SUMMARY OF CHANGES

A pilot trial of AVD and brentuximab vedotin (SGN-35) in the treatment of stage II-IV HIV-associated Hodgkin lymphoma

Version 19.0

NCI Protocol #: AMC-085
Local Protocol #: AMC-085

NCI Version Date: 15APR2019
Protocol Date: 15APR2019

I. Revisions in response to the updated RRA for brentuximab vedotin (SGN-35) from Dr. Elad Sharon (sharone@mail.nih.gov), dated 01 APR 2019

#	Section	Description of Change
1.	6.1 Appendix XV	The CAEPR Version 2.4, January 31, 2018 was updated to CAEPR Version 2.5, February 13, 2019. The SPEER grades have been updated. **Increase in Risk Attribution**: • Changed to "Rare but Serious" from "Also Reported on SGN-35 Trials But With Insufficient Evidence for Attribution:" Infusion related reaction **Provided Further Clarification**: • Infections and infestations - Other (herpes zoster) is now reported as Shingles (CTCAE 5.0 language). • Investigations - Other (blood LDH increased) is now reported as Blood lactate dehydrogenase increased (CTCAE 5.0 language).
2.	ICD	The Risk Profile was updated to clarify a risk in the **RARE, AND SERIOUS** risk category for brentuximab vedotin (SGN-35). **Provided Further Clarification:** • "A tear or hole in the stomach that may require surgery" (under Rare) is now reported as "A tear or hole in internal organs that may require surgery" (under Rare).

II. Administrative and Editorial Changes

#	Section	Description of Change
3.	Global	The U.S. protocol version number has been updated from 18.0 to 19.0 and the date has been updated from 06MAR2019 to 15APR2019. The LYSARC protocol version number has been updated from 5.0 to 6.0 and the date has been updated from 14/11/2016 to 15/04/2019.
4.	Global	The protocol statistician has been changed from Page Moore to Milan Bimali.
5.	Appendix XV	All remaining references to CTCAE version 4.0 in the LYSARC protocol were corrected to version 5.0.

AMC PROTOCOL #085:
A Pilot Trial of AVD and Brentuximab Vedotin (SGN-35) in the treatment of stage II-IV HIV-associated Hodgkin Lymphoma

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	CTEP, Division of Cancer Treatment and Diagnosis, NCI and The Lymphoma Study Association (LYSA), conducted by The Lymphoma Academic Research Organisation (LYSARC), l'Institut National du Cancer
Supported by:	Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT01771107
CTEP IND Number:	
Protocol Chair:	Paul G. Rubinstein, MD
Protocol Co-Chair:	Ariela Noy, MD

Version 19.0, 15APR2019
NCI Version Date: 15APR2019

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol #085 -** A Pilot Trial of AVD and Brentuximab Vedotin (SGN-35) in the treatment of stage II-IV HIV-associated Hodgkin Lymphoma **(Version 19.0, 15APR2019),** as written according to AMC, NCI and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (mm/dd/yyyy)

TABLE OF CONTENTS

LIST OF TABLES

PROTOCOL ROSTER

AMC Protocol #085

A Pilot Trial of AVD and Brentuximab Vedotin (SGN-35) in the Treatment of Stage II-IV HIV-associated Hodgkin Lymphoma

Protocol Chair:
Paul G. Rubinstein, MD
John H. Stroger Jr. Hospital of Cook County
(Cook County Hospital)
Section of Hematology/Oncology
Administration Building
1900 W. Polk Street, Suite 755
Chicago, IL 60612
Tel: 312-864-7277
Fax: 312-864-9002
Email: prubinstein@cookcountyhhs.org

Protocol Statistician:
Milan Bimali, PhD
AMC Statistical Center
University of Arkansas for Medical Sciences
4301 West Markham Street
Little Rock, AE 72205
Tel: 501-686-8204
Fax: 501-526-6729
Email: mbimali@uams.edu

Protocol Co-Chair:
Ariela Noy, MD
Memorial Sloan-Kettering Cancer Center
Lymphoma Service
1275 York Avenue
New York, NY 10065
Tel: 212-639-7423
Fax: 646-422-2284
Email: noya@mskcc.org

Data Management/Operations:
AMC Operations and Data Management Center
The Emmes Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850
Tel: 301-251-1161
Fax: 240-238-2842
Email: amcpm@emmes.com

AMC Biorepository:
Sylvia Silver, DA
AMC Biorepository Director
George Washington University Medical Center
2300 I Street, NW
Room 118
Washington, DC 20037
Tel: 202-994-2945
Fax: 202-994-5056
Email: ssilver@gwu.edu
amc-bio@emmes.com

LYSARC sites (accrual concluded 30NOV2017):

APHP - Hôpital Antoine Béclère (Bicêtre-Béclère):
Pr. François Boué
157, Rue de la Porte de Trivaux,
92140 Clamart, France
Email: francois.boue@abc.aphp.fr

APHP - Hôpital Henri Mondor:
Pr. Corinne Haioun
Unité Hémopathies Lymphoïdes
51 avenue de Lattre de Tassigny
94010 Créteil, France
Email: corinne.haioun@hmn.aphp.fr

APHP - Hôpital St Louis:
Pr. Eric Oksenhendler
Service d'immunologie Clinique -
1 avenue Claude Vellefaux -
Coquelicot 6 -
75475 Paris 10, France
Email: eric.oksenhendler@sls.aphp.fr

APHP - Hôpital St Antoine:
Pr. Paul Coppo
Service hématologie
Bâtiment Robert André 2ème étage
184, rue du Fg. Saint Antoine
75012 Paris, France
Email: paul.coppo@sat.aphp.fr

CHU de Nice:
Pr. Nicolas Mounier
Service d'onco hématologie
151 route Saint Antoine de Ginestière
06202 Nice, France
Email: mounier.n@chu-nice.fr

Hospice Civils de Lyon – Centre Hospitalier Lyon Sud:
Pr. Gilles Salles
Service Hématologie
165 chemin du Grand Revoyet
69495 Pierre Bénite cedex, France
Email: gilles.salles@chu-lyon.fr

CHU de Toulouse:
Dr. Pierre Delobel
Service des maladies infectieuses
place Baylac
Hôpital Purpan
31059 TOULOUSE Cedex 9, France
Email: delobel.p@chu-toulouse.fr

PROTOCOL SYNOPSIS

Title:	A Pilot Trial of AVD and Brentuximab Vedotin (SGN-35) in the treatment of stage II-IV HIV-associated Hodgkin Lymphoma
Phase of Study:	Phase I /II
Participating Institutions:	This protocol will be open to all AMC member sites.
Accrual Target:	Phase I/II: Minimum of 6 participants Phase I: Maximum of 18 participants Phase II: Maximum of 51 participants
Population:	Previously untreated individuals diagnosed with stage II-IV, HIV-associated, CD30-positive, classic Hodgkin Lymphoma (cHL), as defined by the 2008 WHO classification of hematological malignancies[1].
Regimen:	**Phase 1:** This portion of the protocol will be a de-escalation design testing 3 dose levels of brentuximab vedotin in conjunction with standard, fixed doses of doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 (AVD) on days 1 and 15 of a 28-day cycle for a total of 6 cycles. The following dose schedule will be used to determine the maximum tolerated dose (MTD) of brentuximab vedotin. Dose levels: Dose - 0: 1.2 mg/kg Dose - 1: 0.9 mg/kg Dose - 2: 0.6 mg/kg On the first cohort, 3 to 6 participants will begin at Dose level 0. If > 1 dose-limiting toxicity (DLT) is encountered, 3 to 6 additional participants will be enrolled at the next lowest dose level. The MTD will be the dose level at which ≤ 1 of 6 participants experience DLT. If more than one participant at any one dose level encounters a DLT, the dose will be de-escalated for all subsequent participants (see Section 4.1.1 for DLT definition). Once a MTD has been confirmed, the phase II portion of the study will commence at that dose level. The phase I MTD was determined to be 1.2 mg/kg. **Phase 2:** The MTD of brentuximab vedotin will be used in conjunction with doxorubicin, vinblastine, and dacarbazine at the same doses and times as stated above.

Duration: Participants will receive brentuximab vedotin, in conjunction with standard, fixed, doses of doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 on days 1 and 15 of a 28-day cycle for 6 cycles. Evaluation of disease response will be performed by PET/CT at the end of cycle 2 and cycle 6 and compared to the baseline PET/CT per the Lymphoma Harmonization criteria. Participants with progressive disease at the end of cycle 2 will be removed from study and those with stable disease can proceed with the study at the discretion of the principal investigator. Participants will be followed for a total of 5 years after the completion of therapy: every 3 months for the first 2 years and every 6 months for years 3 to 5 of follow up.

Primary Objective:

Phase 1: To identify the MTD of brentuximab vedotin when combined with the AVD chemotherapy regimen in the treatment of HIV-associated stage II-IV Hodgkin lymphoma.

Phase 2: To establish an estimate of the two-year progression-free survival (PFS) for participants with HIV-associated stage II-IV Hodgkin lymphoma when treated using brentuximab vedotin plus the AVD chemotherapy regimen.

Secondary Objectives:

Phase 1 and 2

- To evaluate the toxicity of AVD and brentuximab vedotin with HAART.
- To estimate the partial response (PR) rate, complete response (CR) rate, overall survival (OS), and event free survival (EFS) at 2 and 5 years.
- To evaluate the effect of AVD and brentuximab vedotin on CD4 and CD8 counts after cycle 1, 4, at the end of therapy, and every 3 months after treatment completion for one year.
- To investigate the prognostic value of FDG-PET/CT scans at baseline, after cycle 2, and at treatment completion, with respect to 2-year progression free survival.
- To evaluate HAART status at baseline and to correlate this with tumor response to therapy and OS and PFS.

