SUMMARY OF CHANGES

Randomized, Phase II Trial of CHOP vs. Oral Chemotherapy with Concomitant Antiretroviral Therapy in Patients with HIV-associated Lymphoma in Sub-Saharan Africa

Version 8.0

NCI Protocol #: AMC-068
Local Protocol #: AMC-068

NCI Version Date: 03DEC2019
Protocol Date: 03DEC2019

Due to early study closure on 30NOV2018 and completion of study therapy, no changes were made in response to the disapproval letters for protocol versions 6 and 7.

I. Scientific and Substantive Changes:

#	Section	Description of Changes
1.	1.3 3.3 4.4 4.5 Appendix I	These sections were modified to include information on early study closure and to reduce total follow-up to 2 years, as the protocol team believes sufficient data will be collected during the first 2 years of follow-up to complete study analysis. Additionally, the clinical evaluations section was reorganized to clarify the procedures for 2 year-follow up. Timelines and windows for these follow-up assessments were modified to refer to the treatment discontinuation visit, including in the schedule of evaluation in Appendix I.

II. Administrative and Editorial Changes:

#	Section	Description of Changes
2.	Global	Version number and version date were updated to version 8.0 dated 03DEC2019.
3.	Global	The protocol was modified to update the CTCAE version from 4.0 to 5.0.
4.	Cover Page Protocol Roster	These sections were updated for current protocol team members and contact information. The site pathologist roster was removed to accurately reflect essential protocol team members and their roles.
5.	Appendix IV	The AMC Data and Safety Management Plan has been updated from v5 to v6.

AMC PROTOCOL #068:

Randomized, Phase II Trial of CHOP vs. Oral Chemotherapy with Concomitant Antiretroviral Therapy in Patients with HIV-associated Lymphoma in Sub-Saharan Africa

A Trial of the AIDS Malignancy Clinical Trials Consortium (AMC)

Sponsored by:	National Cancer Institute
Supported by:	Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT01775475
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Protocol Co-Chairs:	Susan E. Krown, MD (IVR-20879) Ariela Noy, MD (IVR-28244)

Version 8.0
NCI Version Date: 03DEC2019

AMC PROTOCOL SIGNATURE PAGE

I,_____, Principal Investigator at site __, agree to conduct and follow this protocol: **AMC Protocol #068 – Randomized, phase II trial of CHOP vs. oral chemotherapy with concomitant antiretroviral therapy in patients with HIV-associated Lymphoma in sub-Saharan Africa, (Version 8.0, 03DEC2019,** as written according to AMC, NCI, and FDA guidelines. I understand that no deviations from the above protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (dd/mm/yyyy)

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ABBREVIATIONS LIST

CTEP-AERS	CTEP Adverse Event Reporting System
ADL	Activities of daily living
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
AMC	AIDS Malignancy Clinical Trials Consortium
AML	Acute myelocytic leukemia
AR-NHL	AIDS-Related Non Hodgkin's Lymphoma
ART	Antiretroviral therapy
AZT	Zidovudine
C	Celsius
CBC	Complete blood count
CCNU	Lomustine
cCR	Clinical complete response
CDC	U.S. Centers for Disease Control and Prevention
CDUS	Clinical Data Update System
CFR	U.S. Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTX	Cyclophosphamide
DARF	NCI Drug Accountability Record Form
DNA	Deoxyribonucleic acid
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group

EFS	Event free survival
EQA	External quality assurance
F	Fahrenheit
FDA	U.S. Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
IATA	International Air Transport Association
ICH	International Conference on Harmonization
ICU	Intensive care unit
IEC	Institutional ethics committee
IRB	Institutional review board
IV	Intravenous
HGB	Hemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
LDH	Lactate dehydrogenase
LTFU	Loss-to-follow-up
LLT	Lower Level Term
LVEF	Left ventricular ejection fraction
Max	Maximum
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NHL	Non Hodgkin's Lymphoma
NCI	U.S. National Cancer Institute
ODMC	Operations and Data Management Center
OHAM	Office of HIV and AIDS Malignancy
OHRP	Office for Human Research Protections
ORR	Objective response rate
OS	Overall survival
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction

PD	Progressive disease
PFS	Progression free survival
PI	Principal investigator
PLTs	Platelets
PR	Partial response
Proc	Procarbazine
PS	Performance status
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SGOT	Aspartate transaminase
SGPT	Alanine transaminase
SOC	System organ class
SPD	Sum of perpendicular diameters
TB	Tuberculosis
ULN	Upper limit of normal
VP-16	Etoposide
WBC	White blood cells
WHO	World Health Organization

SITES PARTICIPATING IN THE STUDY

This protocol will be open for participant enrollment at the AMC core sites in Africa named in the protocol roster, as approved by the AMC Executive Committee and the protocol leadership for participation.

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PROTOCOL SYNOPSIS

TITLE:	Randomized, phase II trial of CHOP vs. oral chemotherapy with concomitant antiretroviral therapy in patients with HIV-associated Lymphoma in sub-Saharan Africa
DESIGN:	Open-label, randomized parallel phase II study
DURATION:	48 months (24 months for recruitment and 24 months for follow-up)
SAMPLE SIZE:	90 evaluable participants (45 participants per arm)
STUDY POPULATION:	Eligible participants will be 18 years of age or older with documented HIV infection, and biopsy-proven, previously untreated, measurable systemic **diffuse large B-cell lymphoma (DLBCL)**
PRIMARY OBJECTIVE:	To compare the efficacy of standard CHOP and an oral chemotherapy regimen for DLBCL in Sub-Saharan Africa with respect to overall survival (OS).
SECONDARY AND EXPLORATORY OBJECTIVES:	Secondary Objectives 1. To compare the objective response rate (ORR) of persons randomized to CHOP and oral chemotherapy 2. To compare the progression free survival (PFS) of persons randomized to CHOP and oral chemotherapy 3. To compare the safety and tolerance of persons randomized to CHOP and oral chemotherapy. Exploratory Objectives 1. To describe the rates of completion of therapy of persons randomized to CHOP and oral chemotherapy 2. To describe adherence to chemotherapy of persons randomized to CHOP and oral chemotherapy 3. To describe adherence to antiretroviral therapy of persons randomized to CHOP and oral chemotherapy 4. To describe the effects of therapy on HIV control, as measured by CD4 counts and HIV viral load 5. To investigate correlates of survival.
TREATMENT REGIMEN:	Patients will be randomized to one of two treatment arms: either standard, intravenously delivered CHOP, delivered over six 3-week cycles or oral chemotherapy delivered over three 6-week cycles. Formal assessment of objective response (complete response [CR]/partial response [PR]/stable disease [SD]) will be performed following cycle 6 for

CHOP and following cycle three for the oral regimen, and the patient will then be followed for relapse and survival. Patients found to have progressive disease (PD) at any time will come off study and receive the local standard of care treatment for their disease.

Regimen A*:

Cyclophosphamide	750 mg/m^2 IV Day 1, each cycle
Doxorubicin	50 mg/m^2 IV Day 1, each cycle
Vincristine	1.4 mg/m^2 IV Day 1, each cycle (max 2.0 mg)
Prednisone	100 mg orally Day 1-5, each cycle

* *Please see 5.3.2 for dosing modifications for poor risk patients*.

Regimen B: All chemotherapy drugs are administered orally. For CCNU, the dose should be rounded to nearest 10 mg; and for each of the other drugs rounded to nearest 50 mg or 25 mg, depending on how supplied (e.g., for calculated dose of 175 may administer 150 mg alternating with 200 mg, if only 50 mg tabs/caps available).

Lomustine (CCNU)	50 mg/m^2 Day 1, cycles 1 and 3 only
Etoposide (VP-16)	100 mg/m^2 Day 1-3, each cycle
Cyclophosphamide (CTX)	100 mg/m^2 Day 22-26, each cycle
Procarbazine (Proc.)	100 mg/m^2 Day 22-26, each cycle

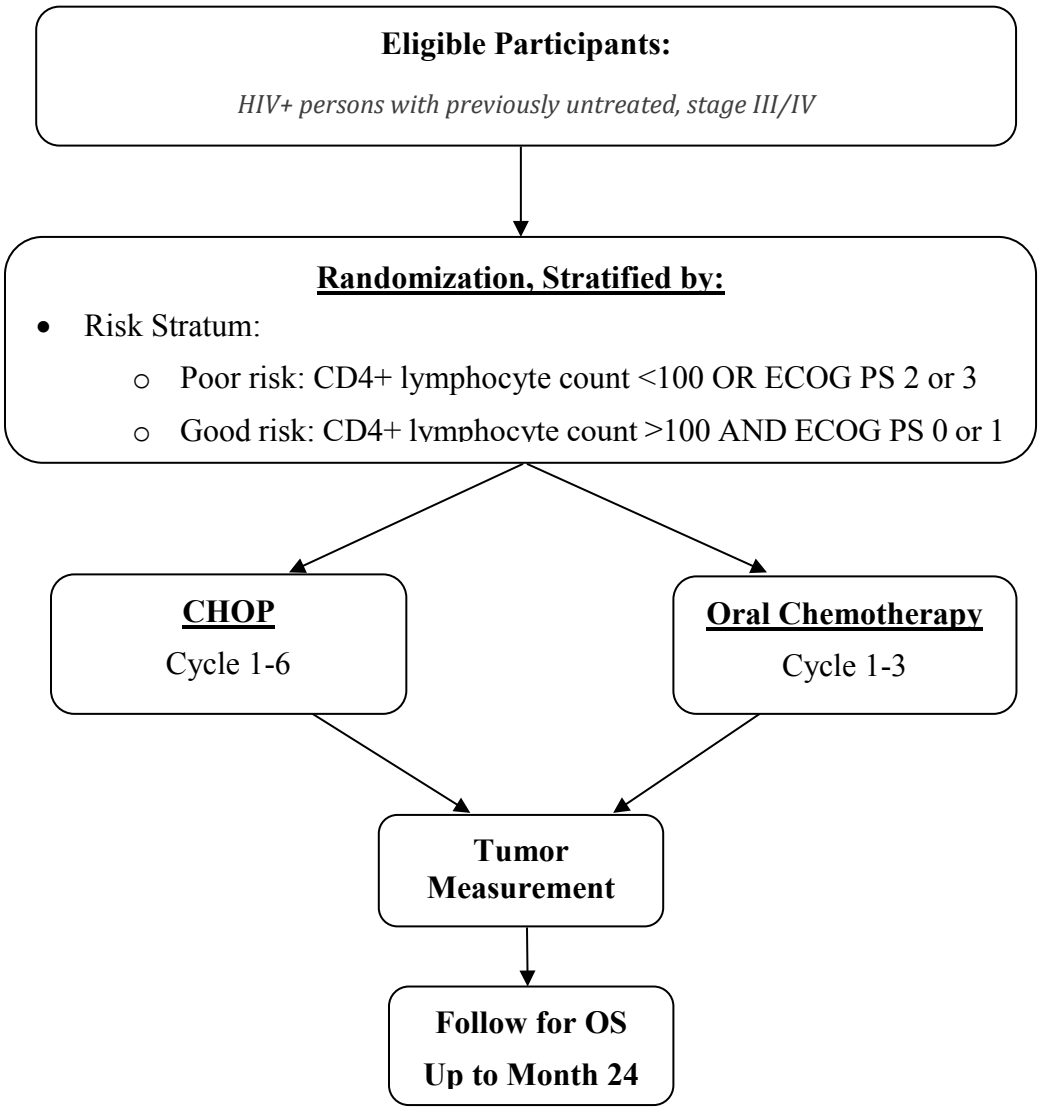
Regimen A: CHOP

Cycle	**1**		**2**		**3**		**4**		**5**		**6**		**Restage and follow (CR, PR, SD)**
Day	**1**	**2-5**	**1**	**2-5**	**1**	**2-5**	**1**	**2-5**	**1**	**2-5**	**1**	**2-5**	
CTX	X		X		X		X		X		X		
Dox	X		X		X		X		X		X		
Vinc	X		X		X		X		X		X		
Pred	X	X	X	X	X	X	X	X	X	X	X	X	

Regimen B: Oral Regimen

Cycle		**1 (D1)**		**Day 42 Cycle 1 Complete**	**2 (D43)**		**Day 84 Cycle 2 Complete**		**3 (D85)**		**Restage and follow (CR, PR, SD)**
Day	**1**	**2-3**	**22-26**		**1-2-3**	**22-26**		**1**	**2-3**	**22-26**	
CCNU	X							X			
VP-16	X	X			X			X	X		
CTX			X			X				X	
Proc.			X			X				X	

PROTOCOL SCHEMA



1.0 BACKGROUND AND RATIONALE

1.1 AIDS-Related Non-Hodgkin's Lymphoma (AR-NHL)

Approximately 10% of the world population lives in sub-Saharan Africa, but the region is home to approximately 68% of the world population living with HIV[1]. Most countries in this region have an HIV prevalence of at least 10% with a number of countries having a prevalence that exceeds 20%[2]. As the AIDS pandemic advances, the burden of related neoplastic disease is increasing in developing nations[3,4]. While under-developed cancer registries in sub-Saharan Africa bar a definitive statement being made regarding increases in incidence and prevalence in Africa, it is felt that AIDS-Related Non-Hodgkin's Lymphoma (AR-NHL) has rising incidence in this setting. Investigators involved in this study have previously published data that outcomes of AR-NHL are worse than NHL in seronegative patients[5]. Unfortunately, building on this observation is difficult, as there have been few published data on the tolerance and outcomes of treatment for HIV-associated non-Hodgkin lymphoma (NHL) in sub-Saharan Africa or on the most effective treatment regimen(s) in the varied clinical settings that exist within the region. Although all of the AMC African trial sites cite CHOP as a "standard of care" for initial treatment of HIV-associated NHL, only one, the Uganda Cancer institute (UCI), has published information on treatment outcomes.

