the AMC web site.)

2. Use a federally approved shipper for biological substance shipment (Category B). Label the shipper with the "Infectious substance" diamond shaped label. On one side, in black marker write “Biological Substance, Category B, UN 3373”, your name or name of responsible person, date of collection and phone number of the person responsible for the package. Package and label the shipment in accordance with the instructions provided for that specific shipper.
3. A Shipper’s Declaration for Dangerous Goods is not required. However, for all dry ice shipments, the following information must be shown in sequence on the airway bill in the “Nature and Quality of Goods” box: Dry Ice, 9, UN1845, number of boxes being shipped, net weight of dry ice per box.

   Please Note: The shipper will be mailed back to the AMC site. The STP-100 SAF-T-PAK shipper (VWR Cat # 11217-163) is a complete kit (bubble wrap, absorbent paper, labels, etc.) for specimen shipment. To reuse the shipper, you will need new labels, wrap, etc. There is a refurbishment kit with extra bubble wrap and absorbent material (STP102) (VWR Cat # 11217-166) sufficient for 15 mailings.

Instructions below for bloods collected on Friday-Sunday:

In the event that blood samples are drawn on a Friday, the Streck Cell-Free DNA BCT® tubes must be kept at ambient temperature and shipped the following MONDAY to the AMC Biorepository.

Billing

Please refer to the Manual of Procedures and AMC Operations website’s (www.AIDSCancer.org) shipping tab for more information and the FedEx account details. It is only to be used for billing shipment of specimens to the lab where the sample is processed and/or stored.

Record of Specimens

This study will track specimens via GlobalTrace^{SM}, a component of the AMC Advantage eClinical^{SM} system. The GlobalTrace^{SM} shipment manifest must accompany all specimen shipments.

Technical Questions

Contact Jeffrey Bethony, PhD or Sylvia Silver, DA

Tel: (202) 590-8342
Fax: (202) 994-5056
Email: jbethony@gwu.edu or ssilver@gwu.edu
George Washington Medical Center
Ross Hall, Room 118
2300 Eye Street, NW
Washington, DC 20037
Monday-Friday (8:00 AM-5:00 PM Eastern Time)

Site(s) performing correlative study: Dirk Dittmer lab/Richard Ambinder lab