- To characterize the histologic subtypes in HIV-HL in the highly active antiretroviral therapy (HAART) era.
- To assess the neurotoxicity of HAART in combination with AVD and brentuximab vedotin.
- To evaluate effect of AVD and brentuximab vedotin on viral load after cycle 1, 4, at the completion of therapy, and every 3 months after treatment completion for one year.
- To perform pharmacokinetic and immunogenicity studies to determine drug levels during therapy (See Section 10.0 and Appendix IX).
- To perform miRNA profile analysis on the HIV-HL tumor specimens and to correlate miRNA expression with OS, PFS, tumor response to therapy, histologic subtype of HIV-HL, and HIV disease characteristics (See Section 10.0 and Appendix VIII).
- To perform tissue microarray analysis on HIV-HL tumor specimens and to correlate the markers studied with OS, PFS, and tumor response to therapy (See Section 10.0 and Appendix VIII).
- To identify EBV-associated tumor derived DNA in the plasma of study participants and to correlate these levels during therapy with disease response and OS (See Section 10.0 and Appendix XI). This objective will only be performed in the Phase II portion of the study.
- To identify cytokines in the plasma of participants during therapy that can be used as tumor and prognostic markers. (See Section 10.0 and Appendix X). This objective will be done only in the Phase II portion of the study.
- To assess latent and expressed HIV reservoirs before, during, and post chemotherapy. To understand how cytotoxic chemotherapeutic agents affect HIV expression (See Section 10.0 and Appendix XII).

LIST OF ABBREVIATIONS

AASD.....Assistance for AIDS Specific Drugs
ABVD ..... Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
ACSR ..... AIDS and Cancer Specimen Resource
ACTG.....AIDS Clinical Trials Group
ADC ..... Antibody-Drug Conjugate
AdvantageEDC^{SM} .....AMC Internet Data Entry System
AE .....Adverse Event
AIDS .....Acquired Immunodeficiency Syndrome
ALCL .....Anaplastic Large Cell Lymphoma
ALT..... Alanine Aminotransferase
AMC ..... AIDS Malignancy Consortium
ANC .....Absolute Neutrophil count
ART.....Antiretroviral therapy
ASCT .....Autologous Stem Cell Transplant
AST .....Aspartate Transaminase
AVD.....Adriamycin, Vinblastine, Dacarbazine
AVD-BR .....Adriamycin, Vinblastine, Dacarbazine-Brentuximab Vedotin
AZT.....Zidovudine
BCSAP.....B-cell Specific Activator Protein
bDNA.....Branched DNA
cART.....Combined Antiretroviral Therapy
CBC..... Complete Blood Count
CDUS.....Clinical Data Update System
CFR.....Code of Federal Regulations
cHL .....Classical Hodgkin Lymphoma
CI.....Confidence interval
cm.....centimeter
CR .....Complete Response
CRADA..... Cooperative Research and Development Agreement
CRF ..... Case Report Form
CSF .....Cerebrospinal Fluid
CT ..... Computed Tomography Scan
CTA..... Clinical Trial Agreement
CTCAE .....Common Terminology Criteria for Adverse Event reporting
CTEP.....Cancer Therapy Evaluation Program
CTEP-AERS ..... CTEP Adverse Event Reporting System
CTMS..... Clinical Trials Monitoring Service
DARF ..... Drug Accountability Record Form

DCTD.....Division of Cancer Treatment and Diagnosis
DDI ..... Didanosine
DFS ..... Disease Free Survival
DHHS.....Department of Health and Human Services
DLCO..... Diffusing Capacity of the Lung for Carbon Monoxide
DLT..... Dose-Limiting Toxicity
DMC .....Data Monitoring Committee
DNA.....Deoxyribonucleic Acid
DTIC .....Dacarbazine
EBV.....Epirubicin, Bleomycin, Vinorelbine
EBVP ..... Epirubicin, Bleomycin, Vinorelbine, Prednisone
EFS..... Event-Free Survival
ELISA .....Enzyme Linked Immunosorbent Assay
ESA ..... Erythropoiesis Stimulating Agents
FDA.....Food and Drug Administration
FDG-PET .....Fluorodeoxyglucose-Positron Emission Tomography
GCSF.....Granulocyte Colony-Stimulating Factor
HAART..... Highly Active Antiretroviral Therapy
HBV .....Hepatitis B Virus
HCV .....Hepatitis C Virus
HIV .....Human Immunodeficiency Virus
HL .....Hodgkin Lymphoma
HRS..... Reed Stemberg Cell
IDB.....Investigational Drug Branch
IDSA ..... Infectious Diseases Society of America
IEC .....Independent Ethics Committee
IND .....Investigational New Drug Application
IPI.....International Prognostic Index
IPS.....International Prognostic Score
IRB..... Institutional Review Board
IV .....Intravenous
JCV ..... John Cunningham Virus
kg..... Kilogram
LDH .....Lactate Dehydrogenase
LVEF.....Left Ventricular Ejection Fraction
mg ..... Milligram
miRNA..... Mature microRNA
MMAE ..... Monomethyl Auristatin E
MRI.....Magnetic Resonance Imaging
MTD..... Maximum Tolerated Dose

MUGA ..... Multiple Gated Acquisition Scan
NADC ..... Non-AIDS Defining Cancer
NCCN ..... National Comprehensive Cancer Network
NCI ..... National Cancer Institute
NCT ..... National Clinical Trials [Registry]
NIH ..... National Institutes of Health
NHL ..... Non-Hodgkin Lymphoma
NLPHL ..... Nodular Lymphatic Predominant Hodgkin Lymphoma
NNRT ..... Non-nucleoside Reverse Transcriptase Inhibitors
NSC ..... National Service Center
ODMC ..... Operations and Data Management Center
OHAM ..... Office of HIV AIDS Malignancy
OI ..... Opportunistic Infections
OS ..... Overall Survival
PCR ..... Polymerase Chain Reaction
PFS ..... Progression-Free Survival
PFT ..... Pulmonary Function Test
PI ..... Principal Investigator
PI ..... Protease Inhibitors
PIO ..... Protocol Information Office
PML ..... Progressive Multifocal Leukoencephalopathy
PO ..... Per oral [by mouth]
PR ..... Partial Response
RISC ..... RNA-induced silencing complex
RNA ..... Ribose Nucleic Acid
SD ..... Stable Disease
SPD ..... Sum of the Product of the Diameters
SUV ..... Standardized Uptake Values
TLS ..... Tumor Lysis Leukoencephalopathy
TMA ..... Tissue Microarray Studies
ULN ..... Upper Limit of Normal
WHO ..... World Health Organization

1.0 OBJECTIVES

1.1 Primary Objective

1.1.1 Phase 1: To identify the MTD of brentuximab vedotin when combined with the AVD chemotherapy regimen in the treatment of HIV-associated stage II-IV Hodgkin lymphoma.

1.1.2 Phase 2: Establish an estimate of the two-year progression free survival for participants with HIV-associated stage II-IV Hodgkin lymphoma when treated using brentuximab vedotin plus the AVD chemotherapy regimen.

1.2 Secondary Objectives

1.2.1 To evaluate the toxicity of AVD and brentuximab vedotin with HAART.

1.2.2 To estimate the partial response (PR) rate, complete response (CR) rate, overall survival (OS), and event free survival (EFS) at 2 and 5 years.

1.2.3 To evaluate the effect of AVD and brentuximab vedotin on CD4 and CD8 counts after cycle 1, 4, at the end of therapy, and every 3 months after treatment completion for one year.

1.2.4 To investigate the prognostic value of FDG-PET/CT scans at baseline, after cycle 2, and at treatment completion, with respect to 2-year progression free survival.

1.2.5 To evaluate HAART status at baseline and to correlate this with tumor response to therapy and OS and PFS.

1.2.6 To characterize the histologic subtypes in HIV-HL in the highly active antiretroviral therapy (HAART) era.

1.2.7 To assess the neurotoxicity of HAART in combination with AVD and brentuximab vedotin.

1.2.8 To evaluate effect of AVD and brentuximab vedotin on viral load after cycles 1, 4, at completion of therapy, and every 3 months after treatment completion for one year.

1.2.9 To perform pharmacokinetic and immunogenicity studies to determine drug levels during therapy (See Section 10.0 and Appendix IX).

1.2.10 To perform miRNA profile analysis on the HIV-HL tumor specimens and to correlate miRNA expression with OS, PFS, tumor response to therapy, histologic subtype of HIV-HL, and HIV disease characteristics (See Section 10.0 and Appendix VIII).

1.2.11 To perform tissue microarray analysis on HIV-HL tumor specimens and to correlate the markers studied with OS, PFS, and tumor response to therapy (See Section 10.0 and Appendix VIII).

1.2.12 To identify EBV associated tumor derived DNA in the plasma of study participants, and to correlate these levels during therapy with disease response and OS (See Section 10.0 and Appendix XI). This objective will only be performed in the Phase II portion of the study.

1.2.13 To identify cytokines in the plasma of participants during therapy that can be used as tumor and prognostic markers. (See Section 10.0 and Appendix X). This objective will be done only in the Phase II portion of the study.

1.2.14 To assess latent and expressed HIV reservoirs before, during, and post chemotherapy. To understand how cytotoxic chemotherapeutic agents affect HIV expression (See Section 10.0 and Appendix XII).