The most comprehensive accounting of newly diagnosed NHL, from the UCI and recently published by Bateganya et al[6], remains limited; between 2004 and 2008 only 51 HIV-infected patients were identified. Although CHOP chemotherapy was administered to approximately two-thirds of all patients, the estimated median survival, even among HIV-seronegative individuals, was less than 1 year and the authors found no evidence that receipt of chemotherapy improved survival. HIV-positive patients receiving antiretroviral therapy had survival rates approximating those of HIV-negative persons, but the adjusted hazard of death was significantly elevated among HIV-positive patients not receiving antiretroviral therapy [adjusted hazard ratio (HR) 8.99, $P < 0.001$] compared with HIV-negative patients. An updated and as yet unpublished analysis (P. Imani and C. Casper, Personal Communication, January 2012) showed that of the 37 HIV+ patients in this study who received CHOP chemotherapy, 34 received at least 70% of the standard dose. However, only 4 of 34 patients received at least 6 cycles of chemotherapy. The estimated median survival for all HIV+ patients who received CHOP was approximately 6 months, and only one patient was known to be alive at 2 years. Interpreting the reason for the poor outcome for both HIV-infected and HIV-uninfected individuals is complicated by a high loss to follow-up rate and lack of information on therapy-related complications and causes of death[7], not to mention issues related to the purity and potency of locally-sourced chemotherapeutic agents.

Except for a single meeting abstract, published data from the other AMC African trial sites in Eldoret, Kenya, Harare, Zimbabwe, and Johannesburg, South Africa, are not available, but investigators at the sites have provided personal observations. The AMC PI in Eldoret stated that while full-dose CHOP is the standard, most patients require dosage reductions because of toxicity (Naftali Busakhala, Moi University, Personal Communication). CHOP is not given in satellite clinics within the Eldoret clinical network because timely blood counts are not available (M. Strother, Indiana University, Personal Communication). Drs. Kadzatsa and Ndlovu, from the AMC site in Harare, presented a retrospective analysis of

their experience in adults with NHL treated from January 2004 to December 2007 at the 14th National Congress of the South African Oncology Societies held in Cape Town in February 2009. Of 127 patients eligible for the study, HIV results were known in only 67/127 (52.8%) and of these, 55 were positive and 12 were negative. Twenty-five of the HIV-positive patients were already on antiretroviral treatment at presentation. High grade histology was found in 93/127 patients and was significantly associated with HIV+ serology ($p<0.001$). Clinical stage III was the most common disease stage. Extra-nodal disease was found in 29/127 (23%) patients, all of whom were HIV positive. Thirty-two patients were considered too ill for active cancer treatment. Of these 32 patients, 20 had an unknown HIV status, 10 were positive and 2 negative. Radiotherapy was offered to 33/127 (26%) patients, 14/127 as a first line treatment. Chemotherapy was offered to 72/127 patients. Of these, 61 patients had chemotherapy administered with 24/61 patients completing 6 cycles and 23/61 receiving less than 3 cycles. Data on response rates, response duration and survival were not available. The investigators noted that prior to the widespread availability of antiretroviral therapy (ART) the number of treatment cycles was deliberately truncated in many HIV+ patients. Although data on their experience since the widespread roll-out of ART in Zimbabwe (post-2007) are not available, the Zimbabwean investigators expressed the opinion that among HIV+ patients receiving concomitant ART, most are now able to complete chemotherapy, but data on response rates, response durations, or survival are not available. Although there are no published data from the University of Witwatersrand in Johannesburg, Dr. Adam Nosworthy, the oncologist providing treatment for HIV+ patients with NHL, has noted that at their center, lymphoma patients "all have very good outcomes" and remarked that "we are fortunate enough to have access to all supportive care including ICU support, growth factors, unlimited antibiotic usage and isolation facilities" which are not available at other African centers (A. Nosworthy, Personal Communication).

1.2 Rationale

Although the available data on the performance of CHOP in HIV+ patients at AMC sites in sub-Saharan Africa are too scant to draw firm conclusions, what little data are available suggest that there are factors that may limit CHOP's optimal activity in resource-constrained settings. Additionally, studies of cytotoxic systemic therapy for AIDS-associated and other virus-associated tumors in similar settings report mortality rates ranging between 20-66% and the median survival duration for AIDS-related Burkitt's lymphoma is 15 weeks[3,5,8,9]. Prospective studies are needed to identify factors that have led to poorer than expected outcomes in NHL to standard CHOP-based approaches in resource-constrained settings and to determine whether these factors can be overcome. Concurrent with this effort, we will assess strategies to facilitate safe and effective delivery of standard chemotherapy, as well as explore potential alternatives developed specifically to avoid the limitations of effective cancer care delivery in resource-constrained settings.

It is in this context that we propose to test an oral chemotherapy regimen in a randomized, phase II study. The regimen we propose to test in parallel with CHOP consists of four drugs, lomustine, etoposide, cyclophosphamide, and procarbazine, which were chosen for their single-agent activity in NHL, their ability to cross the blood-brain barrier (lomustine and procarbazine), and the in vitro antitumor synergy between etoposide, cyclophosphamide and nitrosoureas. In a pilot study in 49 HIV+ NHL patients conducted

in Kampala, Uganda and Nairobi, Kenya before the widespread availability of ART[10], two cycles of oral therapy over 12 weeks (intended to approximate 4 cycles of a standard IV regimen) induced objective responses in 78% of patients, with median EFS and OS of 7.9 (95% CI, 3.3-13.0) and 12.3 (95% CI, 4.9-32.4) months, respectively; 33% of patients survived 5 years. Only 18 patients (37%) had access to ART, 63% had poor performance status, and 69% had advanced stage disease. Treatment was well tolerated, with only 4 episodes of febrile neutropenia and three treatment-related deaths (6%). Building on these promising pilot data, it seems reasonable to pursue the investigation of an oral regimen that extends treatment to 3 cycles (approximating 6 cycles of a standard IV regimen) and that ensures receipt of ART in all patients.

The current proposal is justified given the limited outcome data regarding administration of IV therapy that is standard-of-care in high resource settings. Although it is technically feasible to administer IV therapy, other factors, such as differences in adherence, a limited ability to manage adverse events, or exposure to nosocomial pathogens such as tuberculosis may diminish the efficacy of CHOP in a resource-limited setting and render it less effective than an oral therapy. Conducting a randomized, phase II trial should help to identify some of these issues and point the way forward toward the development of future trials.

1.3 Study Design

This is a randomized phase II trial for HIV-associated diffuse large B-cell lymphoma (DLBCL) to compare CHOP and an oral chemotherapy regimen in terms of efficacy and tolerability.

Population

HIV-positive adults with measurable, advanced stage (stage III/IV) systemic DLBCL who have not received prior NHL treatment.

Randomization

Randomization will be performed by the AMC Operations and Data Management Center (ODMC) at the time of participant registration in AdvantageEDC. Stratification factors will include:

1. CD4+ lymphocyte count < 100 OR ECOG PS 2 or 3 (poor risk stratum), vs. CD4+ lymphocyte count ≥100 AND ECOG PS 0 or 1 (good risk stratum).
2. By country/trial site.

All participants will be randomized. However, sites will be permitted to enroll study participants into both risk strata, or may elect to enroll participants in only the poor-risk stratum. Sites electing to enroll and randomize only participants in the poor-risk stratum will treat good risk patients according to their local standard of care.

On 30 November 2018, the study was closed to further accrual because of slow enrollment. Participants on study at the time of study closure to accrual will continue to be followed for up to 2 years following treatment discontinuation.

1.4 Correlative Study Background

Previous work with this oral combination chemotherapy in AR-NHL has shown the chemotherapy regimen did not adversely affect the underlying HIV infection[11]. This is

consistent with other results that have failed to show an effect of anti-neoplastic chemotherapy on virologic control of HIV[12]. However, given the study setting, in which many programs have limited options of ART, it is particularly relevant to determine the effect of the treatment of AR-NHL on HIV control; therefore, we will follow HIV viral loads, along with assessments of ART adherence while participants are on protocol.

2.0 STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

To compare the efficacy of standard CHOP and an oral chemotherapy regimen for HIV-associated DLBCL in Sub-Saharan Africa with respect to overall survival (OS).

2.1.2 Secondary Objectives

2.1.2.1 To compare the objective response rate (ORR) of persons randomized to CHOP and oral chemotherapy.

2.1.2.2 To compare the progression free survival (PFS) of persons randomized to CHOP and oral chemotherapy.

2.1.2.3 To compare the safety and tolerance of persons randomized to CHOP and oral chemotherapy.

2.1.3 Exploratory Objectives

2.1.3.1 To describe the rates of completion of therapy of persons randomized to CHOP and oral chemotherapy.

2.1.3.2 To describe adherence to chemotherapy of persons randomized to CHOP and oral chemotherapy.

2.1.3.3 To describe adherence to antiretroviral therapy of persons randomized to CHOP and oral chemotherapy.

2.1.3.4 To describe the effects of therapy on HIV control, as measured by CD4 counts and HIV viral load.

2.1.3.5 To investigate correlates of survival.

3.0 PARTICIPANT SELECTION

All protocol participants must meet 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.

3.1 Inclusion Criteria

3.1.1 Ability to understand and the willingness to provide informed consent to participate.

3.1.2 Adults, 18 years of age or older. Date of birth and age should be determined based on the best possible information or source documentation available.

3.1.3 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or confirmed by HIV-1 antigen or plasma HIV-1 RNA viral load > 1,000 copies/mL.

NOTE: The term "licensed" refers to a U.S. FDA-approved kit or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

3.1.4 Biopsy-proven, systemic DLBCL with a proliferation rate ≤90%, that has been confirmed by an AMC-approved site pathologist using H&E and immunohistochemical stains as defined in Appendix III. If a hard copy of the pathology report is unavailable at the time of enrollment into the Screening Segment, a verbal report by the pathologist confirming the diagnosis must be documented in the medical chart. A hardcopy of the pathology report must be available prior to randomization (enrollment into the Treatment Segment). **Note**: Measurable disease is not an entry requirement. See section 8.0 for response assessments with and without measurable disease.

3.1.5 Pathology slides from tumor tissue obtained by surgical excision or core biopsy must be reviewed by the designated site pathologist, or backup pathologist, prior to study entry. Confirmation of the diagnosis must be documented by the AMC-approved pathologist prior to study entry. *Please reference the AMC-068 MOP for further instructions on documenting the diagnosis.*

The site pathologist for NHL must be approved through the AMC's EQA process.

3.1.6 Participants must have fifteen blank (unstained) slides or a diagnostic tissue block must be available for external quality assurance by the AMC Core Pathology Laboratory (see Appendix III for instructions on preparation and submission of

materials for external quality assurance).

3.1.7 ECOG performance status of 0 - 3 within 7 days of enrollment (Appendix II).

3.1.8 Participants must have an estimated life expectancy of > 6 weeks.

3.1.9 The following acceptable end organ function/laboratory parameters within 7 days prior to enrollment:

- Hematologic (Participants may enroll with lower hematologic values, if bone marrow involvement is documented. In this case, patients should be transfused to hemoglobin ≥ 8 g/dL):
  - WBC ≥ 3,000 cells/μL (3.0 x 10^9 L) or absolute granulocytes ≥ 1500 cells/μL (1.5 x 10^9 L);
  - Platelets ≥ 100,000 cells/μL (75 x 10^9 L); and,
  - Hemoglobin ≥ 8 g/dL (5.0 mmol/L)
- Renal – estimated creatinine clearance of >50 ml/min (0.84 mL/s) by the Cockcroft-Gault equation; and
- Hepatic
  - Total bilirubin ≤ 1.5 times the institutional upper limit of normal (ULN), unless elevated secondary to lymphomatous involvement of liver or biliary system, or due to other HIV medications (e.g., indinavir, tenofovir, or atazanavir). If secondary to lymphomatous involvement, an initial upper limit of total bilirubin 5 mg/dL (85.5 μM/L) should be utilized - for direct bilirubin > 1.2 mg/dL (20.5 μM/L) see section 5.5.2 for the initial dose of CHOP drug adjustment
  - AST/ALT < 2.5 times the institutional ULN (unless elevated secondary to lymphomatous involvement of the liver, in which case the AST/ALT must be ≤ 5 times the institutional ULN)

3.1.10 Participants must have a lumbar puncture with negative cerebral spinal fluid cytology within 4 weeks prior to enrollment.

3.1.11 All participants must be prescribed combination antiretroviral therapy with the goal of virological suppression using an acceptable regimen that adheres to national guidelines for treatment of HIV infection. Non-suppressed, treatment experienced patients, defined as patients with a viral load > 400 copies/mL who have been on antiretroviral therapy for more than 4 months can be enrolled if an alternative ART regimen is available that includes at least two ART drugs that, in the opinion of the site investigator, are expected to have activity based on genotypic testing (if available) and treatment history. Patients are not allowed to receive zidovudine (AZT) as part of concurrent chemotherapy and ART regimen, since it is myelosuppressive. Zidovudine may be discontinued and substituted as clinically indicated prior to or at the time of enrollment.

3.1.12 Participants of childbearing potential, defined as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months), must have a pregnancy test

within 7 days prior to enrollment and agree to use an effective form of contraception (e.g., barrier contraception, highly effective hormonal contraception).

3.1.13 Participants must, in the opinion of the investigator, be capable of complying with the protocol.

3.1.14 Participants must be able to take oral medications.

3.1.15 Participants must have a CD4 count performed within 30 days of enrollment.

3.2 Exclusion Criteria

3.2.1 Inability to provide informed consent.

3.2.2 Participants who received any lymphoma directed chemotherapy or radiotherapy with the exception of a single dose of intrathecal chemotherapy given at the time of the diagnostic lumbar puncture (spinal tap.) Patients who received chemotherapy or radiotherapy for Kaposi's sarcoma > 2 years prior to study enrollment are allowed as long as the prior treatment did **not** include doxorubicin in its non-liposomal form. Prior exposure to liposomal doxorubicin is allowed. Prior exposure to intrathecal therapy given as prophylaxis within 30 days is allowed.

3.2.3 Participants who received greater than 10 days of corticosteroids in doses greater than physiologic replacement in the preceding 30 days prior to enrollment. Physiologic dosing of steroid is 4-5 mg/m^2/day prednisone, 0.03-0.15 mg/kg/day dexamethasone, or 0.5-0.75 mg/kg/day hydrocortisone. Contact the AMC Protocol Team for physiologic dosing limits for other corticosteroids.