2.0 BACKGROUND

2.1 Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a lymphoid neoplasm first described by Thomas Hodgkin in the 1890s[2]. The disease presents with or without splenomegaly, fevers, night sweats, weight loss, and occasionally pruritus. In 2008, 8,220 new cases of HL were diagnosed resulting in 1,350 deaths[1,3]. The transformed cell that defines classic Hodgkin lymphoma (cHL) is the Reed Sternberg cell (HRS), a large multinuclear cell expressing surface antigens CD15 and CD30 without B or T cell surface antigens[1]. The cell of origin was unclear until the mid-1990s, when it was shown that the tumor originated from germinal B cell lymphocytes, as demonstrated by the expression of PAX 5, B-cell Specific Activator Protein (BCSAP), and B cell clonality based on single cell PCR of the IgH gene[4-8]. Based on these data, the World Health Organization (WHO) changed the name from Hodgkin disease to Hodgkin lymphoma[1]. The four histological subtypes of cHL recognized by the WHO are mixed cellularity, nodular sclerosis, lymphocytic depletion, and lymphocyte predominant HL[1]. Nodular lymphocytic predominant HL (NLPHL) is quite different from cHL in that HRS present in NLPHL expresses mature B cell antigens, CD20, CD79a, does not express CD15 or CD30, and has a slow progressive course[1]. This trial will only include participants with HIV infection and cHL (HIV-cHL) in light the lack of CD30 expression, differences in disease biology, and the rarity of NLPHL in the HIV-positive population.

2.2 Hodgkin Lymphoma in HIV Patients

HIV-cHL is one of the most common non-acquired immunodeficiency syndrome (AIDS)-defining tumors[9]. Multiple large database studies of linked cancer and HIV/AIDS registries from 1992-2005 in the United States showed that HL represents the second to third most common non-AIDS defining cancer (NADC)[9,10]. One of these studies showed that the risk for HIV-cHL was 68% higher in 1996-2002, the post HAART era (SIR 13.6), than in 1990-1995 (SIR 8.1)[10]. In a comparative study conducted from 1992 to 2003, the trend over time in cancer rates for the HIV-cHL was elevated despite stable rates of HL in the general population[11]. Studies on HRS microenvironment in non-HIV associated HL showed that the HRS were surrounded by B and CD4 cells, eosinophils, macrophages, and fibroblasts, all of which affect its survival and disease course[12,13]. This trophic effect, due in part to CD4 cells, has been postulated to explain the increase in incidence of HIV-cHL in the post HAART era[12-14]. In addition, many observational studies consistently showed that HIV-HL patients present with higher CD4 counts compared to other HIV-associated lymphoproliferative disorders, with the exception of Burkitt's lymphoma[9-14].

As a population, patients with HIV have a 10-25 -fold increase risk of developing HL, and they present with many high-risk characteristics that distinguish it from non-HIV cHL[15]. The differences are seen in patient presentation, histology, immunohistochemistry, molecular changes, and overall outcome[15]. The International Prognostic Score (IPS) for patients with advanced non- HIV-HL defined the following adverse risk factors: age over 45 years, male gender, stage IV disease, low albumin, anemia, lymphopenia, and leukocytosis[16]. Eighty percent of patients with HIV-cHL present with stage III/IV disease, and 70-96% presents with B symptoms[15]. B symptoms, defined as one of the following: 1) drenching night sweats, 2) fever of over 100.4°F for 3 consecutive days, and 3) a weight loss exceeding 10% of body weight in 6 months. These are also poor prognostic signs in

stage I/II non-HIV HL. The two most aggressive histological forms of HL, mixed cellularity and lymphocytic depletion are predominate in HIV-cHL compared to the non-HIV population[15]. In addition, histologically, the HRS is found in much higher concentrations in HIV-cHL than non- HIV-cHL[15]. HIV-cHL is associated in 80-100% of the cases with EBV co-infection of the HRS, though in the non-HIV cHL patients this occurs only with a frequency of 30-40%[15,17,18]. The expression of the Epstein-Barr Virus (EBV) has been identified by both single cell polymerase chain reaction (PCR) and co-immunohistochemical analysis of the HRS in HIV-infected patients[15,17,18]. The HRS in non-HIV patients are derived from germinal center B cell lymphocytes, on the other hand, the origin of HIV-associated HRS have been linked to post germinal lymphocytes[19]. It is interesting to note that diffuse large B-cell lymphoma derived from non-germinal center have a worse prognosis than germinal cell derived large cell lymphoma in most studies. It is unclear the role each factor plays in disease outcome (i.e., HRS origin, EBV co-infection status, presentation, and histology) but it is clear that outcomes for patients with HIV-cHL are inferior to HIV-negative patients.

For HIV-cHL, the median complete remission rate is about 58% with a median survival 8-20 months in the pre HAART era, which is substantially lower than the median complete remission rate of approximately 90% with a median survival of 7 years for HIV-negative patients[15,20,21]. Retrospective data showed improved overall survival in the post HAART compared to treatment without HIV therapy[21,22]. Both studies showed an improved 2 year overall survival while taking HAART, ranging from 16 to 42% depending on the study[21,22]. Similarly, of the four HIV-HL trials completed while utilizing combined antiretroviral therapy (cART), the overall survival has varied from 86% at 2 years to 51% at 3 years, an improvement compared to the historical controls in the pre HAART era, but still lagging behind historical controls of non-HIV infected patients [23-26]. Explanations for poorer survival are likely multifactorial, including treatment-related toxicity, EBV status, HRS non-germinal cell of origin, tumor biology, histology, and presentation. More prospective trials and newer treatments are needed to improve on the outcomes of HIV-positive patients to where they are comparable to the HIV-negative population.

2.3 Current Treatment for HIV-Related HL

Currently, no standard of care exists for the upfront treatment of HIV-cHL. Outcomes of clinical trials for HIV-cHL in the pre- and post-HAART era are summarized in Table 2-A. In the pre-HAART era, the AIDS Clinical Trials Group (ACTG 149) performed a prospective multi-institutional clinical trial of ABVD with supportive GCSF[27]. Antiretroviral therapy was not used. Among 21 patients enrolled between 1992 and 1996, 90% had B symptoms at presentation, and 67% had stage IV disease. Complete remission (CR) was attained in only 9 patients (43%; 95% CI: 24%-63%), a partial remission (PR) in 4 participants (19%), resulting in a 2-year OS was 48%[27]. Even with routine GCSF use, 10 patients developed severe neutropenia and opportunistic infections (OIs) occurred in 6 patients (29%) during the study. A similar study with EBVP utilizing only zidovudine (AZT) or didanosine (DDI) as HIV therapy showed an equivalent 2-year OS of 40%[28].

Retrospective data showed a positive effect of HAART on OS, disease free survival (DFS), and infectious complications, though these benefits have been limited to studies implementing HAART. As illustrated above, the difference between no HAART and single agent antiretroviral therapy is minimal[27,28]. Comparing sequential HIV-cHL studies with

ABVD with cART and without HAART, the OS improved from 48% at 2 years to 76% at 5 years[27,24].

In the post HAART era, only 5 prospective studies have been completed all with cART[23-26,30]. A study of therapy with ABVD regimen in patients with advanced stage HIV-HL assessed the outcome in 62 patients (1996-2005) with advanced stage HL from multiple centers in Spain[24]. Six patients died during induction, 54 (87%) achieved CR and 2 had resistant disease. After a median follow up of 39 and 47 months, 5-year EFS probability was 71% and OS was 76%[24]. An immunological response was observed in 56% and a virological response in 68%. The immunological response to HAART had a positive impact on OS and EFS[24].

The VEBEP, Stanford V, and BEACOPP standard studies included all stages of HIV-cHL, and despite the inclusion of earlier stages, OS in each study did not compare well to ABVD, (see Table 2-A)[23-33]. The BEACOPP regimen did show an improved CR rate compared to ABVD (100% vs. 87%), but only 66% of participants were able to tolerate the 6 courses of BEACOPP compared to 82% in the ABVD trial. Also, 3 of the 12 participants in the BEACOPP trial died during chemotherapy (25%). Thus, based on OS, adverse events, and PFS, ABVD currently is the most promising regimen studied for advanced stage HIV-cHL[23-30].

Table 2-A: Summary of Retrospective and Prospective Trials of HIV-cHL

Regimen	Trial Type	HAART	# Patients	Year	Stage III/IV%	OS% (Months)
MOPP or ABVD or MOPP/ABVD +/- RT[31]	Retrospective	Pre-HAART	71	1992	80%	Median Survival (14)
MOPP or ABVD or MOPP/ABVD +/- RT[32]	Retrospective	Pre-HAART	45	1993	75%	Median Survival (20)
MOPP or ABVD or MOPP/ABVD +/- RT[28]	Retrospective	Pre-HAART	46	1994	89%	Median Survival (15)
MOPP or ABVD or MOPP/ABVD +/- RT[28]	Retrospective	Pre-HAART	24	1991	92%	Median Survival (15)
MOPP or ABVD or MOPP/ABVD +/- RT[28]	Retrospective	Pre-HAART	23	1991	74%	Median Survival (8)
MOPP/ABVD +/- RT[28]	Retrospective	Pre-HAART	13	1988	92%	Median Survival (14)
EBV[29]	Prospective	No- HAART	17	1994	88%	11 months
ABVD[27]	Prospective	No-HAART	21	1992-6	67%	48% (24)
EBVP[28]	Prospective	AZT or DDI	35	1993-7	66%	40% (24)
ABVD[30]	Prospective	HAART	8	2002	75%	43 Months
Stanford V[23]	Prospective	HAART	56	2005	71%	59% (60)
BEACOPPstd[26]	Prospective	HAART	12	2002	92%	75% (36)
VEBEP[25]	Prospective	HAART	28	1996-05	71%	69% (24)
ABVD[24]	Prospective	HAART	62	2007	100%	76% (60)

Regimen abbreviations: ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), VEBEP (vinorelbine, epirubicin, bleomycin, cyclophosphamide, prednisone), EBVP (epirubicin, bleomycin, vinorelbine, prednisone), EBV (epirubicin, bleomycin, vinorelbine), BEACOPPstd (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), and RT (radiation therapy).