3.2.4 Participants with evidence for CNS lymphoma on neurological exam and/or with radiographic evidence (if radiographic studies are done) of CNS lymphoma (inclusive of parenchymal, vitreal, or leptomeningeal involvement).

3.2.5 Participants with active infection(s) for which they are receiving drug treatment unless the clinical status is judged to be stable and survival is estimated to be at least 6 weeks.

3.2.6 A medical or psychiatric illness that precludes ability to give informed consent or is likely to interfere with the ability to comply with the protocol stipulations.

3.2.7 Participants with circumstances that will not permit completion of the study or required follow-up. For instance, if travel to and from treatment site is an issue.

3.2.8 Pregnant or breastfeeding

3.2.9 Inability to swallow oral medications

3.2.10 Participants with known congestive heart failure (CHF). If known, patients with left ventricular ejection fraction (LVEF) $\leq$40% are excluded.

3.3 Number of Participants to be Enrolled

The study was planned to enroll 90 evaluable participants (45 on each treatment arm). The study was terminated on 30NOV2018 after enrolling 7 participants. For the purposes of this study evaluable participants are those defined as participants who initiate study treatment. Participants who are enrolled and fail to initiate study treatment will be replaced.

3.4 Accrual Targets

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Female		**Male**		**Total**
Hispanic or Latino	0	+	0	=	0
Not Hispanic or Latino	45	+	45	=	45
Ethnic Category: Total of all subjects	45 (A1)	+	45 (B1)	=	90 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	45	+	45	=	90
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	0	+	0	=	0
Racial Category: Total of all subjects	45 (A2)	+	45 (B2)	=	90 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

3.4.1 Accrual Rate

It is estimated that accrual will be 3-4 patients/month for duration of 24 months to obtain a sample size of 90 evaluable total patients.

3.5 Study Enrollment Procedures

This study will be available for enrollment at the African AMC sites. Sites must have this protocol approved by their Institutional Review Boards (IRB), national regulatory authority (where required) and be registered with the AMC Operations and Data Management Center (ODMC) before they may enroll participants. Protocol registration instructions and forms will be made available on the AMC Operations website (**www.amcoperations.com**). Participating sites may not order study drugs until protocol registration with the AMC ODMC is complete.

3.5.1 Registration for Screening

After an informed consent form has been signed by the participant, the participant must be registered for screening (AMC-068, Screening Segment) on-line via the AMC AdvantageEDC^{SM} Internet Data Entry System. After successful registration into the screening segment, the participant will receive a nine-digit participant ID and will then enter the screening process (Screening and Pre-entry visits). Participants will be enrolled on-line via the AMC Internet Data Entry System no more than 4 weeks prior to the initiation of treatment. Once the eligibility checklist is submitted, a system-generated confirmation will be sent to the site staff, AMC ODMC, and Protocol Chair upon successful registration.

Please reference the AMC-068 MOP for additional details regarding the required tests prior to enrollment in the screening segment.

If the on-line system is inaccessible for Screening Registration (Screening Segment), the site should notify the AMC ODMC via email at **amipm@emmes.com** or via phone at 1-301-251-1161 for further instructions. Please refer to the AMC-068 MOP for additional instructions.

3.5.2 Enrollment and Randomization

After a written pathology report confirming the lymphoma diagnosis is available, the participating site will complete the protocol-specific eligibility checklist and enroll the participant into the AMC-068 Treatment Segment on-line via the AMC AdvantageEDC^{SM} Internet Data Entry System. The participating site will ensure the participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist. Participants will be enrolled on-line via the AMC Internet Data Entry System no more than 1 week prior to the initiation of treatment (enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted, a system-generated confirmation will be sent to the site staff, AMC ODMC, and Protocol Chair with the participant's randomization assignment upon successful registration.

If the on-line system is inaccessible for Randomization Registration (Treatment Segment), the site should notify the AMC ODMC via email at **amipm@emmes.com** or via phone at 301-251-1161 for further instructions.

3.6 Required Pathology Material and Data

Local pathology must be performed according to local standard procedures to confirm the diagnosis of non-Hodgkin's lymphoma. The local pathology review must be done prior to enrollment to confirm participant eligibility. Appropriate pathology reports from the participating institution are required to be maintained as source documents.

An external quality assurance will be performed according to Appendix III. The purpose of the external quality assurance is to provide a consistent review and confirmation of the diagnosis and histology of DLBCL for all study participants, and to build diagnostic pathologic capacity at the participating institutions. This requirement applies to all cases, regardless of the country in which the participant is enrolled.

4.0 CLINICAL AND LABORATORY EVALUATIONS

Please see Appendix I, Schedule of Evaluations, for a tabular schedule.

The designated study personnel at each site will explain the study to the participant. The informed consent document will be given/read to the participant in the local language(s) (this will be English or a language understandable to the participant and/or his/her representative), and a copy given to the participant. Once a participant's questions have been answered the participant will sign the informed consent document if the participant wishes to participate.

All patients will undergo thorough physical examination with assessment of involved sites of disease including thorough tumor measurement (including assessment of extranodal sites of disease that can be determined on physical examination), bone marrow aspiration biopsy, and cerebrospinal fluid analysis to exclude leptomeningeal disease. If lumbar puncture is to be performed there should be no CNS mass/lesion by CT scan or suggested by clinical exam. On-study staging chest radiograph, abdominal ultrasound and CT scans of the chest, abdomen and pelvis (the latter if available and can be done within the time period for study entry) are required.

Response criteria will be aligned with conventional response criteria for lymphoma (36, 37), outlined in section 8.0. Clinical CR will be allowed in situations where radiographic studies were done at the time of initial on-study evaluation and cannot be repeated due to costs or other reasons.

4.1 Baseline Evaluations

4.1.1 Medical history, history of drug allergies, history of current and past anti-retroviral regimens, if available, review of concomitant medications; and history of any prior AIDS-defining conditions. Date of the initial lymphoma diagnosis is required with a copy of the pathology report. The presence or absence of systemic "B" symptoms should be noted, as well as other symptoms of NHL.

4.1.2 Physical exam including performance status, vital signs (height, weight, pulse, blood pressure, temperature, and body surface area), a neurologic exam and tumor measurements must be assessed within 48 hours of initiating therapy. Tumor measurements refers either to bi-dimensional (long axis and short axis) measurement on CT imaging or physical measurement (long axis and short axis) of palpable disease. Patients must not have clinical signs of CNS involvement by neurologic exam at time of enrollment.

4.1.3 All baseline blood work should be done within 1 week (7 days) prior to treatment unless otherwise specified, and will suffice as Day 1 pretreatment laboratory tests. Results from baseline blood work must be clinically appropriate for participant to receive treatment. NOTE: If laboratory tests performed to determine eligibility has been performed within the timeframe required for baseline, they do not need to be repeated.

4.1.4 Complete blood count (CBC) with differential and platelet count.

4.1.5 Electrolyte panel (sodium, potassium, chloride) with creatinine.

4.1.6 Serum chemistries to include: SGOT (AST) or SGPT (ALT); total bilirubin;

albumin; uric acid; and lactate dehydrogenase (LDH).

4.1.7 Women of child bearing potential must have a negative urine pregnancy test within 48 hours prior to Day 1 and Day 22 for all cycles of treatment in the oral regimen and prior to Day 1 for all cycles of the CHOP regimen.

4.1.8 Chest radiograph, abdominal ultrasound and CT scan of chest, abdomen and pelvis must be done within 4 weeks prior to initiation of therapy. Imaging within 2 weeks prior to the initiation of therapy is preferred.

4.1.9 Bone marrow core biopsy, with or without aspiration, will be performed in all patients at baseline. Bilateral biopsies are encouraged, but not required. This should be done within 4 weeks of the first treatment, although results need not be reported before treatment. If the bone marrow is initially involved with lymphoma, it must be repeated in patients thought to have clinical CR at the time of restaging or treatment completion.

4.1.10 HIV-1 plasma RNA viral load is to be performed within 1 week prior to treatment. HIV-1 RNA plasma level will be measured by RNA PCR. (Results need not be reported before treatment.)

4.1.11 A lumbar puncture with cell count, total protein, cytology and flow cytometry (where available) must be completed within 4 weeks prior to enrollment. Results are required prior to study enrollment.

4.2 Evaluations During Treatment

The time frames for evaluations exclude the assessments performed at baseline (refer to section 4.1). Except as noted in the Schedule of Evaluations, Appendix I, evaluations during treatment must be performed on Cycle 1, Days 1* and 22, Cycle 2 Days 1 and 22, and Cycle 3 Days 1 and 22 for participants on the oral regimen and on Cycle 1, Day 1*, Cycle 2, Day 1, Cycle 3, Day 1, Cycle 4, Day 1, Cycle 5, Day 1, and Cycle 6, Day 1 for participants receiving IV CHOP).

*Cycle 1, Day 1 can be combined with the baseline/eligibility assessments if they are completed within the allowable window. Cycle 1, Day 1 labs and assessments must be performed within 7 days prior to treatment initiation, with the exception of imaging. Imaging is encouraged to be done as closely as possible prior to Cycle 1, Day 1, but must be performed within 28 days prior to Cycle 1 Day 1.

At any time if progression of disease has been unequivocally documented on the basis of physical exam findings, the participant will be considered off study therapy and should be followed for survival only.

If progression of disease by physical exam is suspected but not confirmed, the investigator can either perform a radiographic assessment to confirm the response status or can continue therapy and evaluate prospectively.

4.2.1 Physical examination (including weight) and clinical tumor measurements are to be performed within the 48 hours prior to Day 1 (oral regimen and IV CHOP) and Day 22 (oral regimen only) of each chemotherapy cycle.

4.2.2 CBC, differential, and platelet counts are to be performed within the 48 hours prior

to Day 1 (oral regimen and IV CHOP) and Day 22 (oral regimen only) of each chemotherapy cycle.

4.2.3 Serum creatinine and total bilirubin are to be performed within the 48 hours prior to Day 1 (oral regimen and IV CHOP) and Day 22 (oral regimen only) of each chemotherapy cycle.

4.2.4 Electrolyte panel; SGOT (AST) or SGPT (ALT); albumin; uric acid; and lactate dehydrogenase (LDH) are performed within the 48 hours prior to Day 1 (oral regimen and IV CHOP) and Day 22 (oral regimen only) of each chemotherapy cycle.

4.2.5 Women of child bearing potential must have a negative urine pregnancy test within 48 hours prior to Day 1 and Day 22 of each chemotherapy cycle prior to treatment.

4.2.6 ART adherence assessment. See Appendix I, Schedule of Evaluations for required time points. Sites are encouraged to do this immediately prior to study drug administration. *Please see the AMC-068 MOP for additional details*.)

4.2.7 Review of interim medical history including concomitant medications and adverse events.

4.2.8 Oral study drug adherence assessment consisting of a review of returned bottles, pill count, participant interview and review of the study drug diary (where appropriate). See Appendix I, Schedule of Evaluations for required time points.

4.3 Evaluations at the Completion of Chemotherapy

Unless otherwise noted, all evaluations will be performed +/- 7 days of completing the final cycle of chemotherapy (completion of the cycle includes the days of the cycle with no treatment). All participants must have these assessments at the completion of chemotherapy, regardless of the reason for treatment discontinuation. Participants discontinuing treatment due to toxicity should be followed until the toxicity resolves or through the end of study follow-up.

4.3.1 The following laboratory tests are required: CBC with differential and platelet count; electrolyte panel and creatinine; SGOT (AST) or SGPT (ALT); total bilirubin; albumin; uric acid; and lactate dehydrogenase (LDH).

4.3.2 CD4+ lymphocyte count.

4.3.3 HIV-1 RNA plasma level.

4.3.4 Complete re-staging will be performed within the 4 weeks following completion of chemotherapy. Imaging studies, including abdominal ultrasound and CT scans, which showed evidence of disease at baseline, are to be repeated at this time. When clinically indicated, fine needle aspiration or open biopsy confirmation should be performed to reconcile equivocal disease status. If the participant has clearly progressed based on clinical examination, it is not necessary to conduct imaging studies at this visit.

If a biopsy is performed for assessment of tumor recurrence or tumor persistence, pathology slides from tumor tissue obtained by surgical excision or core biopsy must be submitted for external quality assurance by the AMC Core Pathology

Laboratory (see Appendix III for instructions on preparation and submission of materials for external quality assurance). Fifteen blank (unstained) slides or a diagnostic tissue block must be submitted.

4.3.5 If pre-treatment bone marrow biopsy showed lymphoma, a repeat bone marrow biopsy will be performed for re-staging following the completion of chemotherapy in participants thought to be in a clinical CR.

4.3.6 ART adherence assessment

4.3.7 Oral study drug adherence assessment consisting of a review of returned bottles, pill count, participant interview and review of the study drug diary (where appropriate).

4.4 Follow-up Evaluations

Participants must be followed for 2 years or until death, whichever occurs first. All follow-up time points for post-treatment evaluations should be calculated in reference to the treatment discontinuation visit. Participants are to be followed at 3 and 6 months (+/-14 days) after the treatment discontinuation visit and then every 6 months for a total of 2 years (at 12, 18, and 24 months, +/- 28 days) with documentation of clinical and disease status (e.g., continuing in remission, relapse, or progression of disease), and performance status by exam. Restaging assessments such as imaging and bone marrow biopsy are at the discretion of the treating physician.

4.4.1 For participants who have not progressed, the following assessments are required at 3, 6, 12, 18, and 24 months unless otherwise noted.

- CD4+ lymphocyte count
- HIV-1 RNA plasma viral load
- Physical examination (including vitals and ECOG PS score), including neurological examination
- Review of interim medical history, including adverse events and concomitant medications. Only adverse events that are possibly, probably, or definitely related to a study drug and those specified in Section 6.0 must be reported. Only concomitant medications administered to treat reportable adverse events and second line therapies for DLBCL must be reported
- CT imaging will be repeated at 6, 12, 18, and 24 months. Other imaging modalities can be employed off-study, as appropriate and at the discretion of the treating physician, at other time points. If the participant has clearly progressed based on clinical examination, it is not necessary to conduct imaging studies at this visit.
- Biopsy confirmation of relapse is required, if clinically feasible, if it occurs within the first 2 years of completing treatment. If a biopsy is performed for assessment of tumor recurrence or tumor persistence, pathology slides from tumor tissue obtained by surgical excision or core biopsy must be submitted for external quality assurance by the AMC Core Pathology Laboratory (see Appendix III for instructions on preparation and submission of materials for

external quality assurance). Fifteen blank (unstained) slides or a diagnostic tissue block must be submitted.

4.4.2 Second line therapy is not provided as part of the protocol. If participants receive additional treatment, the treatment regimens should be documented during the 2-year follow-up period. Adverse event information regarding second-line therapies will not be collected. Participants will be followed only for vital status, adverse events related to study treatment, and a recording of the second-line and subsequent regimens which fall within the 2-year window following completion of protocol treatment.

4.4.3 Participants who have progressed either on study or during the 2-year follow-up will be followed for overall survival, Grade 2 and greater adverse events related to study treatment, and additional treatment regimens only, for the duration or remainder of follow-up. This can be done by phone, mail or other contact.

4.4.4 Participants who received the oral regimen who show disease progression, or who subsequently show relapse after a prior response, should be offered CHOP or a CHOP-like regimen off study if medically appropriate. If the participant is not offered CHOP, the reason for not doing so must be documented in the source. If the participant is offered CHOP and does not receive it, the reason must be documented in the source.

4.4.5 Participants are followed for OS as primary endpoint. Causes of death need to be documented and categorized as either progressive HIV disease/AIDS; progressive lymphoma; or death from other causes.

4.5 Final Evaluations, Off Study

4.5.1 The participant is considered off-study (a) upon reaching two years of follow-up from discontinuation of treatment, or (b) death, or (c) the participant withdraws consent, or (d) is lost to or refuses follow-up. Lost to follow-up will be defined for this purposes of this study as 12 months of inability to contact or determine the participant's vital status, in spite of at least 3 documented attempts to contact the participant. The final study visit evaluation will include clinical and disease status (e.g., continuing in remission, relapse or progressive disease and residual treatment-related toxicity).

4.6 Procedures in the Event of Contraceptive Failure

In the event of contraceptive failure, the use of an emergency contraceptive is an option. A levonorgestrel-only emergency contraceptive (i.e., Plan B) is preferred to minimize the occurrence of nausea, which may interfere with adherence to protocol medications. Combined ethinyl estradiol/levonorgestrel emergency contraceptive is, however, an acceptable option if a levonorgestrel-only emergency contraceptive is unavailable.

Emergency contraceptives will not be provided by the AMC.

4.7 Procedures in the Event of On-Study Breastfeeding or Pregnancy

Female participants who become pregnant or initiate breastfeeding while on protocol treatment must immediately discontinue protocol treatment. Participants will continue to be followed for the remainder of the study visit schedule and procedures. AMC-068 will

not provide perinatal care for women. Women who become pregnant will be referred to local clinics and/or other research studies for prenatal and postpartum care.

Pregnancy reporting and outcomes will be documented by completion of the appropriate eCRFs.

5.0 TREATMENT PLAN

5.1 Study Drugs

5.1.1 CHOP (IV)

5.1.1.1 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's lymphoma.

- Common side effects and toxicity:
  - Nausea and vomiting
  - Myelosuppression
  - 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.
- Source of study medication: Study medication will be provided by the AMC.
- Study medication formulation: 500 mg vial lypholized powder
- See the AMC-068 MOP for preparation instructions.
- Storage and stability: Store at or below 25°C (77°F).

5.1.1.2 Doxorubicin

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.

- Special precautions: Doxorubicin is given intravenously and is a vesicant causing severe local necrosis at the site of injection if extravasation occurs.
- Common side effects and toxicity:
  - Myelosuppression
  - Nausea and vomiting
  - Alopecia
  - 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/m2.
- Please refer to the approved package insert for complete prescribing and toxicity information.
- Source of study medication: Study medication will be provided by the AMC.

- Study medication formulation: 50 mg/25 ml vial
- Storage and stability: Store unreconstituted vial at controlled room temperature, 15°C to 30°C (59°F to 86°F). Protect from light. Retain in carton until time of use. Discard unused portion.

5.1.1.3 Vincristine Sulfate

Vincristine sulfate is a vinca alkaloid from the plant Cantharanthus 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.

- Common side effects and toxicity:
  - The major and dose-limiting side effect of vincristine is neurotoxicity. The main manifestation is a mixed sensorimotor peripheral neuropathy.
  - Reduction 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.
  - Mild myelosuppressive effects
  - Special precautions: Vincristine is given intravenously and is a vesicant causing severe local necrosis at the site of injection if extravasation occurs.
- Please refer to the approved package insert for complete prescribing and toxicity information.
- Source of study medication: Study medication will be provided by the AMC.
- Study medication formulation: 1 mg/ 1 mL vial
- Storage and stability: Store refrigerated between 2°C - 8°C (36°F - 46°F). Discard unused solution. Protect from light. Store upright.

5.1.1.4 Prednisone

Prednisone is a corticosteroid and its mechanism of action as a cytotoxic agent is not clearly understood.

- Common side effects and toxicity
  - 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.
- Source of study medication: Study medication will be provided by the AMC.
- Study medication formulation: 50 mg tablets
- Storage and stability: Store at controlled room temperature between 20°

to 25°C (68° to 77°F)

5.1.2 Oral Regimen

5.1.2.1 Lomustine

- Other name(s) and abbreviation: CeeNU®, CCNU
- Mechanism of action: Alkylation and carbamylation by lomustine metabolites interfere with the synthesis and function of DNA, RNA and proteins.
- Metabolism and excretion: lipid soluble and easily enters the CNS. Rapidly metabolized into toxic products. Fifty percent of products in blood are bound to plasma protein. Most of the intact drug and metabolites are excreted in urine. Some products have an entero-hepatic cycle,
- Usual dosage and schedule: 100-130 mg/m2 orally every 6 to 8 weeks (lower dose used for patients with compromised bone marrow function).
- Special precautions: Because of delayed myelosuppression (3-6 weeks), do not treat more than every 6 weeks. Await return of normal platelet and granulocyte counts before repeating therapy.
- Common side effects and toxicity:
  - Myelosuppression – universal and dose-limiting. Leukopenia and thrombocytopenia are delayed 3 to 6 weeks after therapy begins and may be cumulative with successive doses.
  - Nausea and vomiting – may begin 3 to 6 hours after oral dose and may last up to 24 hours.
  - Stomatitis and alopecia are rare.
  - Additional side effects – confusion, lethargy and ataxia are rare. Mild hepatoxicity is infrequent. Secondary neoplasia is possible.
- Source of study medication: Study medication will be provided by the AMC.
- Study medication formulation: 10 mg capsules
- Storage and stability: Store at room temperature in well closed containers. Avoid excessive heat (over 40° C or 104° F).

5.1.2.2 Cyclophosphamide

- Other name(s) and abbreviation: Cytoxan®, CTX
- Mechanism of action: metabolism of cyclophosphamide by hepatic microsomal enzymes produces active alkylating metabolites. Primary effect is alkylation of DNA with resultant inhibition of DNA synthesis.
- Metabolism and excretion: The native drug is inactive and must be activated by the hepatic microsomal oxidase system. Drugs that induce microsomal enzymes (e.g., barbiturates, griseofulvin) may enhance toxicity, liver disease may decrease toxicity. Native drug is not protein bound, but active metabolites are 50% bound. Active metabolites are excreted in the urine.
- Usual dosage and schedule: 1000-1500 mg/m2 intravenously every 3 to

4 weeks; 60-120 mg/m2 orally daily; and 100 mg/m2 daily for 2 weeks with a repeat cycle every 4 weeks.

- Special precautions: Adequate fluid hydration, oral or intravenous, must be maintained and have patient empty bladder several times daily to diminish likelihood of hemorrhagic cystitis. Metabolites of cyclophosphamide are injurious to bladder urothelium.
- Common side effects and toxicity:
  - Myelosuppression – is dose-limiting. Platelets are relatively spared. Granulocyte nadir is about 10-14 days after IV dose with recovery by day 21.
  - Nausea and vomiting are seen frequently with large intravenous doses; less commonly after oral doses. Symptoms begin several hours after treatment and usually subside by the next day.
  - Reversible alopecia is common. Skin and nails may become darker. Mucositis is uncommon.
  - Bladder – hemorrhagic or non-hemorrhagic cystitis may occur in 5-10% of patients treated. It is usually reversible on discontinuation of the drug, but it may persist and lead to fibrosis or death. Frequency is diminished by ample fluid intake and voiding of the bladder.
  - Additional side effects – immunosuppression, amenorrhea, and azoospermia are common. Inhibition of antidiuretic hormone is only of significance with very large doses. Interstitial pulmonary fibrosis is rare. Secondary neoplasia is possible.
- Source of study medication: Study medication will be provided by the AMC.
- Study medication formulation: 50 tablets
- Storage and stability: Storage at or below 77°F (25°C) is recommended; this product will withstand brief exposure to temperatures up to 86°F (30°C) but should be protected from temperatures above 86°F (30°C).

5.1.2.3 Etoposide

- Other name(s) and abbreviation: Vepesid®, epipodophyllotoxin, VP-16-213, VP-16
- Mechanism of action: Induce DNA strand breaks by inhibition of topoisomerase II, a DNA reparative enzyme.
- Metabolism and excretion: Highly bound to plasma protein with a terminal half-life of 11.5 hours. Excreted in bile and urine as intact and degraded drug.
- Usual dosage and schedule: When given intravenously, 100-125 mg/m2 daily (day 1-3, day 1-5), or intermittently (days 1, 3, 5). Oral dose is doubled (200 mg/m2/d) and given in a divided dose, if total dose is 400 mg or greater.
- Special precautions: cause hypotension if given rapidly by intravenous injection.
- Common side effects and toxicity:
  - Myelosuppression – leukopenia in particular, is dose-limiting. Nadir

usually observed at 16 days with recovery by day 20 to 22.
    - Nausea and Vomiting – are usually minor problems in one-third of patients.
    - Alopecia is common and stomatitis rare.
    - Additional side effects – severe allergic reactions including bronchospasm, wheezing, and anaphylaxis are rare. Chemical phlebitis is uncommon but caution is advised to avoid extravasation when drug is given intravenously. Secondary neoplasia is possible.
- Source of study medication: Study medication will be provided by the AMC or a pharmaceutical sponsor.
- Study medication formulation: 50 mg soft gelatin capsule
- Storage and stability: Store between 2°C – 8°C (36°F – 46°F). Do not freeze. After dispensing to participants, etoposide may be stored for up to 30 days at room temperature.

5.1.2.4 Procarbazine

- Other name(s) and abbreviation: Natulane®,methylhydrazine, Proc. (for protocol purposes)
- Mechanism of action: Causes formation of free hydroxyl radicals and thus mimics the effect of ionizing radiation. Depolymerizes DNA. Inhibits DNA, RNA and protein synthesis.
- Metabolism and excretion: Readily enters the CSF. Degraded in the liver to inactive compounds. Inactive products are excreted in the urine.
- Usual dosage and schedule: 100 mg/m2 orally for 7 to 14 days every 4 weeks when given in combination with other drugs. Procarbazine is a monoamine oxidase inhibitor and has various drug interactions. The clinical incidence of these interactions is low
- Special precautions: May cause disulfiram-like reactions in patients consuming alcohol. May cause additive depression with CNS depressants. May interact with sympathomimetic amines causing hypersensitive crises.
- Common side effects and toxicity:
    - Myelosuppression – pancytopenia is dose-limiting.
    - Nausea and vomiting are frequent during first few days until tolerance develops.
    - Stomatitis and diarrhea are uncommon. Alopecia, pruritus and drug rash are also uncommon.
    - CNS effects – include paresthesias, neuropathies, headache, dizziness, depression, apprehension, nervousness, insomnia, nightmares, hallucinations, ataxia, confusion, convulsions and coma. These have all been reported with variable frequency.
- Additional side effects – visual disturbances and postural hypotension are rare. Secondary neoplasia is possible.
- Source of study medication: Study medication will be provided by the AMC or a pharmaceutical sponsor.
- Study medication formulation: 50 mg capsules

- Storage and stability: Store below 40°C (104°F), preferably between 15 and 30°C (59 and 86 °F), in a tight, light-resistant container.

5.2 Drug Orders, Transfers, Returns, and Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received using the NCI Drug Accountability Record Form (DARF) (available on the CTEP home page (**http://ctep.cancer.gov**) or by calling the Pharmaceutical Management Branch at 301-496-5725). The DARFs document the drug delivery date to the site, inventory at the site, use by each study participant, and disposal of the drug (if applicable). A site-specific accountability record, either manual or electronic, may be used if it includes all the information required on the NCI Investigational Drug Accountability Record and if the paper printout is identical to the NCI accountability record. A separate DARF is required for each protocol using the same agent. The investigator will ensure that the drugs are used only in accordance with this protocol.

Drug will be shipped through a third party vendor. Instructions for drug ordering are available on the AMC website (**www.amcoperations.com**).

5.2.1 Drug Dispensing

The clinic pharmacist or an alternative qualified person at each participating AMC site will be responsible for dispensing study medication. The total amount of drug necessary for a single cycle of treatment (prednisone for CHOP regimen) or a 3 to 5 day supply (oral regimen) will be dispensed to the subject at the beginning of the cycle (CHOP regimen) or Day 1 and Day 22 (oral regimen), with instructions on the number of capsules to be taken at each dose.

Oral agents will be provided in bulk supply bottles. Since oral study agents are not subject-specific, site pharmacists must dispense agent from opened bulk supply bottles (break bottles) before opening a new bulk agent supply bottle to avoid unnecessary drug wastage. A new bottle may be opened prior to exhausting the supply in an open bottle if the agent in the open bottle is expired or the open bottle has not been stored in accordance with the package insert.