2.4 Study Agents

2.4.1 Rationale for the use of brentuximab vedotin in HIV-cHL

Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: (a) the antibody cAC10, specific for human CD30, (b) the highly potent anti-microtubule agent, monomethyl auristatin E (MMAE), and (c) a protease-cleavable linker that covalently attaches MMAE to cAC10[34]. The biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage[34]. Binding of MMAE to tubulin prevents its polymerization, thus disrupting the microtubule network within the cell, inducing cell cycle arrest, and apoptotic death of the CD30-expressing tumor cell[34]. MMAE was found to be a quasi-irreversible, mechanism-based CYP3A inhibitor, and, to the limited extent that metabolism occurred, the primary metabolites were formed by CYP3A4[34,35]. CD30, a member of the TNF-receptor (TNF-R) super family, is a transmembrane glycoprotein receptor normally found on the surface of activated T cells but present on a variety of cell types of hematopoietic origin. The CD30 antigen has a very low expression on normal cells but is found on the HRS cells of HL, anaplastic large cell lymphoma (ALCL), and other T cell lymphoproliferative disorders. While the function of CD30 has not been clearly defined, CD30 has been implicated both in cell death and proliferation[34,35]. The utility of CD30 as a diagnostic marker for malignancies (including HL and ALCL), its limited normal tissue expression profile, and its apoptosis-inducing characteristics have led to the investigation of this antigen as a target for immunotherapy. Brentuximab vedotin has been studied and is FDA approved in the relapsed/refractory setting for ALCL and non-HIV cHL[36-40]. In the frontline setting, a phase I study is currently ongoing with brentuximab vedotin for non-HIV-cHL in combination with AVD[41].

A phase 1 study of brentuximab vedotin was performed in relapsed and refractory CD30 positive malignancies, including ALCL and HL. Patients had a median of 3 prior chemotherapy regimens (range 1-7) with 73% of patients having previously received an autologous stem cell transplant (ASCT)[36]. The brentuximab vedotin dose levels ranged from 0.1 to 3.6 mg/kg (2-hr outpatient IV infusion) every 3 weeks. Brentuximab vedotin was generally well-tolerated in the study. The most common adverse events, which occurred in 20% of patients or more, were fatigue, pyrexia, nausea, and diarrhea. The neutropenia observed appeared to be dose-related. The maximum tolerated dose was 1.8 mg/kg every 3 weeks. One patient treated at 3.6 mg/kg developed febrile neutropenia and presumed sepsis, and died 14 days after the first dose of brentuximab vedotin. Neuropathy was also observed in some patients, especially after repeated dosing. Approximately 75% of patients reporting B symptoms at baseline experienced symptom resolution while on study. Despite a median 3 prior chemotherapy regimens per patient including 75% with prior ASCT, 88% of the patients in the study experienced tumor reductions. The objective response rate (CR+PR) was 46% (n=13), with a CR rate of 25% (n=7).

Two additional PRs were observed in the 0.6 mg/kg cohort. Median response duration to date was 22 weeks (range, 0.1+ to 38+ weeks) [39-41].

A phase 2 study of brentuximab vedotin (SGN-35) studied 102 patients with relapsed or refractory HL post autologous stem cell transplant[41]. Patients received brentuximab vedotin every three weeks at a dose of 1.8 mg/kg. The median duration of brentuximab vedotin treatment was 27 weeks (range 3-54). The most common treatment-related adverse events (AEs) of any grade in >15% of patients were peripheral sensory neuropathy (43%), fatigue (40%), nausea (35%), neutropenia (19%), diarrhea (18%), and pyrexia (16%). Most events were Grade 1 or 2. The Grade 3 treatment-related AEs reported in more than 1 patient were neutropenia (14%), peripheral sensory neuropathy (5%), thrombocytopenia and hyperglycemia (3% each), and fatigue (2%). The only Grade 4 treatment-related events were neutropenia (4%), and thrombocytopenia, abdominal pain, and pulmonary embolism (1% each). There we no related Grade 5 events. Eighteen patients discontinued treatment due to an adverse event[41]**.** While no interim analysis was presented with respect to overall response rate, there was a 95% reduction of tumor size and an 83% resolution of B symptoms[41].

2.4.2 Rationale for substitution of brentuximab vedotin for bleomycin in ABVD regimen

Bleomycin is associated with significant pulmonary toxicity, particularly in the setting of radiation involving lung fields as is typically prescribed in the context of bulky mediastinal Hodgkin lymphoma. There are no large studies addressing the incidence of bleomycin-associated pneumonitis in the setting of HIV-HL. Outside of HIV, the incidence of bleomycin-associated pneumonitis with ABVD in HL has been reported in the range 10-15%. A randomized trial comparing ABVD to Stanford V (25% of the bleomycin dose) reported a 10% versus 2% incidence of pulmonary toxicity, respectively, requiring early discontinuation of bleomycin in 20/23 participants[42,80]. A separate, single institution retrospective study demonstrated a 15% incidence in bleomycin pneumonitis in 184 HL patients treated with ABVD[43]. In this study, low albumin and use of GCSF were the factors most predictive of bleomycin toxicity. These factors are both likely to occur with high incidence in the HIV HL population where more advanced HL presentation is typical and the increased risk of marrow suppression with chemotherapy, use of GCSF is often required to maintain or approximate optimal chemotherapy dose density in the setting of HIV and aggressive lymphomas.

The substitution of brentuximab vedotin for bleomycin is being explored in the general HL population. A phase 1, open-label, multicenter study is currently underway to evaluate the safety of brentuximab vedotin when administered in combination with standard therapy with AVD (ClinicalTrials.gov #NCT01060904) as the combination with ABVD had intolerable pulmonary toxicity[41]. Patients have received doses of 0.6, 0.9, or 1.2 mg/kg brentuximab vedotin with standard doses of ABVD or 1.2 mg/kg brentuximab vedotin with AVD, depending upon cohort assignment. The combination regimens were administered on Days 1 and 15 of each 28-day cycle for up to 6 cycles of therapy. Each regimen evaluated a dose limiting toxicity (DLT) period, defined as any Cycle 1 toxicity requiring a delay of ≥7 days in standard ABVD or AVD therapy[41]. This is the first trial to dose

brentuximab vedotin every two weeks and in combination with multi-agent chemotherapy. Interim data of the first 31 patients treated were recently presented[41]. Six patients received 0.6 mg/kg, 13 received 0.9 mg/kg, and 6 received 1.2 mg/kg with ABVD; 6 patients received 1.2 mg/kg with AVD. Patient baseline characteristics included: Stage IV, 55%; IPS score ≥4, 29%; male, 77%; median age, 35 years (range, 19-59). The combination of chemotherapy and brentuximab vedotin treatment had no DLT observed up to 1.2 mg/kg in either regimen[41]. AEs reported in ≥45% of patients, regardless of severity, were nausea and neutropenia (77% each); peripheral sensory neuropathy (48%); and fatigue (45%). Infusion-related reactions occurred in 23% of patients. Grade 3/4 AEs observed in >10% of patients were neutropenia (74%), febrile neutropenia (16%), and anemia (13%). No Grade 5 AEs were observed. Overall, 6 patients discontinued combination treatment due to an adverse event. In the ABVD cohorts (n=25), AEs of pulmonary toxicity, dyspnea, and interstitial lung disease that could not be distinguished from bleomycin toxicity led to discontinuation of bleomycin in 7 patients. Five of these 7 patients continued treatment with AVD and brentuximab vedotin[41]. The expansion cohort of approximately 20 patients is currently enrolling at the 1.2 mg/kg brentuximab vedotin dose combined with AVD therapy[41]. An international phase III study comparing ABVD versus AVD in combination with brentuximab vedotin is currently under development. This AMC trial will help define more clearly how this regimen can be used in the HIV-infected population.

While it is desirable to replace bleomycin with a less toxic alternative in the general HL population, the argument is even more compelling in the HIV-HL population with a higher prevalence of risk factors associated with bleomycin toxicity, i.e., intercurrent infection, and a higher prevalence of tobacco use. In replacing bleomycin, risk of reduced efficacy exists. Given this, as well as the preliminary efficacy data of brentuximab vedotin + AVD in the general HL population, a dose de-escalation design is chosen for this study to maximize anti-tumor activity of the regimen for each cohort.

2.4.3 Considerations regarding brentuximab vedotin, CD30, and HIV

CD30 has also been studied in HIV replication, in addition to lymphoma. In fact, increased levels of the soluble form of CD30, sCD30, are predictors of progression to AIDS[44-47]. Levels of sCD30 also have been shown to correlate with HIV viremia levels and clinical outcome in patients with primary HIV infection in the pre-HAART era[47]. Furthermore, CD30 stimulation directly induces HIV expression through activation of the transcription factor NF-kB[45-47]. In addition, CD30/CD30L interactions lead to virus production also in primary CD4+ T cells from HIV-positive patients[47]. Both agonistic anti-CD30 antibodies and CD30L-expressing, glutaraldehyde-fixed CD8+ human T cell clones significantly enhanced HIV expression in human CD4+ T cells obtained from HIV-infected individuals[44-47]. This data suggests that the activation of CD30 expression in HIV-infected CD4+ T cells may allow the interaction of these cells with CD30L-expressing cells and, therefore, favor HIV replication[44-47]. The result of the use of the brentuximab vedotin and its effects on HIV replication will be monitored closely in this study. All participants on study must be on concurrent HAART therapy. We will test for

a multiplexed inflammatory marker panel that includes sCD30, as well as several other molecules (several soluble cytokine receptors and BAFF/BLyS and CXCL13 (BLC/BCA-1) for changes with the use of brentuximab vedotin and correlate this with changes in HIV viral load as well as clinical outcome. See Section 2.6 for a description of all correlative studies.

2.4.4 Considerations regarding progressive multifocal leukoencephalopathy associated with HIV, brentuximab vedotin, and HIV-cHL

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the lytic replication of the John Cunningham Virus (JCV). It typically occurs in immunocompromised individuals and is nearly uniformly fatal[48-54]. In a clinical study conducted by Koralnik et al, 80% of reported PML patients had AIDS, 13% had hematologic malignancies, 5% were transplant recipients, and 2% had chronic inflammatory diseases[49]. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%)[48]. The onset of neurological deficits may occur over weeks to months[48]. In a retrospective study, data showed the incidence of PML in patients with NHL is 8 per 100,000 patient years, though the incidence in cHL or HIV-cHL is not known. In the onset of the HIV epidemic, the incidence of the PML was 3.4 per 1000 patient years at risk with HIV[50,51]. But in the era of HAART, the incidence has decreased to 1.3 patients per 1000 patient years[51]. In a Swiss HIV cohort study, a multivariate analysis showed that of the 226 patients diagnosed with PML from 1998 to 2007, HAART was associated with a hazard ratio of 0.22 ($p<0.01$). A trend was seen for decreased incidence with elevated CD4 counts[52]. Compared to patients with CD4 counts below 50 cells/µl, the hazard ratio for patients with CD4 counts above 100 cells/µl was 0.75 ($p<0.38$)[52].

Recently PML has been reported in HIV negative patients receiving antibody based immunomodulatory therapies for lymphoma, multiple sclerosis, and collagen vascular diseases treated with antibodies rituximab, efalizumab, and natalizumab[53]. To date 3 patients treated with brentuximab vedotin have developed PML, each in the relapsed refractory setting, with 3 to 6 chemotherapeutic regimens before treatment with brentuximab vedotin[54]. To curtail the risk of PML in this study, no patients with a CD4 count below 50 cells/µl will be permitted on study, all participants will be required to take HAART, and MRI scans pre-study will be required. In addition, we will incorporate stopping rules should any patient develop PML with a CD4 count > 50 at the time of PML diagnosis.

2.4.5 Rationale for use of concurrent HAART with HL treatment

The improvement in outcomes of HIV-cHL patients to standard treatment in the HAART era is partially related to the HAART therapy itself. Given this and concerns above regarding HIV viremia with CD30 perturbation and PML, we will require participants to be on HAART. Chemotherapy-HAART interactions have become more pronounced in the transition from single agent HIV therapies to the era of cART as protease inhibitors (PI) and non-nucleoside reverse transcriptase

inhibitors (NNRT) are potent inhibitors or inducers of the cytochrome p450 system[55]. In early studies with HIV-cHL treated with EBVP, where only AZT or DDI was used as antiviral therapy, 1% neurotoxicity all grades, 7% Grade 3/4 leukopenia, and 3% G3/4 anemia were observed. However, in a single institution retrospective study of 23 patients treated with ABVD, while taking HAART, 31% were found to have neuropathy (all grades), 68% G3/4 neutropenia, and 57% G3/4 anemia[56]. Correlations were then made comparing all adverse events with HAART therapy. Of the patients with neuropathy, 13% had grade 3 sensory neuropathy and each developed the symptoms before cycle 2 of ABVD. Many had symptoms years after therapy. One hundred percent of the patients with neuropathy were taking ritonavir based HAART[56]. Similarly, 75% of the patients who were taking ritonavir based HAART developed G3/4 neutropenia, as opposed to only 21% taking non-ritonavir-based HIV-therapy. Lastly, it was noted that 82% of the patients with Grade 3/4 anemia were taking ritonavir and or AZT in some combination. Based on these data, at this institution made a policy to utilize only non-ritonavir and non-AZT based HAART regimens during treatment for HIV-cHL[57]. Twelve patients were subsequently treated, and neuropathy, febrile neutropenia, G4 neutropenia, and G4 anemia had decreased by 100%, 100%, 20%, and 15% respectivly[57].

One concern to be managed in the current study is the overlapping toxicities of brentuximab vedotin and vinblastine, both of which have been shown to cause neuropathy and neutropenia. To prevent potentiating any adverse events, we will require participants' HAART regimens to exclude ritonavir or AZT. Cobicistat, another potent inhibitor of the CYP 3A4 enzyme system, will also be excluded from the study. Any new forthcoming CYP 3A4 inhibitors will be excluded.

Despite these changes, many of the HAART drugs undergo metabolism by and can induce or inhibit various CYP450s enzyme systems. Therefore, all participants will be closely monitored for AEs throughout the entire study. In addition, pharmacokinetics will be studied in a subset of participants to confirm whether alterations in exposure correlate with the AEs.

2.4.6 Rational for use of PET scans in HIV patients and HIV-HL

The use of FDG-PET scans in HL patients is increasingly being used for prognostic significance in during treatment in the HIV negative setting. Data by Galamini et al. showed a FDG-PET scan done at the completion of cycle 2 was more prognostic than the IPS score for advanced Hodgkin lymphoma[58,59]. A negative PET scan after two cycles of ABVD predicted a 96% 2-year PFS. Similar data reported in abstract form regarding ABVD and rituximab showed a negative PET correlated with a 5-year EFS of 93% vs. 75% for those who remained PET positive ($p=0.05$)[58-60]. The prognostic significance of PET scanning in the HIV patients with HL is unknown. At issue is FDG-PET scanning in the setting of HIV alone without malignancy is frequently positive. One report suggested FDG activity might correlate with detectable HIV viral loads[61]. Thus, it is important to correlate FDG-PET in combination with CT scans (FDG-PET/CT scan). Experience with PET scanning in the HIV setting with malignancy requires further study. Therefore, we plan to use baseline, post cycle #2 interim, and post-treatment FDG-PET/CT scans prospectively in this study, to correlate scan positivity with PFS and OS. The

Deauville 5-point criteria will be used to record the interim FDG-PET scan[91,92]. The Deauville criteria capture gradations of FDG uptake from no uptake (1 point) to new disease (5 points). For the purposes of this study, we will record the Deauville score and determine whether scores of 3-5 or 4-5 are predictive of relapse. Notably, SUVs can be affected by inflammation related to therapy as in the case of rituximab or HIV related inflammation.

2.4.7 Brentuximab vedotin relevant preclinical data

Little to no data exists on the dosing of 1.2mg/kg of brentuximab vedotin to be used in this study, and no information exists on its interactions with anti-HIV medications. The data summarized below were obtained using 1.8mg/kg.

Pharmacokinetic parameters for individual patients were determined using concentrations of serum brentuximab vedotin ADC, plasma MMAE, serum TAb, and actual sampling times relative to the start of the infusion. The maximum concentrations for the serum PK of brentuximab vedotin ADC following an IV dose of 1.8 mg/kg were typically observed at the end of infusion. A multi-exponential decline in ADC serum concentrations was observed with a terminal half-life (t1/2) of approximately 4 to 6 days. Exposures were approximately dose proportional. After administration of multiple doses of brentuximab vedotin, steady-state was achieved by 21 days, consistent with the t1/2 estimate. Minimal to no accumulation was observed with multiple doses with the q3wk regimen, and ADC exposure did not decrease with subsequent doses.

The plasma PK profile of MMAE following an IV dose of 1.8 mg/kg brentuximab vedotin appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. Tmax ranged from approximately 1 to 3 days. Exposures were linear and approximately dose proportional with MMAE exposures decreasing after multiple doses with approximately 50% to 80% of the exposure of the first dose observed at subsequent doses. After administration of multiple doses of brentuximab vedotin, MMAE steady-state was achieved by 21 days, similar to ADC. Total antibody exposures were approximately dose proportional and higher than brentuximab vedotin ADC exposures while Tmax was similar.

2.5 Study Design and Rationale

Based on the evidence presented above, specifically the remarkably high response of brentuximab vedotin in the relapse setting, we will conduct a phase 1 clinical trial with a de-escalation design evaluating 3 doses of brentuximab vedotin (1.2 mg/kg, 0.9 mg/kg, and 0.6 mg/kg) given every 2 weeks with AVD in a 28-day cycle. Three to six participants will be enrolled at dose level 0 (1.2 mg/kg). If > 1 DLT is encountered, up to six additional participants will be enrolled at the next lowest dose level. If no more than 1/6th of the participants at dose level 0 encounter a DLT, this dose (1.2 mg/kg) will be used in the phase II portion. If dose de-escalation is required, we will follow the algorithm presented in Table 4-A in Section 4.1.

Bleomycin is omitted, due to the pulmonary toxicity of ABVD plus brentuximab vedotin demonstrated in the phase I trial for non-HIV cHL. Based on the bleomycin omission, and

based on phase I efficacy data, a dose de-escalation design was chosen for this study to maximize anti-tumor activity of the regimen for the initial cohort in a curable disease. Fifty-one participants in the phase II trial will be treated for 6 cycles for a 5-year follow up. The primary end point of the phase II portion will estimate the two-year progression free survival for AVD-brentuximab vedotin. The secondary endpoints of both phases will be to evaluate AVD-brentuximab vedotin with regard to 1) the toxicity of participants taking concurrent HAART, 2) the effects on viral load, CD4, and CD8 counts, and 3) PR, OS, EFS. Other non-treatment related endpoints for both phases will be the predictive value of FDG-PET on 2-year PFS and a characterization of HIV-cHL subtypes in the post HAART era.

We hypothesize that AVD-brentuximab vedotin will 1) improve HIV-cHL OS to be more consistent with the non-HIV population 2) be administered safely with cART regimens lacking ritonavir or AZT. We also anticipate cycle 2 FDG/PET-CT will be prognosticate OS in the HIV population.

We will perform immunological, viral, and molecular correlative studies to monitor the effects brentuximab vedotin will have on the viral replication of HIV. With respect to HIV replication, we will assess viral loads and CD4 counts every 2 cycles during therapy and every 3 months for 1 year post treatment. We will also perform pharmacokinetic and immunogenicity to help understand the interaction between brentuximab vedotin and HAART. Studies will determine drug and anti-brentuximab vedotin antibody levels during treatment.