5.3 Dosing

5.3.1 CHOP

Intravenous chemotherapy medication is given on the following schedule:

Cyclophosphamide	750 mg/m^2 IV Day 1, each cycle
Doxorubicin	50 mg/m^2 IV Day 1, each cycle
Vincristine	1.4 mg/m^2 IV Day 1, each cycle (max, 2.0 mg)
Prednisone	100 mg orally Day 1-5, each cycle

**Total six 3-week cycles*

A cycle of therapy is 3 weeks. A total of six 3-week cycles of therapy will be administered (18 weeks). Vincristine should be rounded to the nearest 0.1 mg. All other drug doses are rounded to the nearest milligram dosage. Doses of

chemotherapy must be recalculated and adjusted if the participant's weight changes greater than 10% from baseline or the prior dose. Otherwise doses may be adjusted in accordance with institutional guidelines.

5.3.2 Modification of Initial Intravenous Chemotherapy Medication

Poor risk patients, defined as those with PS 2-3 or CD4 < 100 or WBC or HGB, or PLTS below the institution normal range, and randomized to CHOP, will be treated in cycles 1 and 2 with a reduced dose CHOP, as follows:

Two, 3-week (21 day) cycles of the following regimen:

Cyclophosphamide	375 mg/m^2 IV Day 1, each cycle
Doxorubicin	25 mg/m^2 IV Day 1, each cycle
Vincristine	1.4 mg/m^2 IV Day 1, each cycle (max, 2.0 mg)
Prednisone	100 mg orally Day 1-5, each cycle

After 2 cycles, patients without major adverse events, defined as no new Grade 3 toxicities attributed to treatment, will have CHOP doses escalated to standard doses for cycle 3. Patients with any new Grade 3 toxicities will continue on the reduced-dose regimen for a total of 6 cycles. This approach represents a consensus approach that is consistent with the AMC African sites' current practice.

5.3.3 Oral Chemotherapy

Oral chemotherapy medication is given on the following schedule:

Lomustine (CCNU):	50 mg/m^2 once daily	Day 1, cycle 1 and cycle 3 only
Etoposide (VP-16):	100 mg/m^{2}once daily	Day 1-3 of each cycle*
Cyclophosphamide (CTX)	100 mg/m^2 once daily	Day 22-26 of each cycle*
Procarbazine (Proc):	100 mg/m^2 once daily	Day 22-26 of each cycle*

**Total three 6-week cycles*

A cycle of therapy is 6 weeks. A total of three 6-week cycles of therapy will be administered (18 weeks). Starting drug and modified drug doses are rounded to accommodate pill size. Lomustine is rounded to the nearest 10 mg increment. All other oral drugs (etoposide, cyclophosphamide, and procarbazine) are rounded to the nearest 25 or 50 mg increment, as available. Rounding should be to the nearest available tablet or capsule size.

If the calculated dose is exactly half way between two available pill sizes, the initial dose should be rounded to the next higher value (e.g., if the calculated dose is 75 mg, and only 50 mg capsules are available, the initial dose would be 100 mg).

If rounding is part of a dose reduction (i.e. for toxicity), rounding should be performed to result in a decrease in the dose of the modified drug (e.g., if the reduced dose is calculated at 75 mg, and only 50 mg capsules are available, the administered dose should be 50 mg).

Please see MOP for additional examples. Doses of chemotherapy must be recalculated and adjusted if the participant's weight changes greater than 10% from baseline or the prior dose. Otherwise doses may be adjusted in accordance with institutional guidelines.

5.4 Dosing Modifications for Hematologic Toxicities

Intravenous and oral chemotherapy dosing will be guided by blood counts performed within 48 hours of the scheduled day initiating of chemotherapy administration (day 1 of each cycle for CHOP and days 1 and 22 for the oral regimen). The exception to this is Cycle 1, Day 1, which allows blood counts to be performed within 7 days of dosing.

All participants will receive chemotherapy provided the post-nadir ANC is ≥ 1,000/μL and the post-nadir platelet count is ≥ 50,000/μL. Specific dosage requirements are detailed below.

G-CSF may be used if it is locally available, however, it will not be provided by the study.

If dose modifications are required for toxicity, the participant must receive a reduced dose for all subsequent cycles.

5.4.1 Oral Chemotherapy Modifications if G-CSF is Not Available

Dose modifications for the oral regimen will be made according to the table below:

If ANC ≥ 1500/mm^3 and platelets ≥ 75,000/mm^3 prior to Day 1 of cycle 2 or any cycle thereafter, or Day 22 of any cycle:	Treat at full dose
If ANC is 1000/mm^3 to 1499/mm^3 and/or platelets are 50,000/mm^3 to 74,999/mm^3 prior to Day 1 of cycle 2 or any cycle thereafter, or Day 22 of any cycle:	Reduce all oral drug doses by 50% of the original dose
If ANC is <1000 mm^3 and/or platelets are < 50,000/mm^3 prior to Day 1 of cycle 2 or any cycle thereafter, or Day 22 of any cycle:	Hold treatment for up to 3 weeks to allow for recovery.*

- If treatment held, weekly CBCs are recommended to monitor count recovery. If, after ≤3 weeks, the ANC is ≥1000/mm^3 and the platelet count is ≥50,000/mm^3, treatment may resume at a 50% dose reduction for all drugs. If the ANC remains <1000/mm^3 and/or the platelet count remains <50,000/mm^3 for >3 weeks after the scheduled start of treatment (day 1 or day 22 of each cycle), study treatment will be permanently discontinued.
- Once the doses of oral drugs have been reduced by 50%, subsequent treatment cycles may be given at this dose if the ANC is ≥1000/mm^3 and the platelet count is ≥50,000/mm^3 within 48 hours of the scheduled treatment.
- Once the doses of oral drugs have been reduced by 50%, if the ANC is <1000/mm^3 and/or the platelet count is <50,000/mm^3 within 48 hours of a scheduled treatment, study treatment will be permanently discontinued.
- G-CSF may be administered per the site standard. G-CSF must be discontinued at least 24 hours before chemotherapy administration and should not be resumed less than 48 hours after the last dose of chemotherapy in each cycle.

5.4.2 Oral Regimen Modifications if G-CSF is Available

Dose modifications are required if either the ANC or the platelet counts meet the

criteria for modification. If different modification criteria are met based on the blood counts, please follow the more stringent dose modification plan. Dose modifications for the oral regimen will be made according to the table below:

ANC Dose Modification Criteria

If ANC is ≥ 1000/mm^3 prior to Day 1 of cycle 2 or any cycle thereafter, or Day 22 of any cycle:	Treat at full dose
If ANC is < 1000/mm^3 administer G-CSF as per site standard and delay treatment by 7 days.	If, after 7 days, the ANC is ≥ 1000/mm3, treatment may be continued at full dose with G-CSF administered per site standard for all remaining cycle.
	If the ANC is 500/mm^3 – 999/mm^3 after 7 days, treatment may resume at a 50% dose reduction for all oral drug doses, with G-CSF administered per site standard for all remaining cycles.
	If the ANC is < 500 mm^3 after 7 days, study treatment will be permanently discontinued.

- G-CSF must be discontinued at least 24 hours before chemotherapy administration and should not be resumed less than 48 hours after the last dose of chemotherapy in each segment of the treatment cycle.
- Once the doses of the oral regimen have been reduced by 50%, subsequent treatment cycles may be given at this dose if the ANC is ≥500/mm^3 within 48 hours of the scheduled treatment.
- Once the doses of the oral regimen have been reduced by 50%, if the ANC is <500/mm^3 and/or within 48 hours of a scheduled treatment, study treatment will be permanently discontinued.

Platelet Dose Modification Criteria

If platelets ≥ 75,000/mm^3 prior to Day 1 of cycle 2 or any cycle thereafter, or Day 22 of any cycle: thereafter:	Treat at full dose
If platelets are 50,000/mm^3 to 74,999/mm^3:	Reduce all oral agents by 50% of the original dose
If platelets are < 50,000/mm^3:	Hold treatment for up to 3 weeks to allow for recovery.*

- If platelets <50,000/mm^3, treatment will be held for up to 3 weeks. Weekly CBCs are recommended to monitor count recovery. If, after ≤3 weeks, the platelet count is ≥50,000/mm^3, treatment may resume at a 50% dose reduction for all oral agents. If the platelet count remains <50,000/mm^3 for >3 weeks after the scheduled start of the cycle, study treatment will be permanently discontinued.
- Once the doses of the oral agents have been reduced by 50%, subsequent treatment cycles may be given at this dose if the platelet count is ≥50,000/mm^3 within 48 hours of the scheduled treatment.
- Once the doses of oral agents have been reduced by 50%, if the platelet count is <50,000/mm^3 within 48 hours of a scheduled treatment, study treatment will be permanently discontinued.

5.4.3 CHOP Modifications if G-CSF is Not Available

Dose modifications for the CHOP regimen will be made according to the table below:

If ANC $\geq$ 1500/mm^3 and platelets $\geq$ 75,000/mm^3 prior to Day 1 of Cycle 2 and any cycle thereafter:	Treat at full dose
If ANC is 1000/mm^3 to 1499/mm^3 and/or platelets are 50,000/mm^3 to 74,999/mm^3 prior to Day 1 of Cycle 2 and any cycle thereafter:	Reduce all cyclophosphamide and doxorubicin doses by 50% of the original dose
If ANC is <1000 mm^3 and/or platelets are < 50,000/mm^3 prior to Day 1 of Cycle 2 and any cycle thereafter:	Hold treatment for up to 3 weeks to allow for recovery.*

- If ANC <1000/mm^3 and/or platelets <50,000/mm^3, treatment will be held for up to 3 weeks. Weekly CBCs are recommended to monitor count recovery. If, after $\leq$3 weeks, the ANC is $\geq$ 1000/mm^3 and the platelet count is $\geq$50,000/mm^3, treatment may resume at a 50% dose reduction for cyclophosphamide and doxorubicin. If the ANC remains <1000/mm^3 and/or the platelet count remains <50,000/mm^3 for >3 weeks after the scheduled start of the cycle, study treatment will be permanently discontinued.
- Once the doses of cyclophosphamide and doxorubicin have been reduced by 50%, subsequent treatment cycles may be given at this dose if the ANC is $\geq$1000/mm^3 and the platelet count is $\geq$50,000/mm^3 within 48 hours of the scheduled treatment.
- Once the doses of cyclophosphamide and doxorubicin have been reduced by 50%, if the ANC is <1000/mm^3 and/or the platelet count is <50,000/mm^3 within 48 hours of a scheduled treatment, study treatment will be permanently discontinued.

5.4.4 CHOP Modifications if G-CSF is Available

Dose modifications are required if either the ANC or the platelet counts meet the criteria for modification. If different modification criteria are met based on the blood counts, please follow the more stringent dose modification plan. Dose modifications for the CHOP regimen will be made according to the table below:

ANC Dose Modification Criteria

If ANC $\geq$ 1000/mm^3 prior to Day 1 of Cycle 2 and any cycle thereafter:	Treat at full dose
If ANC is < 1000/mm^3 administer G-CSF as per site standard and delay treatment by 7 days.	If, after 7 days, the ANC is $\geq$ 1000/mm^3, treatment may be continued at full dose with G-CSF administered per site standard for all remaining cycle.
	If the ANC is 500/mm^3 – 999/mm^3 after 7 days, treatment may resume at a 50% dose reduction for cyclophosphamide and doxorubicin, with G-CSF administered per site standard for all remaining cycles.

	If the ANC is < 500 mm^3 after 7 days, study treatment will be permanently discontinued.

- G-CSF must be discontinued at least 24 hours before chemotherapy administration and should not be resumed less than 48 hours after the last dose of chemotherapy in each cycle.
- Once the doses of cyclophosphamide and doxorubicin have been reduced by 50%, subsequent treatment cycles may be given at this dose if the ANC is ≥500/mm^3 within 48 hours of the scheduled treatment.
- Once the doses of cyclophosphamide and doxorubicin have been reduced by 50%, if the ANC is <500/mm^3 and/or within 48 hours of a scheduled treatment, study treatment will be permanently discontinued.

Platelet Dose Modification Criteria

If platelets ≥ 75,000/mm^3 prior to Day 1 of Cycle 2 and any cycle thereafter:	Treat at full dose
If platelets are 50,000/mm^3 to 74,999/mm^3:	Reduce all cyclophosphamide and doxorubicin doses by 50% of the original dose
If platelets are < 50,000/mm^3:	Hold treatment for up to 3 weeks to allow for recovery.*

- If platelets <50,000/mm^3, treatment will be held for up to 3 weeks. Weekly CBCs are recommended to monitor count recovery. If, after ≤3 weeks, the platelet count is ≥50,000/mm^3, treatment may resume at a 50% dose reduction for cyclophosphamide and doxorubicin. If the platelet count remains <50,000/mm^3 for >3 weeks after the scheduled start of the cycle, study treatment will be permanently discontinued.
- Once the doses of cyclophosphamide and doxorubicin have been reduced by 50%, subsequent treatment cycles may be given at this dose if the platelet count is ≥50,000/mm^3 within 48 hours of the scheduled treatment.
- Once the doses of cyclophosphamide and doxorubicin have been reduced by 50%, if the platelet count is <50,000/mm^3 within 48 hours of a scheduled treatment, study treatment will be permanently discontinued.

5.5 Dosing Modifications for Other Toxicities

Any dose reduction for treatment related toxicities will be permanent. All subsequent treatment cycles must be given at the reduced dose.

5.5.1 Oral Chemotherapy Dose Modifications

5.5.1.1 Hemorrhagic cystitis: If this occurs, a 50% dose reduction in cyclophosphamide is to be made for the next cycle of therapy, provided the patient has recovered from this event. A treatment delay of up to 3 weeks is permissible. If this occurs again, eliminate the cyclophosphamide from the chemotherapy regimen.

5.5.1.2 Procarbazine skin rash/allergy: Procarbazine allergy is manifested by a

generalized rash and must be differentiated from drug reactions secondary to other agents or a related problem due to underlying immunodeficiency. If procarbazine rash occurs, eliminate procarbazine from the chemotherapy regimen.