2.6 Rationale for Correlative Studies

Improving the ability to predict which participants with HIV-HL will respond best to therapy is an important goal of this clinical trial and in its correlative studies as well. As stated earlier, Galamini et al., was able to correlate a negative cycle 2 FDG-PET scan with improved OS and PFS in non-HIV cHL[58,59]. A negative cycle 2 FDG-PET scan was more prognostic than the IPS itself[58,59]. Thus, to validate this in the HIV population is an important goal to help identify which patients can maybe benefit from chemotherapy intensification to improve outcomes. We hypothesize that the biological features of a participant's tumor, identified as immunohistochemical markers, circulating cytokines, and tumor DNA and microRNA (miRNA), can also be more predictive than the IPS. In addition to their prognostic significance, we believe that these markers can also help us gain insight into tumor biology. See Section 10.0 below for a detailed description of each correlative study (also see Appendix VIII, IX, X, and XI). The final correlative study will be to assess the chemotherapy effects on the latent and HIV reservoirs, an area in need of investigation. The changes in the viral copy numbers in both the plasma and the peripheral blood mononuclear cells (PBMC) will be studied before, during, and after chemotherapy, to correlate the effects chemotherapy with viral expression (Appendix XII).

3.0 PARTICIPANT SELECTION

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

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

Participant ID Number: 085 - ___ ___ ___ - ___ ___ ___

Patient's Initials (L, F, M): ___ ___ ___

3.1 Eligibility Criteria

___ 3.1.1 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of brentuximab vedotin in combination with AVD in patients <18 years of age, children are excluded from this study.

___ 3.1.2 HIV positive. Documentation of HIV-1 infection by means of any one of the following:

- Documentation of HIV diagnosis in the medical record by a licensed health care provider;
- Documentation of receipt of ART by a licensed health care provider;
- HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating > 1000 RNA copies/mL;
- Any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed HIV assay such as a HIV-1 Western blot confirmation or HIV rapid multispot antibody differentiation assay.

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

___ 3.1.3 Histologic diagnosis of CD30-positive classical HL as defined by the 2008 WHO Classification of Hematological diseases. **Nodular lymphocyte predominant Hodgkin Lymphoma is not eligible.**

___ 3.1.4 Stage II, III, or IV disease as defined by the Ann Arbor Staging System.

___ 3.1.5 Participants must have previously untreated HIV-cHL, with the exception of up to 14 consecutive days of steroids, emergency radiation, or 1 prior cycle of cyclophosphamide to reduce tumor burden and improve hyperbilirubinemia in the setting of lymphoma related liver involvement.

___ 3.1.6 Normal baseline cardiac ejection fraction ≥ 50%.

___ 3.1.7 Serum creatinine of ≤ 1.5 mg/dL. If creatinine >1.5 mg/dL, creatinine clearance must be ≥ 60 mL/minute.

___ 3.1.8 ANC ≥ 1000/µL and platelets ≥ 75,000/µL unless related to bone marrow involvement by HIV-cHL.

___ 3.1.9 Total bilirubin must be < 1.5 x the upper limit of normal, unless the elevation of bilirubin is thought to be secondary to Gilbert's syndrome or cART. If, however, the elevated bilirubin is felt to be secondary to antiretroviral therapy, the total bilirubin must be ≤ 3.5 mg/dL, provided that the direct bilirubin is normal and the AST and ALT ≤ 3 x the upper limit of normal. Also, if the elevated bilirubin is thought to be secondary to cHL the same criteria for hyperbilirubinemia should be applied; however 1 prior cycle of cyclophosphamide is permitted in attempt to make the participant eligible (see Section 3.1.5). Patients should not be excluded from study participation unless dosing cannot be safely established as per Section 5.2.5.

___ 3.1.10 Female participants must have a negative pregnancy test within 1 week of enrollment and **all** participants must agree to **use two reliable methods of contraception simultaneously** if conception is possible during the study and for 6 months after stopping treatment. Should a woman participant become pregnant or suspect she is pregnant while the participant is participating in this study, she should inform her treating physician immediately. The participant will then be removed from protocol therapy. Participants who father a child while participating in the study will be permitted to continue with the protocol. The participant, however, is required to notify the investigator if he fathers a child.

___ 3.1.11 Ability to understand and the willingness to sign a written informed consent document.

___ 3.1.12 Karnofsky performance status > 30% (given the aggressiveness of this disease and the often severely debilitated nature of the patients at initial presentation). See Appendix III.

___ 3.1.13 Measurable or non-measurable (evaluable) tumor parameter(s). Non-measurable tumor parameters will be defined as not having bi-dimensional measurements (i.e., gastric or marrow involvement) but can be followed for response by other diagnostic tests such as gallium, PET imaging and/or bone marrow biopsy.

___ 3.1.14 Patients already receiving erythropoietin or GCSF for treatment of HIV-related cytopenia are eligible.

___ 3.1.15 CD4 count ≥ 50 cells/µL.

___ 3.1.16 Participants are required to be on antiretroviral regimens that are in accordance with the current International AIDS Society guidelines concurrently with chemotherapy. The specific agents are at the discretion of the Investigator and the use of investigational agents currently available on an expanded access basis is allowed. Use of experimental antiretroviral agents or those containing zidovudine (including Combivir and Trizivir) or ritonavir (includes Norvir® or Kaletra®), Cobicistat, Didanosine (Videx® or Videx EC®), or similar potent CYP3 inhibitors are

prohibited, as explained in Section 2.4.5. In order to be eligible, participants taking zidovudine or ritonavir, Cobicistat, Didanosine, or other CYP3 inhibitors must change to a different regimen 7 days prior to therapy initiation. Changes to HAART therapy during the study may be made if medically necessary (toxicity, failure of regimen, etc.). Participants must be on HAART for at least 7 days prior to therapy.

___ 3.1.17 Negative for Hepatitis B, or if infected with Hepatitis B, receiving anti-Hepatitis B therapy. All participants will be required to be screened for Hepatitis B. Per IDSA and AASD guidelines, those participants that show no immunity, defined by the lack of Hepatitis B surface antibody, and show evidence of chronic infection (i.e., HBsAg+, HBcore+, HBsAB-) will be required to be on anti-Hepatitis B therapy during the study in order to be eligible. Patients will be permitted to enroll in the study provided normal liver function tests (see Section 3.1.9) and no evidence of cirrhosis. The exact Hepatitis B therapy will be at the discretion of the infection disease specialist or investigator. However, all patients who present with acute hepatitis B or show normal transaminases and are HBsAg+ and IgM+ for Hepatitis core antigen will not be eligible for trial enrollment.

___ 3.1.18 Patients diagnosed with Hepatitis C who are Hepatitis C antibody positive, whether Hepatitis C RNA level is measurable or not, must have no evidence of cirrhosis and have liver function tests that conform to Section 3.1.9.

___ 3.1.19 Brentuximab vedotin is partially metabolized via the CYP3A4 pathway and is cleared from the cells via the P-glycoprotein pump. Therefore, participants must discontinue use of the following agents within 7 days prior to therapy as per Appendix XIII.

- Strong CYP 3A4 inhibitors that treat HIV, see 3.1.16.
- Other strong CYP3A inhibitors.
- Moderate CYP3A4 inhibitors should be Used with Caution but are not excluded. If 2 moderate CYP3A4 inhibitors are used concurrently, one must be discontinued at least 7 days (1 week) prior to the initiation of chemotherapy.
- P-glycoprotein inhibitors.
- If patients are taking any of these excluded medications, they must be discontinued at least 7 days (1 week) prior to the initiation of chemotherapy.

All concomitant medications must be reviewed by the study chair or co-chair prior to enrollment by email.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

3.2 Exclusion Criteria

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

___ 3.2.1 Patients with prior anthracycline therapy will be excluded.

___ 3.2.2 Female participants who are pregnant or breast-feeding. Confirmation that the

participant is not pregnant must be established by a negative serum b-human chorionic gonadotropin (b-hCG) or urine pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.

___ 3.2.3 Medical illness unrelated to HL, which in the opinion of the study physician will preclude administration of chemotherapy safely. This includes patients with uncontrolled infection (including opportunistic), chronic renal failure, myocardial infarction (MI) within the past 6 months, unstable angina, cardiac arrhythmias other than chronic atrial fibrillation, or second malignancy requiring active treatment.

___ 3.2.4 Prior malignancy within 2 years before enrollment other than curatively treated cutaneous basal cell or squamous cell carcinoma, carcinoma in situ of the cervix, anal intraepithelial neoplasia, or cutaneous Kaposi's sarcoma (KS). Participants with prior malignancies must have completed all therapy at least 2 years before enrollment with no evidence of disease since therapy completion.

___ 3.2.5 Grade 2 or greater peripheral neuropathy.

___ 3.2.6 Evidence of PML identified on the pretreatment MRI.

___ 3.2.7 Central nervous system disease.

___ 3.2.8 Patients with history of JC Virus identified in the CSF or previous history of PML will be excluded from the study.

___ 3.2.9 Cirrhosis secondary to any cause will be excluded.

Physician Signature: _____ Date: _____
(Optional unless this section is used as an eligibility checklist)

3.3 Number of Participants to be Enrolled

3.3.1 Proposed Sample Size

- For Phase I/II, this study will enroll a minimum of 6 participants.
- For Phase I, this study will enroll a maximum of 18 participants.
- For Phase II, this study will enroll a maximum of 51 participants.
- If there are no DLTs observed in the Phase 1 portion of the study, and if 100% of all of the Phase 1 participants are treated identically to participants in Phase 2, accrual from the Phase 1 and 2 portions can be combined to complete the phase 2 portion of the study.

3.3.2 Accrual Rate

- Approximately 2 participants per month.