5.5.1.3 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.

5.5.1.4 Renal toxicity: Dose modifications are recommended for etoposide in participants with reduced creatinine clearance. A 25% reduction in etoposide dose is recommended if the calculated creatinine clearance is between 15 and 50 mL/min, and a 50% reduction is recommended if the calculated creatinine clearance is below 15 mL/min.

5.5.1.5 Other–Non-Hematologic Toxicities: All drugs will be withheld for a Grade 3 or higher non-hematologic toxicities other than those specified above. A treatment delay of up to 3 weeks is permissible. If after 3 weeks the toxicity does not resolve to ≤ Grade 1, the patient is to discontinue study treatment. If the toxicity resolves to ≤ Grade 1 within 3 weeks, treatment may be resumed at a 50% dosage reduction for all drugs. If Grade 3 or higher non-hematologic toxicity recurs at the reduced dose, the patient is to discontinue study treatment.

5.5.2 CHOP Modifications

5.5.2.1 Hepatic toxicity: All drugs will be withheld for a direct serum bilirubin of >5.0 mg/dL. A treatment delay of up to 3 weeks is permissible at which point a determination is to be made as to whether the hepatic dysfunction is secondary to progressive NHL or toxicity. If after 3 weeks the serum bilirubin remains >5.0 mg/dl, the patient is to discontinue study treatment.

Direct Bilirubin	Agent (s)	Reduction
1.2-3.0 mg/dL	Doxorubicin	50% based on full dose initially or previous dose for cycles 2-6
>3.0-5.0 mg/dL	Vincristine	50% based on full dose initially or previous dose for cycles 2-6
	Doxorubicin	75% based on full dose initially or previous dose for cycles 2-6

- If direct bilirubin >5.0 mg/dl, doxorubicin and vincristine should not be administered.
- No dosage adjustment is required for isolated indirect hyperbilirubinemia associated with the use of indinavir, tenofovir, or atazanavir.

5.5.2.2 Renal toxicity: All drugs will be withheld for a serum creatinine >3.0

mg/dL. A treatment delay of up to 3 weeks is permissible at which point a determination is made as to whether the renal dysfunction is secondary to progressive NHL or toxicity. If the participant is receiving tenofovir, the tenofovir dose can either be adjusted based on the creatinine clearance or stopped and an alternative NRTI substituted. If the creatinine returns to normal, chemotherapy may be resumed. If after 3 weeks despite these maneuvers, the serum creatinine remains >3.0 mg/dl, the patient is to discontinue study treatment.

5.5.2.3 Hemorrhagic cystitis: If this occurs, a 50% dose reduction in cyclophosphamide is to be made for the next cycle of therapy, provided the patient has recovered from this event. A treatment delay of up to 3 weeks is permissible. If this occurs again, eliminate the cyclophosphamide from the chemotherapy regimen.

5.5.2.4 Cardiac toxicity: If clinical findings suggesting congestive heart failure are present, doxorubicin will be discontinued and evaluation by MUGA or echocardiogram should be performed**.**

5.5.2.5 Neurological

Neurotoxicity	**Vincristine Dose**
Moderate paresthesias (inability to button)	No change
Inability to walk on heels or obstipation	25% reduction
Ambulation difficulties	No vincristine

5.5.2.6 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.

5.5.3 Antiretroviral Modifications

Tenofovir and Emtricitabine: Participants with reduced creatinine clearance who are receiving tenofovir (TDF) and/or emtricitabine (FTC) as part of their ART regimen should have the doses of these drugs modified. Please see the TDF/FTC, TDF and FTC package inserts for dosage adjustment recommendations.

5.6 Duration of Treatment

5.6.1 All participants shall be removed from treatment upon documentation of PD, unacceptable toxicity as defined by the dose modification guidelines, or at the discretion of the treating physician (See section 8.0).

5.6.2 Total duration of chemotherapy prescribed in this protocol is 18 weeks of therapy (as either six 3-week cycles of CHOP, or three 6-week cycles of oral chemotherapy). Patients are to be restaged following completion of therapy. Tumor

response and clinical safety/toxicity status are assessed by international criteria and the NCI Common Terminology Criteria for Adverse Events (Version 5.0) (11-13) Categories of objective response (described in section 8.0) include CR/cCR and PR, SD, and PD.

5.6.3 All patients with PD at any point are to be removed from study treatment. They will continue to be followed for overall survival. Patients developing CNS involvement (i.e., lymphomatous meningitis, vitreal involvement, parenchymal metastasis, or epidural spinal cord compression) will be considered to have PD. Patients experiencing persistent or unusual toxicity as outlined in sections 5.4 and 5.5 will also be removed from treatment.

5.6.4 All supportive therapy measures consistent with optimal patient care will be given throughout the duration of the study, including, if appropriate, to the standard of care in the country where the participant is enrolled, blood transfusions, G-CSF and antibiotics. There is no prescribed second-line or 'salvage' chemotherapy regimen for patients with PD. Subsequent chemotherapy regimen(s) for second-line treatment and tumor response should be documented, if possible. Adverse event information regarding second-line therapies will not be collected. Participants will be followed only for vital status and a recording of the second-line and subsequent regimens which fall within the two year window following completion of first line therapy.

5.7 Concomitant Medication(s) and Diet

5.7.1 Required and Permitted Medications

- All participants must be prescribed combination antiretroviral therapy with the goal of virological suppression using an acceptable regimen that adheres to national guidelines for treatment of HIV infection. Participants can already be on a regimen and remain on that regimen during treatment on this protocol. Participants can begin ART on the day of enrolling in this study to meet eligibility criteria. The prescribed ART regimen at the time of enrollment cannot contain zidovudine (AZT)
- The antiretroviral regimen must be recorded in the case report form at baseline. Any changes to the participant's ART regimen must be recorded through 12 month follow-up.
- There will be no specific prescribed antiemetic regimen, although use of antiemetics is recommended, if available, during this protocol. Antiemetics are prescribed by the treating physician team. Pre-hydration and allopurinol are not required but are permitted and encouraged, if appropriate to avoid tumor lysis syndrome. Patients should be encouraged to increase oral fluid intake during the period of cyclophosphamide administration.
- PCP prophylaxis must be administered for the duration of treatment using drugs available in the participant's country of enrollment unless medically contraindicated.
- Other prophylactic interventions are prescribed at the discretion of the treating physician. Routine TB prophylaxis should not be given; however, patients already on TB prophylaxis at the time of entry on this study may continue it

during the study at the discretion of the treating physician.

- CNS prophylaxis is recommended, where feasible, in patients who meet the following criteria: lymphomatous involvement of bone marrow, testes, sinuses, or epidural regions. One of the following regimens is recommended: IT liposomal cytarabine (Depocyt®), IT cytarabine, or IT methotrexate. The specific regimen will be at the discretion of the primary oncologist but should include 4-6 doses of therapy. IT chemotherapy will not be provided by the study.

5.7.2 Prohibited Medications

Zidovudine (AZT) in the absence of G-CSF administration is known to be myelosuppressive, which may adversely impact the dose intensity of the chemotherapy regimens prescribed in this protocol. As most of the patients who are enrolled in this study will not have access to G-CSF support, AZT is not permitted as an ART agent during concurrent chemotherapy.

5.7.3 Diet: There are no specific dietary recommendations or restrictions.

5.7.4 Medications Reported in the eCRF: All concomitant medications must be reported in the source documents. However, only antiretroviral medications, PCP prophylactic medications, TB prophylactic medications, opportunistic infection prophylactic medications, antineoplastic agents other than study drugs, and systemic corticosteroids other than those administered as part of CHOP must be reported in the eCRF.

5.8 Treatment Compliance

5.8.1 Intravenous medications will be administered as per study protocol. The oral component of CHOP (prednisone) will be dispensed at the start of each cycle of therapy.

5.8.2 Oral chemotherapy medications will be dispensed on Days 1 and 22 (every 3 weeks) of each cycle of therapy for three 6-week cycles.

5.8.3 Patients will be required to bring their study medication bottles with them to subsequent follow-up visits to document that oral medications have been taken (i.e., Days 1 and 22 of each cycle or every 3 weeks). Site personnel must collect the bottles, perform a pill count, compliance interview and review the completed participant diary.

5.8.4 Site personnel should present literate participants with the appropriate oral study drug diary based upon the study regimen (Appendix V). The diary should be completed by the participant to the best of his/her ability and returned to the site for review. The diary should be used to verify the pill count to determine medication compliance. Failure of the participant to properly complete or return the diary will not be considered a protocol deviation.

6.0 REPORTING OF ADVERSE EVENTS

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 AdvantageEDC^{SM}).

This study will utilize the Common Terminology Criteria for Adverse Event (CTCAE) version 5.0 for adverse event reporting. A copy of the CTCAE version 5.0 can be downloaded on the CTEP website at **http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm**. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. The document "NCI Guidelines: Adverse Event Reporting Requirements for NCI Investigational Agents clearly outlines reporting criteria.

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

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

6.1.1 Common Terminology Criteria for Adverse Events (CTCAE) is designed as an instrument to be used to document AEs identified through a combination of clinical and laboratory evaluation. CTCAE is NOT a tool to assist with data extraction from source documents without the direct participation and supervision of clinical investigators. AE grading and assignment of attribution require documentation by medical personnel who are directly involved in the clinical care of protocol participants.

6.1.2 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to severity for the purposes of regulatory reporting to NCI as follows:

Grade	Description
0	No AE (or within normal limits).
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE, which is defined in section 2.1.22 of the NCI Guidelines (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

6.1.3 Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference of Harmonization [ICH] E2A, E6).

6.1.4 Life-Threatening Adverse Event

Any AE that places the participant, in view of the Investigator, at immediate risk of death from the reaction. It does NOT include an AE that, had it occurred in a more severe form, might have caused death (FDA 21 CFR 312.32, ICH E2A).

6.1.5 Serious Adverse Event (SAE)

Any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

- Death.
- A life-threatening adverse drug experience.
- Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the participant 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).

Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events that result in an inpatient hospital stay equal to or greater than 24 hours must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. Hospitalization is used as an indicator of the seriousness of the AE and should ONLY be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example, a hospital visit where a patient is admitted for observation or minor treatment such as hydration and released in less than 24 hours should not be reported, but do report an admission for a myocardial infarction.

6.1.6 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.

6.1.7 Expectedness (Unexpected Adverse Event)

An unexpected AE is any AE, the specificity or severity of which is not consistent with the known side effects or toxicities described in the drug package insert or the Instructions for Use or other such documents. Additionally the ICH E2A defines an unexpected adverse drug reaction as an AE, the nature and severity of which is not consistent with the applicable product information (for example, Investigator's Brochure for investigational agent).

6.1.8 CTEP Adverse Event Reporting System (CTEP-AERS)

An electronic system for expedited submission of AE reports. Available at https://eapps-ctep.nci.nih.gov/ctepaers/. A username and password are not required for this system.

6.1.9 Attribution

An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily "caused by a therapeutic intervention." After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention[1]	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related to investigational agent/intervention[1]	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

NOTE: AEs listed as "possibly, probably, or definitely" related to the investigational agent/intervention in CTEP-AERS are considered to have a suspected "reasonable causal relationship" to the investigational agent/intervention (ICH E2A). For routine, CDUS adverse event reporting purposes, "Attribution" defines the relationship between the adverse event and the investigational agent(s)/intervention as defined in Clinical Data Update System (CDUS) Instructions and Guidelines that can be found at: **http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/cdus_ig_3r5.pdf**.

6.2 Expedited AE Reporting Procedures

6.2.1 Expedited AE reporting for this study must use CTEP-AERS, 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.

Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death

2) A life-threatening adverse event

3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours

4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

5) A congenital anomaly/birth defect.

6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Effective Date: May 5, 2011

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted above. 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.

6.2.2 Expedited AE reporting timelines defined:

"24 hours; 5 calendar days"– The Investigator must initially report the AE via CTEP-AERS, according to the procedures outlined in section 6.2, within 24 hours of learning of the event, and followed by a complete AE report submitted via CTEP-AERS within 5 calendar days of the initial 24-hour report. Use the NCI protocol number and protocol-specific participant ID assigned during trial registration on all reports. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 1-301-897-7497, or 1-301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

"10 calendar days"– A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the Investigator learning of the event. Use the NCI protocol number and protocol-specific participant ID assigned during trial registration on all reports.

Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited AE reporting exclusions.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS according to the guidelines as described above.

6.2.3 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.

6.2.4 Each participating institution will be responsible for submitting adverse event reports to the appropriate national regulatory authorities in the country. All adverse events that require expedited reporting to national regulatory authorities as a serious adverse events must be reported via CTEP-AERS.

6.3 Routine AE Reporting

All AEs reported through CTEP-AERS must also be reported in routine study data submissions using the Adverse Event electronic case report form. Routine reporting using the Adverse Events electronic case report form is required for all Grade 2 AEs and higher, regardless of attribution, for adverse events that occur within 30 days of the last administration of investigational agent. Routine reporting using the Adverse Events

electronic case report form is only required for adverse events that are possibly, probably, or definitely related to investigational agent(s) for adverse events that occur more than 30 days after the last administration of investigational agent(s). All adverse events must be assessed by a study investigator and documented in the medical record.

Adverse event information regarding second-line therapies will not be collected. Participants will be followed only for vital status, adverse events related to study treatment, and a recording of the second-line and subsequent regimens which fall within the two year window following completion of first line therapy.

6.4 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 mechanism (via AdvantageEDC^{SM} in the Adverse Event Form).

6.5 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 (via AdvantageEDC^{SM} in the Adverse Event Form).

7.0 CRITERIA FOR DISCONTINUATION

7.1 Permanent Treatment Discontinuation

7.1.1 Specified drug-related toxicity. Please see criteria for discontinuation due to drug toxicities as has been clearly outlined in sections 5.4 and 5.5.

7.1.2 Requirement for prohibited concomitant medications (see section 5.7.2).

7.1.3 Completion of treatment as defined in the protocol.

7.1.4 Request by participant to terminate treatment.

7.1.5 Clinical reasons believed life threatening or no longer in the best interest of the participant by the site investigator, such as pregnancy or breastfeeding, even if not addressed in the toxicity section of the protocol.