3.3.3 Replacement of inevaluable participants

A participant who does not complete cycle 1 can be replaced if, based on a review of the available safety for that dose level, the principal investigator agrees that the events leading to participant withdrawal are unlikely to constitute a safety risk for further participant enrollment and dose escalation. This means that as long as

participant safety is not compromised, a participant who withdraws from the study for administrative reasons prior to experiencing DLT during cycle 1 of therapy can be replaced by another participant to complete the number of participants evaluable per dose level required by the protocol. Similarly, as long as participant safety is not compromised, if an eligibility criterion or protocol violation occurs that substantially impairs evaluation of DLT during cycle 1, another participant can enter the cohort to complete the number of participants evaluable per dose level required by the protocol. Any replacement participant will be enrolled into the same dosing cohort as that for the participant who withdrew. Participants withdrawn because of brentuximab vedotin -related DLT may not be replaced.

3.4 Recruitment Plan

Participants seen in the inpatient or outpatient setting who meet eligibility criteria will be recruited to this study. Participation is voluntary. The participant will be made aware of his or her diagnosis and current nature of this treatment program. All participants will be required to sign a statement of informed consent that conforms to FDA regulations and Institutional Review Board (IRB) guidelines. IRB-approved advertisements to local periodicals, participant groups, or physicians may be used by each participating site.

3.5 Participant Enrollment Procedures

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

After it has been determined that the participant is eligible and an informed consent has been signed by the participant, the participant must be registered on-line via the AMC AdvantageEDC^{SM} Internet Data Entry System (AdvantageEDC). Enrollment and data collection will occur via the AMC Internet Data Entry System.

The participating site will ensure a participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist in AdvantageEDC for enrollment. Participants will be enrolled on-line via AdvantageEDC 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 email will be sent to the enroller upon successful completion of the participant enrollment. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at amcpm@emmes.com or via phone at 301-251-1161) for further instructions.

4.0 TREATMENT PLAN

4.1 Phase I: AVD-Brentuximab Vedotin Therapy

AVD will be given in conjunction with the brentuximab vedotin on days 1 and 15 on a 28-day cycle for 6 cycles. Standard, fixed-doses of AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2) will be administered intravenously. Brentuximab Vedotin will be administered *after* AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2). Brentuximab vedotin dosing will be determined by the phase I dose de-escalation schema with the starting dose of 1.2 mg/kg (See Table 4-A). For participants with weight exceeding 100kg, the dosage of Brentuximab vedotin will be calculated based on a weight of 100kg.

On the first cohort, three to six participants will begin at dose level 0. If > 1 dose-limiting toxicities (DLT) are encountered, 3 to 6 additional participants will be enrolled at the next lowest dose level. This will then be the MTD as long as no more than 1/6th of the participants experience DLT (1 participant of the 6 enrolled at that particular dose level). If more than one participant at any one dose level encounters a DLT, the dose will be de-escalated for all subsequent participants (see Section 4.1.1 for DLT definition). Once a MTD has been confirmed, this will be the standard dose used in the phase II portion of the study. The phase I MTD was determined to be 1.2 mg/kg.

Table 4-A: Phase 1 Dose Finding Schema for AVD-BV Regimen*

	Doxorubicin	Vinblastine	Dacarbazine	Brentuximab Vedotin**
Dose Level	**Day 1, 15 Of 28-day cycle**	**Day 1, 15 Of 28-day cycle**	**Day 1, 15 Of 28-day cycle**	**Day 1, 15 Of 28-day cycle**
0	25 mg/m^2	6 mg/m^2	375 mg/m^2	1.2 mg/kg**
-1	25 mg/m^2	6 mg/m^2	375 mg/m^2	0.9 mg/kg**
-2	25 mg/m^2	6 mg/m^2	375 mg/m^2	0.6 mg/kg**

*See Section 4.4.1 for instructions on GCSF supportive treatment.

**For participants with weight exceeding 100kg, the dosage of Brentuximab Vedotin will be calculated based on a weight of 100kg.

4.1.1 Definition of Dose-Limiting Toxicity (DLT)

During cycle 1, any AE resulting in a dose delay in AVD-BV therapy of ≥ 7 days is considered a DLT, which requires discontinuation of protocol-specified therapy and withdrawal from the study. Please refer to Table 5-A in Section 5.1 for specific guidelines. In subsequent cycles, the brentuximab vedotin dose may be withheld or reduced according to the guidelines provided in Section 5.1. If two sequential doses of AVD+BV or AVD alone are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), protocol treatment will be discontinued. Please see Section 4.6.1 for criteria for permanent treatment discontinuation.

4.2 Phase II: AVD-Brentuximab Vedotin Therapy

AVD dosing will be as described in Table 4-A, in conjunction with brentuximab vedotin at the MTD determined in the phase 1 portion of the study. The phase I MTD was determined to be 1.2 mg/kg. As in phase 1, drugs will be given on days 1 (+/- 2 days) and

15 (+/- 2 days) on a 28-day cycle for a total of 6 cycles. Brentuximab vedotin will be administered *after* AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2).

If treatment is delayed (<7 days if during cycle 1, or <2 weeks if occurring during subsequent cycles), once treatment is resumed the next dose will be scheduled two weeks after treatment is restarted.

4.3 Radiation Therapy

Involved field radiotherapy should be given at the discretion of the investigator after chemotherapy if there was bulky (> 10cm) disease at diagnosis as suggested in the NCCN guidelines. Radiation therapy initiation will be within 2 weeks after protocol therapy. Radiotherapy may be performed during the follow-up period according to institutional standards.

4.4 Supportive Therapy

4.4.1 Growth Factor

GCSF will be administered on Days 2-10 and 16-24 throughout each 28-day cycle using standard doses. Pegfilgrastim may be substituted for GCSF and be administered on days 2 and 16, either by clinical staff or via autoinjector applied on the day of protocol treatment.

4.4.2 HAART

HAART is a requirement for the duration of the study. Participants must be on HAART therapy for at least 7 days before therapy. The specific agents are at the discretion of the Investigator and use of agents currently available on an expanded access basis is allowed. Use of experimental antiretroviral agents or those containing zidovudine (including Combivir® and Trizivir®), ritonavir (including Kaletra®), Cobicistat (Stribild®), or another potent CYP3 inhibitor are prohibited. In order to be eligible, participants taking zidovudine- or ritonavir-based HAART must change to a different regimen 7 days prior to therapy initiation. Changes to HAART therapy may be made if medically necessary (toxicity, failure of regimen, etc.).

4.4.3 Pneumocystis prophylaxis

Trimethoprim sulfamethoxazole (Bactrim) must be given at the onset of therapy for Pneumocystis and Toxoplasmosis prophylaxis, according to current CDC guidelines which can be found here: https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0

Alternatively, dapsone (50 mg PO twice daily), atovaquone, or aerosolized pentamidine may be substituted for Pneumocystis prophylaxis in participants allergic to sulfonamides. Pneumocystis prophylaxis will be continued once therapy has been discontinued.

4.4.4 Mycobacterium avium complex (MAC) prophylaxis

Azithromycin 1,200 mg PO once weekly must be initiated for prophylaxis if the

CD4 count falls below 50 cells/µL or is expected to drop below 50 cells/µl while on chemotherapy. Prophylaxis may be discontinued once the CD4 count is deemed reliably above 50 cells/µL by the treating investigator.

Due to the glycoprotein P inhibition properties of azithromycin, this may increase the chemotherapy drug exposure and contribute to increased toxicity. Sections 3.1.19, 7.3.7, and Appendix XIII state that P-glycoprotein inhibitors, including azithromycin, are disallowed medications on protocol. This limited exception is permitted in the case of MAC prophylaxis.

Based on the pharmacokinetics of azithromycin and brentuximab vedotin, the study team recommends giving the azithromycin on Days 5, 12, 19, and 26 of each cycle.

4.4.5 Pre-infusion prophylaxis

Pre-infusion prophylaxis (e.g., diphenhydramine) may be administered per institutional guidelines.

4.4.6 Quinolone antibacterial prophylaxis

For participants with a CD4+ T cell count of < 100/mm^3 at baseline or whose CD4 count decreases below 100/mm^3 during protocol therapy, antibiotic prophylaxis covering the nadir is recommended with quinolone or equivalent. Ciprofloxacin is not preferred due to being a moderate CYP3A4 inhibitor and caution should be exercised due to drug-drug interactions (See Appendix XIII).

4.5 Study Duration

Participants will receive brentuximab vedotin in conjunction with standard, fixed, doses of doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 on days 1 and 15 of a 28-day cycle for 6 cycles. Participants will be followed for a total of 5 years, every 3 months for the first 2 years and every 6 months for years 3 to 5 of follow up.

Participants who discontinue all protocol therapy after having a CR or PR are followed for up to 5 years after treatment for recurrence and survival. Participants who discontinue protocol therapy due to disease progression or other reasons (Section 4.6) are followed for survival only for up to 5 years after treatment or until death, whichever occurs first. Participants who cross over to non-protocol therapy (if PR or stable disease at physician discretion), or other reasons will be followed for survival for up to 5 years after treatment. Participants removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.6 Criteria for Permanent Removal from Treatment

After enrollment, participants will be permanently withdrawn from study treatment for any of the following reasons. In the event of withdrawal from treatment, the reason for study treatment removal and the date the participant was removed must be documented in the Off Protocol Treatment Form in AdvantageEDC^{SM}. See Section 8.4 on evaluations to be performed at early discontinuation of therapy.

4.6.1 Participants who experience a delay of over 7 days in cycle 1 will be removed from protocol therapy. For subsequent cycles, if two sequential doses of AVD + BV or AVD alone are held due to unresolved toxicity, leading to a treatment delay of an

additional 2 weeks (i.e., 4 weeks between doses), the participant will be taken off protocol therapy. The participant will be followed for survival and may resume AVD treatment off study.