7.1.6 As outlined in 5.6.1, and as defined in 8.1.2.6, all patients with PD at any point are to discontinue study treatment. Patients developing CNS metastases (i.e., lymphomatous meningitis, vitreal involvement, parenchymal metastasis, or epidural spinal cord compression) will be considered to have progressive disease.

7.1.7 Chemotherapy will be discontinued during pregnancy and breastfeeding.

7.1.8 Window for missed chemotherapy visit for any reason (graded AE, missed appointment) is 3 weeks. The patient can come back "late" only up to 3 weeks. If the participant discontinues treatment due to toxicity, the toxicity should be followed until resolution or the toxicity level returns to baseline.

7.1.9 Request by the investigator if s/he thinks the participant to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self

7.1.10 A participant returns to the study center late (> 7 days) for two consecutive chemotherapy visits for reasons other than protocol-mandated treatment delay for an AE. Every effort will be made to follow the participant for the primary outcome measure.

7.1.11 The participant is not adherent with the oral regimen. Non-adherence is defined as missing $\geq$ 20% of the prescribed oral doses in a 42 day cycle. Adherence should be determined based on the pill count and participant report. A completed diary can also be used as a supplemental tool to determine adherence. Please consult with Protocol Chair(s) for questions related to drug adherence.

7.2 Premature Study Discontinuation

7.2.1 Request by the participant to withdraw.

7.2.2 Request by the protocol chairs, AMC, IRB, NCI, OHRP, local government agencies, or pharmaceutical sponsors.

8.0 EVALUATION OF RESPONSE

Response assessment will be based on response definitions of the 2014 International Conference on Malignant Lymphoma Imaging Working Group (i.e. Lugano Classification)[13]. Only CT based response assessment will be used. CT/PET evaluation, which is not readily available in many places in Africa, will not be used to assess response. Traditional tumor response assessment allows evaluation of measureable disease on physical examination and requires that all studies performed at baseline be repeated to document complete or partial response (CR or PR) [12, 13].

Additionally, patients with residual lymphadenopathy less than 3 cm that remains stable for > 3 months, and in the opinion of the investigator could be attributable to residual HIV-related lymphadenopathy may also be considered to have a CR/cCR (41). When feasible, fine needle aspiration or open biopsy confirmation will be performed when clinically indicated to reconcile equivocal disease status. See definitions of 2014 International Conference on Malignant Lymphoma Imaging Working Group below[13].

Unless the participant has clearly progressed based on clinical criteria, final CT scans to confirm PE findings of response should be performed at the end of treatment. This should be done 6-8 weeks post-treatment.

8.1 Definition of Response

8.1.1 Definitions of Measurability

- Patients without bi-dimensionally measureable disease are eligible for this study and can be assessed for all response categories except partial response (PR) as shown below.
- Patients with bi-dimensionally measurable disease will have serial disease assessments defined below.
    - Bi-dimensionally measureable disease is malignant disease measurable in two dimensions by ruler or calipers with surface area determined by multiplying the longest diameter by the greatest perpendicular diameter. Measurements must be made by the same method, consistently, and preferably by the same observer. Malignant disease with sharply defined borders visualized by plain radiography (x-ray) or ultrasonography (sonogram) is considered measurable. Repeat studies should be performed at the same pre-therapy site(s) of malignant disease.
    - Six target lesions will be identified. Preferably these will be on a CT scan, but physical findings may be substituted if necessary.

8.1.2 Definition of Response

8.1.2.1 Complete Response (CR)

- Complete response is dated from the time all lesions disappeared. Complete disappearance (resolution) of all detectable lesions, and all disease related symptoms, if present before therapy, and normalization of biochemical abnormalities definitely assigned to NHL (e.g., lactate dehydrogenase [LDH]).

- Lymph nodes and nodal masses must have regressed to normal size (≤1.5cm for nodes >1.5cm before therapy) and in nodes 1.1-1.5cm prior to therapy a decrease to < 1cm or by >75% in sum of the products of the greatest diameters (SPD).
- A bone marrow involved by lymphoma before treatment must be cleared on repeat bone marrow aspirate and/or biopsy of the same site.
- Radiographic or ultrasound resolution of all abnormalities attributed to lymphoma from pre-treatment imaging.

8.1.2.2 CR/Clinical CR (cCR)

- Clinical CR (cCR) was utilized in the initial report of the dose-modified oral chemotherapy trial[11]. It includes those patients who fulfill all the criteria in section 8.1.3, but with the following exception and features:
- In the event radiographic studies cannot be repeated to ascertain disease status from baseline, unconfirmed or clinical CR can be assigned provided a thorough assessment of findings on physical examination is documented. In this scenario, complete disappearance on physical exam of clinically detectable disease is allowed.
- All patients with known bone marrow involvement must have a repeat negative bone marrow aspiration biopsy to have a CR or cCR.
- Findings on physical examination with assignment of clinical complete response must be reviewed and confirmed by an independent end point review team.

8.1.2.3 Partial Response (PR)

- A 50% or greater decrease of all tumors as measured by the sum of the products of the 2 largest perpendicular diameters (SPD) of all measurable lesions, but not complete resolution of all disease.
- No new sites of disease.
- No increase in size of other areas of tumor involvement.

8.1.2.4 Stable Disease (SD)

- Neither meets the criteria for a CR or PR (see above) nor meets the criteria for progressive disease (see below).

8.1.2.5 Relapsed Disease (from CR, cCR)

- Appearance of any new lesions after complete response or clinical complete response.

8.1.2.6 Progressive Disease (PD, non-responders)

- Greater than 50% increase from nadir in the SPD of any previously identified abnormal node; OR
- Appearance of new lesions (unless these lesions appear prior to

completion of the first 3 weeks of therapy).

9.0 DATA COLLECTION AND MONITORING

9.1 Records to Be Kept

CRFs will be provided for each participant via the AMC AdvantageEDC^{SM} Internet Data Entry System upon enrollment. Data will be recorded on the CRFs using the unique participant identification number assigned at registration. Participants must not be identified by name, initials, birthdates, name codes, or any other personally identifying numbers or codes on any study documents that are transmitted outside of the site. Sample CRFs will be available on the AMC ODMC website (**www.amcoperations.com**).

9.2 CRF Instructions

Instructions concerning the recording of study data on CRFs will be provided by the AMC ODMC.

9.3 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study. This role extends from protocol development to generation of the final study database.

9.4 Clinical Site Monitoring and Record Availability

This protocol has a Data and Safety Monitoring Plan (DSMP) that adheres to the master AMC Data and Safety Monitoring Plan for international trials (see Appendix IV).

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design

Randomized, phase II trial of CHOP vs. oral chemotherapy with concomitant antiretroviral therapy in patients with HIV-associated Diffuse Large B Cell Lymphoma in sub-Saharan Africa.

10.2 Statistical Analyses of Clinical Outcomes

The log-rank test will be used to compare the two treatment arms with respect to overall survival. The one-sided 0.20 significance level will be used for this comparison. Proportional hazards models will be used to evaluate the association between covariates (e.g. CD4 count and HIV viral load) and overall survival.

The overall response rate will be estimated for each of the treatment arms using the binomial proportion and its 95% confidence interval. The two arms will be compared with respect to overall response rate using Fisher's exact test. The log-rank test will be used to compare the two treatment arms with respect to progression-free survival.

For each treatment arm, the frequency and severity of adverse events will be summarized. For adverse events that occur in more than 5% of either arm, the two treatment arms will be compared with respect to the proportion of patients who experience that adverse event using Fisher's exact test. Similarly, the proportion of patients who complete treatment will be compared using Fisher's exact test.

Fisher's exact test will be used to compare the two treatment arms with respect to the proportions of patients who complete therapy. Patients will report whether they have missed any ARV medications since the last visit to assess adherence. Oral study drug adherence assessment consists of a review of returned bottles, pill count, and participant interview; patients who take $\geq$90% of their study medication during a given cycle will be classified as adherent for that cycle. General estimating equations for binary data will be used to compare treatment arms and to evaluate the effect of duration of therapy on ARV and oral study drug adherence adjusting for intrapatient variation. Effects of therapy on HIV control will be measured as the change from baseline to off-treatment level in CD4 count and HIV load. The Wilcoxon rank sum test will be used to compare the two treatment arms with respect to changes in CD4 count and HIV load. The proportional hazards model will be used to evaluate the association of covariates on overall survival and progression-free survival.

10.3 Proposed Sample Size

The objective of this study is to compare CHOP and an oral regimen with respect to overall survival. Using the log-rank test, 45 patients per treatment arm will be sufficient to test the null hypothesis that the two arms do not differ with respect to overall survival with the alternative hypothesis that the median overall survival duration is 18 months for CHOP and 12 months for the oral regimen at the one-sided 0.20 significance level with power of 0.81, assuming that overall survival duration is exponentially distributed, the accrual period is 24 months and the minimum follow-up duration is 24 months. The projected overall survival duration for CHOP is based on the median overall survival duration reported in AMC-010 for patients treated with CHOP (Kaplan L et al, Blood 2005; 106:1538-43).

10.4 Lost to Follow-Up and Trial Futility

The loss-to-follow-up (LTFU) rate will be calculated as Poisson rate. Each patient's follow-up duration will be defined as the time elapsed from the date of randomization to the date of data cut-off for calculation of the LTFU rate. The LTFU rate will be estimated as the number of study participants for whom vital status is unknown and is not expected to be observed divided by the sum of the follow-up duration for all patients on the study. The LTFU rate will be estimated 12 months and 24 months after the enrollment starts on the study. If the lower bound of the 95% Poisson confidence interval of the LTFU rate is > 15 per 100 person-years, then the study team will consider termination of the study due to the high LTFU rate.

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Ethical Committee or Institutional Review Board (IRB) Review and Informed Consent

The principles of informed consent described in OHRP regulations (45 CFR Part 46) must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

The 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. 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. 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.

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the ethics or IRB committees responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, parent, or legal guardian, and this fact will be documented in the participant's record.

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. Amendments significantly affecting the safety of participants, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB and national regulatory body approval depending upon the local regulations. A copy of the written approval of the IRB/IEC/REB and the national regulatory body (if applicable), must be sent to the ODMC.

11.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the AMC Operations Center, the IRB, the NCI, the OHRP, or designee.

11.3 Study Discontinuation

The study may be discontinued at any time by the Ethical Committee/IRB, the NCI, the Office of Human Research Protections (OHRP), or other government agencies as part of their duties to ensure that research participants are protected.

11.4 Women and Minorities

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

11.5 NIH Guidance Regarding Post-Trial Access

For protocols conducted in developing countries, the National Institutes of Health (NIH) has a guidance document regarding post-trial access available at: **http://grants.nih.gov/grants/policy/anitretroviral/guidance.doc**. Participating centers by virtue of their selection to join this AMC international trial are required to make arrangements through national drug procurement, NGO, or other clinical drug access programs in their country to provide post-trial access to ART. This is stated in the informed consent document. Additionally, the AMC will commit to develop successor clinical trials for the treatment of AIDS-related lymphoma in Africa if this trial yields results that warrant further study of the investigational agents.

12.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by AMC policies.

13.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control (CDC) and Prevention and the National Institutes of Health (NIH).

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to the instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

14.0 REFERENCES

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APPENDIX I: SCHEDULE OF PATIENT ASSESSMENT(S) AND EVALUATION(S)

Parameter(s)	Baseline	Cycle 1 Day 1	Cycle 1 Day 22 (oral) Cycle 2, Day 1 (CHOP)	Cycle 2, D1 (oral) Cycle 3, Day 1 (CHOP)	Cycle 2, D22 (oral) Cycle 4, Day 1 (CHOP)	Cycle 3, D1 (oral) Cycle 5, Day 1 (CHOP)	Cycle 3, D22 (oral) Cycle 6, Day 1 (CHOP)	Off-Treatment Day 128	Follow-up until off-study: 3M, 6M, 12M, 18M, 24M [3]
History & Physical Exam including neurological exam[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]	x[1]
Review of interim medical history, adverse events, and concomitant medications		x	x	x	x	x	x	x	x
Tumor measurements[1,2]	x[1]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[1,2]	x[1,2]
CBC, diff. & plts.[4]	x[1,4]	x[4]	x[4]	x[4]	x[4]	x[4]	x[4]	x[4]	
Serum creatinine and total bilirubin[5]	x[1,5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	
Electrolytes and serum chemistries[6]	x[1,6]	x[6]	x[6]	x[6]	x[6]	x[6]	x[6]	x[6]	
Chest x-ray[2]	x[2]							x[2]	
Abdomen & pelvic sonogram and CT scan[2]	x[2]							x[2]	
Bone marrow aspiration/ biopsy[7]	x[7]							x[7]	
Lumbar puncture	x[10]								
CD4 lymphocyte count, HIV-1 plasma RNA and viral load[8]	x[1,9]							x[8]	x[8]
Tumor biopsy	x								
Urine pregnancy test	x	x	x	x	x	x	x		
ART Adherence Assessment			x	x	x	x	x	x	
Oral Study Drug Adherence Assessment		x	x	x	x	x	x	x	

1. Baseline history and physical exam (including neurological exam) must be assessed within 48 hours of initiating therapy and may count as history and physical exam requirement for Day 1, cycle 1. Subsequent history and physical exams are performed within the 48 hours prior to Days 1 and 22 of each cycle of chemotherapy, at time of treatment completion (Day 128), and at specified time points following discontinuation of chemotherapy. Blood work of CBC, differential, platelet count, electrolyte

panel (sodium, potassium, chloride) with creatinine and serum chemistries including SGOT (AST) or SGPT (ALT), total bilirubin, albumin, uric acid and LDH must be done within 7 days prior to treatment and will suffice as Day 1 pretreatment laboratories.

2. Baseline assessments of tumor measurements, sonograms, CT scans or X-rays used to document measurable/evaluable disease should be done within 4 weeks prior to initiation of therapy. Imaging studies performed within 2 weeks of treatment initiation are preferable. Lesions on physical examination must be assessed within 48 hours of initiating therapy. Complete restaging including tumor measurements, is performed upon completion of cycle 3 of therapy. Imaging studies which showed evidence of disease at baseline must be repeated at time of re-staging (following cycle 3). Unless the participant has progressed either during treatment or during post treatment follow-up, CT imaging will be repeated at the 6, 12, 18, and 24 month follow-up visits.
3. Upon treatment completion, patients are followed at time points 3, 6, 12, 18 and 24 months following the treatment discontinuation visit (unless loss to follow up or death). Clinical status will be documented by exam and appropriate imaging modality at the discretion of the treating physician. Participants who have progressed either during study treatment or during post-treatment follow-up will be followed for vital status, adverse events related to study treatment, and for new treatment regimens ONLY, for the duration or remainder of follow-up.
4. Complete blood count (CBC), differential, and platelet counts are performed within the 48 hours prior to Day 1 and Day 22 of each period of chemotherapy administration, and at treatment completion. It is advisable, but not required, to obtain nadir blood counts on Day 15 and Day 36.
5. Serum creatinine and total bilirubin are performed within the 48 hours prior to Day 1 and Day 22 of each cycle of chemotherapy (three 6-week cycles total) and at treatment completion.
6. Electrolyte panel and serum chemistries are performed within the 48 hours prior to Day 1 and Day 22 of each cycle of chemotherapy (three 6-week cycles total) and at treatment completion: SGOT (AST) or SGPT (ALT), albumin, uric acid and lactate dehydrogenase (LDH).
7. Bone marrow biopsy - This is performed in all patients at baseline, and must be repeated in patients thought to have clinical complete response if bone marrow was initially involved.
8. CD4 lymphocyte count and HIV-1 plasma RNA (i.e., viral load determination) - These studies are to be performed at Baseline; and after cycle 3 at completion of treatment (Day 128). Viral load will be measured by HIV plasma RNA PCR. In addition, the antiretroviral regimen must be recorded in the source documents at time of on-study and any changes recorded as well. Furthermore, unless the participant progressed either during treatment or during post treatment follow-up, CD4 lymphocyte count and viral load determination will be performed at one 3 month time point after completing cycle 3 and then at 6 month intervals (i.e. at months 3, 6, 12, 18 and 24) until patient off-study (death or completion of 2 years of follow-up).
9. The baseline CD4 count must be collected within 30 days prior to enrollment on to the Treatment Segment.
10. A lumbar puncture must be completed within 4 weeks prior to enrollment.

APPENDIX II: ECOG PERFORMANCE SCALE

Grade	Descriptions
0	Normal activity. Fully active, able to carry out all pre-disease performance without restriction.
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 house work or office work).
2	In bed < 50% of the time. Ambulatory and capable of all self care, but unable to carry out work activities. Up and about for more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self care. Confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead

APPENDIX III: INITIAL PATHOLOGY REVIEW AND EXTERNAL QUALITY ASSURANCE AND HANDLING OF TISSUES

Diagnostic Pathology

Initial pathologic diagnosis will be performed by an approved pathologist at the site, and a report confirming a diagnosis of DLBCL will be issued and signed by an approved pathologist prior to a patient entering the trial. This diagnosis will be based on:

a) H&E showing a lymphoma with large cell morphology

b) CD20 or Pax5 immunohistochemistry showing loss of normal architecture, and that the large cells are of B cell origin.

c) Ki67 to evaluate the percentage of proliferating large cells. Cases with a proliferation rate of >90% will be excluded from the trial.

These parameters limit the trial to inclusion of patients with the 2008-WHO-defined DLBCL. It excludes Burkitt and Burkitt-like lymphoma and all other subtypes of non-Hodgkin's lymphoma. Additional immunostains performed at the site are allowed but not required, and should be described in the pathology report.

Drs. Cesarman, Ely or Tam will be available for consultation on any cases where the site pathologist has questions about the diagnosis or eligibility. In this case, microscopic images of diagnostic areas will be emailed to ecesarm@med.cornell.edu, wtam@med.cornell.edu, and sae2001@med.cornell.edu. A record of cases excluded from the trial will be kept for eventual review. Case review conferences will be held on a regular basis via conference calls.

Handling of Tissues for External Quality Assurance

The appointed pathologist at each site will collect the tissues from each patient entered into the protocol. Either a formalin-fixed, paraffin embedded (FFPE) tissue block, or 15 unstained tissue slides must be made available for centralized pathology review, to be completed upon termination of the trial. A copy of the local pathology report must be submitted with the tissue block or slides for central pathology review.

Tissues for external quality assurance pathology review must be batched at each site, and shipped via express mail, every six months to the AMC External Quality Assurance Laboratory at:

Sharon Barouk, MA
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, NY 10065 USA
Phone: (212) 746-6357
Fax: (212) 746- 8173
Email: shb2016@med.cornell.edu

The Weill Cornell Laboratory will destroy residual materials, when a block was submitted upon completion of the pathology review. For sites that request return of the slides and/or blocks, all the materials will be returned by the laboratory to the clinical site.

Each sample must be labeled using a Sharpie pen, or other waterproof, permanent marker with the following information:

Protocol #: AMC-068
9 digit Patient #
Date of collection
Specimen type: Tissue (tissue block) or Tissue (unstained slide)
Specimen purpose: External quality assurance

*Note: if unstained slides are collected, only one specimen label should be used for each set and applied to the bag or slide holder in which the slides are kept. The number of slides will need to be entered into the AMC's specimen tracking system, GlobalTrace[SM].

Specimen Accessioning

Upon receipt at Weill Cornell Medical College, each specimen from AMC will receive an Immunopathology Laboratory accession number which will be sequential with the other specimens received. 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 by Dr. Tam or Dr. Ely within a month of receipt, with a diagnosis based on the microscopic review of H&E-stained sections, results of immunohistochemistry, in situ hybridization (EBER) and molecular or cytogenetic analysis (if requested or considered informative for final diagnosis),. All the reports will be sent by FAX to the AMC ODMC as well as to the submitting physician and pathologist, and hard copies will follow.

Record of Specimens

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

Pathology Review

Specimens received from AMC will undergo histopathologic diagnosis and classification, immunostaining and molecular analysis. Pathologic evaluation will be performed by Dr. Tam or Dr. Ely; all interesting, atypical and unusual cases will also be reviewed by Drs. Orazzi and/or Knowles. Specifically, cases will be processed as follows:

1. H&E
3. Ten immunostains (CD20, CD3, BCL6, BCL2, Mum, CD10, PRDM1, Ki67, p53, LANA)
4. In situ hybridization (EBER)
5. FISH (cMYC, BLC6, BCL2).
6. Pathologist interpretation.

APPENDIX IV: AMC DATA AND SAFETY MONITORING PLAN

Version 6.0 • March 17, 2017

Monitoring the Progress of Trials and the Safety of Participants

All AMC protocols that collect safety data follow the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (http://ctep.cancer.gov/guidelines/index.html). All adverse events that meet the NCI's expedited reporting requirements are reported to the Investigational Drug Branch (IDB) of the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application. All expedited adverse event reports are also required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. If NCI holds the IND or no IND is required for a study, the AMC site reports serious adverse events directly to the AMC Operations and Data Management Center (ODMC) via CTEP-AERS; expedited reporting via AdvantageEDC/Advantage eClinical may be permitted for select commercial agent studies per protocol requirements. In some instances, the AMC sites may report serious adverse events directly to a commercial sponsor holding the IND, who will then report the event to the AMC ODMC. Most AMC protocols require sites to report all serious adverse events via CTEP-AERS and the AMC ODMC to forward a copy of the report to the sponsor. The AMC ODMC also distributes all IND safety reports to all investigators upon receipt, and makes these reports available on the password-protected section of the AMC Operations web site. Unless an AMC protocol specifies an alternate plan for the review and submission of serious adverse events, all serious adverse events received by the AMC ODMC will be reviewed by the AMC Medical Monitor at the AMC ODMC. For protocols for which the IDB does not have an assigned drug monitor to review serious adverse event reports, in the event of disagreement between the reporting physician and the AMC Medical Monitor regarding the attribution of the event to the investigational agent(s) (i.e., determination of whether the relationship is unrelated, unlikely, possible, probable, or definite), the AMC Medical Monitor will provide the final determination of the relationship.

The AMC ODMC provides listings of all reported adverse events and serious adverse events to the Protocol Chair and Co-chair(s) for review on a regular basis. The AMC ODMC compiles these events in a tabular format and posts them on the password-protected section of the AMC web site where these reports are updated nightly. The AMC web site is accessible to all AMC investigators, co-investigators, and their staff. Email notification that this information is available on the web site will be sent to all site PIs. It is the responsibility of each site to provide this information to their respective IRBs, if required by their IRB. For blinded studies, the serious adverse events are reviewed and tabulated without treatment assignment. The AMC Medical Monitor will review listings of all reported adverse events on a quarterly basis for safety concerns.

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 disease-oriented Working Group during scheduled conference calls. For pilot or 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 Group Statistician determine whether these criteria have been met. 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 Group Statistician determine whether these criteria have been met.

For phase III trials and other select studies requiring additional oversight, the AMC has formed an independent Data and Safety Monitoring Board (DSMB). Voting members of the DSMB are physicians, a statistician, and a patient advocate. All voting members are from outside the AMC. Nonvoting members are the AMC Group Statistician, the protocol statistician, an AMC Operations Center staff member, two representatives (normally a clinician or statistician) from the Office of HIV AIDS Malignancy (OHAM) or from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, of the National Cancer Institute (NCI). The DSMB reviews AMC phase III studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all phase III trials 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 concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB Chair to the 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 is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group 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 NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group 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 formal amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, a summary of the serious adverse events reported to the DSMB is posted to the AMC web site. It is each site's responsibility for conveying this information to its IRB.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)

For trials monitored by the NCI's Clinical Data Update System (CDUS), adverse event information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), adverse event information is transmitted electronically to NCI every two weeks.

The Protocol Chair, AMC Group Chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with the protocol requirements for adverse event reporting. All AMC investigators certify compliance with NCI and FDA requirements for adverse event reporting by signing the AMC Adherence Statement for site membership, the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration and IND studies sponsored by AMC investigators. Investigators are responsible for identifying and reporting all adverse events to the AMC ODMC, CTEP-AERS, and/or sponsors according to

the protocol requirements, and assuring compliance with reporting to the local IRB. Protocol compliance with adverse event reporting requirements is assessed by the AMC ODMC during routine site audits by reviewing the site's source documentation.

The data entry system used for AMC studies, AdvantageEDC/Advantage eClinical (a web-based data entry and enrollment system), is programmed to notify the site investigator, protocol chair, AMC Medical Monitor, and AMC ODMC via email in the event that a site reports an adverse event that meets expedited reporting criteria to NCI and/or FDA. 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 adverse events on a routine basis to identify adverse events reported by sites that require expedited reporting. The Protocol Chair, AMC Group Chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

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 termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. 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) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) 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 AdvantageEDC/Advantage eClinical. 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. AMC ODMC staff routinely interacts with site staff to resolve any data 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 preventive 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 of taking action against 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 V: AMC-068 STUDY DRUG DIARY (ORAL CHEMOTHERAPY REGIMEN)

AMC-068 Oral Regimen Study Drug Administration Instruction Sheet

Site Staff: Please complete the study drug instruction worksheet below. Circle the picture of the agent the participant should take.

Please take your study drugs as follows:

Drug Name: _____

Please take _____ pills for _____ days.

You should take this medication on (day and date):

_____

_____

_____

_____

_____

Drug Name: _____

Please take _____ pills for _____ days.

You should take this medication on (day and date):

_____

_____

_____

_____

_____

AMC-068 Oral Regimen Drug Diary

The following fields are to be completed by the site staff before the diary is given to the study participant.

Participant Number: _____

Treatment Cycle: _____

Date Agent Dispensed: _____

Number of Lomustine pills/day: _____

Number of Etoposide pills/day: _____

Participants: The study investigator or nurse will tell you how many pills to take. Please write the date you took each drug and how many pills you took.

		Day 1	**Day 2**	**Day 3**
Date				
Medication (name)	**Medication (photo)**	**Number of Tablets Taken**	**Number of Tablets Taken**	**Number of Tablets Taken**
Lomustine (CCNU)				
Etoposide (VP-16)				

AMC-068 Oral Regimen Drug Diary

The following fields are to be completed by the site staff before the diary is given to the study participant

Participant Number: _____

Treatment Cycle: _____

Date Agent Dispensed: _____

Number of Cyclophosphamide pills/day: _____

Number of Procarbazine pills/day: _____

Participants: The study investigator or nurse will tell you have many pills to take. Please write the date you took each drug and how many pills you took.

		Day 22	**Day 23**	**Day 24**	**Day 25**	**Day 26**
Date						
Medication (name)	**Medication (photo)**	**Number of Tablets Taken**	**Number of Tablets Taken**	**Number of Tablets Taken**	**Number of Tablets Taken**	**Number of Tablets Taken**
Cyclophosphamide (CTX)						
Procarbazine (Proc.)						

APPENDIX VI: AMC-068 STUDY DRUG DIARY (CHOP REGIMEN)

AMC-068 CHOP Regimen Study Drug Administration Instruction Sheet

Site Staff: Please complete the study drug instruction worksheet below. Circle the picture of the agent the participant should take.

Please take your study drugs as follows:

Drug Name: _____

Please take _____ pills for _____ days.

You should take this medication on (day and date):

_____

_____

_____

_____

_____

AMC-068 CHOP Regimen Drug Diary

The following fields are to be completed by the site staff before the diary is given to the study participant

Participant Number: _____

Treatment Cycle: _____

Date Agent Dispensed: _____

Number of Prednisone pills/day: _____

Participants: The study investigator or nurse will tell you have many pills to take. Please write the date you took each drug and how many pills you took.

		Day 1	Day 2	Day 3	Day 4	Day 5
Date						
Medication (name)	**Medication (photo)**	**Number of Tablets Taken**	**Number of Tablets Taken**	**Number of Tablets Taken**	**Number of Tablets Taken**	**Number of Tablets Taken**
Prednisone						