4.6.2 Severe toxicities as outlined in Section 5.0.

4.6.3 Progressive lymphoma at any time while on study.

4.6.4 Voluntary withdrawal.

4.6.5 The investigator has the right to remove participants from study for clinical reasons which he or she believes to be life threatening or resulting in significant morbidity to the participant.

4.6.6 Any participant who develops HBV reactivation or acute Hepatitis B as defined by the reappearance of a previously suppressed hepatitis B surface antigen, a positive IgM hepatitis B core antibody, and a positive viral load. Any participant with Hepatitis B or C who has worsening liver function as defined by Section 5.2.5 will also be removed from study.

4.6.7 Participants who become pregnant or breast-feed.

4.6.8 Participants with progressive disease at the end of cycle 2 will be removed from study treatment, while participants with stable disease may be removed from the study treatment at the discretion of the local responsible investigator. Progressive or stable disease defined at cycle 2 will be based by CT criteria only, as FDG-PET has yet to be validated in HIV-associated HL.

4.6.9 If found by central pathology review to not have the diagnosis of HIV-HL.

4.6.10 If the participant has had two cycles of AVD + brentuximab vedotin and develops recurrent Grade 3 peripheral neuropathy despite dose reductions of brentuximab vedotin and vinblastine, the participant may continue the study receiving AVD with dose adjustments in vinblastine as clinically necessary, keeping in mind to maintain the dose and schedule as in standard therapy, or may be removed from protocol treatment. This decision will be at the discretion of the investigator.

4.7 Criteria for Early Study Termination

4.7.1 An early stopping rule will be established such that the trial will be terminated if either or both of the following conditions hold:

1. If the highest dose, the 1.2mg/kg dose, moves forward into the phase II portion of the study, and if more than 10% of the participants experience a grade 3 motor or sensory neurotoxicity lasting for more than 4 weeks, the trial will be terminated. The first 10 participants in the phase II portion of the study at the 1.2 mg/kg dose will be monitored for this outcome. If more than 3 out of the 10 participants experience grade 3 neurotoxicity, this will be considered sufficient to stop the trial. With an underlying probability of grade 3 neuropathy of no more than 10%, the probability of observing > 3 participants with grade 3 neuropathy is less than 5%.
2. If any PML case is diagnosed when the CD4 count is above 50, the trial will be terminated.

4.7.2 Request by the protocol chairs, AMC, IRB, NCI, OHRP, or pharmaceutical sponsors.

5.0 DOSE MODIFICATIONS/TOXICITY MANAGEMENT

5.1 Brentuximab Vedotin Dose Modifications

Intrapatient Dose Reductions for Starting Dose of 1.2 mg/kg Every 2 Weeks.

No further dose reductions will be permitted beyond 0.6 mg/kg of brentuximab vedotin. Participants not tolerating a dose of 0.6mg/kg will continue with standard dose AVD at the discretion of the investigator.

Dose Level
1.2 mg/kg
0.9 mg/kg
0.6 mg/kg

Table 5-A: Treatment Modification Guidelines for Brentuximab Vedotin for All Cycles

Event	CTCAE v5.0 Grade	Action to be Taken
Allergic reactions, or Acute infusional reactions/ cytokine release syndrome	Grade 1-2	For first reaction: • Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity). • Treat reactions with diphenhydramine 1 mg/kg (max 50 mg), or follow local institution guidelines. Depending on the reaction severity, dexamethasone 0.2mg/kg (max 10mg) IV should be used or follow local institution guidelines. • Upon resolution of the symptoms, at the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. Acetaminophen can also be considered. Brentuximab vedotin may be administered at half of the previously administered rate at the discretion of the investigator. For subsequent doses: • Utilize diphenhydramine with or without acetaminophen as pre-treatment for all subsequent infusions. • Dosing will be administered over the shortest infusion period that was well tolerated. If Grade 1-2 infusion reactions recur despite the above measures, either during re-challenge or subsequent treatments:

Event	CTCAE v5.0 Grade	Action to be Taken
		• Take the measures outlined above. • With subsequent dosing, add dexamethasone 0.2 mg/kg (max 10mg) IV or equivalent to medications above prior to infusion.
	Grade 3	• Stop infusion immediately. • Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2mg/kg (max 10mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. • Once symptoms recover, brentuximab vedotin should not be resumed for that course. Subsequent courses of brentuximab vedotin may be considered at physicians' discretion. • All subsequent infusions will use the following premedications prior to infusion, diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2mg/kg (max 10mg) IV (or equivalent). In addition, the infusion will be administered at 50% of the previous infusion rate.
	Grade 4	• Stop infusion immediately. • Administer diphenhydramine hydrochloride 1 mg/kg (max 50mg) IV, dexamethasone 0.2 mg/kg (max 10mg) IV (or equivalent), and other anaphylaxis medications as indicated. • Epinephrine or bronchodilators at the discretion of the investigator will be administered as indicated. • Hospital admission for observation may be indicated • Discontinue brentuximab vedotin.
Anaphylaxis	Any grade	If anaphylaxis occurs, immediately and permanently discontinue administration of brentuximab vedotin and administer appropriate medical therapy.
Pancreatitis	Grade 2	• Withhold dose until toxicity has returned to baseline, then continue on protocol therapy but resume at one dose reduction. • If Grade 2 pancreatitis recurs after one dose reduction, the participant must be removed from protocol therapy.
	Grades 3-4	• Permanently discontinue brentuximab vedotin.
Peripheral	Grade 1	Continue at same dose level.

Event	CTCAE v5.0 Grade	Action to be Taken
Neuropathy	Grade 2	• Treatment is to be delayed until neuropathy improves to Grade 1 or baseline. • Brentuximab vedotin will be reduced by one dose level for subsequent treatments once peripheral neuropathy returns to baseline or returns to a grade 1. • Participants who experience a delay of over 7 days in cycle 1 will be removed from the study. For subsequent cycles, if two sequential doses of brentuximab vedotin are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), participant will discontinue brentuximab vedotin. Participants will have the option to discontinue protocol therapy or continue study with AVD with dose adjustments in vinblastine as clinically necessary based on the level of neuropathy on the day of treatment as per standard label/summary product characteristics.
	Grade 3	• Treatment is to be delayed until neuropathy improves to Grade 1 or baseline. Brentuximab vedotin will be reduced by one dose level for subsequent treatments once peripheral neuropathy returns to baseline or returns to a grade 1. • Participants who develop grade 3 neuropathy after dose reduction will have to discontinue brentuximab vedotin. Participants will have the option to be taken off protocol or continue study with AVD with dose adjustments as clinically necessary. • Participants who experience a delay of over 7 days in cycle 1 will be removed from the study. For subsequent cycles, if two sequential doses of brentuximab vedotin are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), the participant will discontinue brentuximab vedotin. Participants will have the option to discontinue protocol therapy or continue study with AVD with dose adjustments in vinblastine as clinically necessary, based on the level of neuropathy on the day of treatment as per standard label/Summary product characteristics.

Event	CTCAE v5.0 Grade	Action to be Taken
	Grade 4	Discontinue brentuximab vedotin.
Neutropenia Occurring on the Day of Treatment[b]	Grade 1-2	Continue at same dose level.
	Grade 3-4	• Reinstitute growth factor support (GCSF) for treatment of neutropenia until recovery to ANC ≥1,000/mm^3. • If myeloid growth factor support was inadvertently omitted in the previous dose, participants should receive the same full dose of brentuximab vedotin in the next treatment dose, along with myeloid growth factor support. • If, as per protocol, the participant was on myeloid growth factor support with the previous dose and presents with treatment day neutropenia, reinstitute daily growth factor support (GCSF) until recovery to ANC ≥1,000/mm^3 and reduce brentuximab vedotin one dose level for all remaining cycles. • Dose reduction below brentuximab vedotin 0.6 mg/kg is not allowed. Brentuximab vedotin should not be given for any subsequent cycles. • If participants have febrile neutropenia, please see Section 5.1.3 for dose modifications.
Thrombocytopenia	Grade 1-2	Continue at same dose level.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but at one dose reduction. • Participants who experience Grade 3-4 thrombocytopenia after dose reduction must be removed from protocol therapy. • Participants who experience a delay of over 7 days in cycle 1 will be removed from the study. For subsequent cycles, if two sequential doses of brentuximab vedotin are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), the participant will be taken off protocol therapy.
Lymphopenia	Grade 1-4	Continue at same dose level.

Event	CTCAE v5.0 Grade	Action to be Taken
Non-hematologic[a] events (not including electrolyte abnormalities or febrile neutropenia) (See Section 5.1.3 for treatment modifications for febrile neutropenia)	Grade 1-2	Continue at same dose level.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but resume at one dose reduction of brentuximab vedotin. • If non-hematological Grade 3-4 toxicity recurs after one dose reduction, the participant must be removed from protocol therapy. • Participants who experience a delay of over 7 days in cycle 1 will be removed from protocol therapy. For subsequent cycles, if two sequential doses of brentuximab vedotin are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), the participant will be taken off protocol therapy, and brentuximab vedotin will be discontinued. Participants will have the option to be taken off protocol or continue study with just AVD without brentuximab vedotin.
Electrolyte Abnormalities	Grade 1-4	• Continue at same dose level, provided electrolyte toxicity is not medically consequential and has been readily corrected. • If electrolyte abnormality is medically consequential, refer to guidelines above for non-hematologic events.

[a] Participants who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption but should receive appropriate medical therapy at the discretion of the investigator.
[b] See Section 4.4.1 for instructions on GCSF supportive treatment.

5.1.1 Dose Modifications for Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML.

If PML is suspected, a diagnostic work-up must be performed. The work-up may include, but is not limited to the following:

- Neurologic examinations and neurology consultation, as warranted.

- Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically non-enhancing and do not have mass effect.
- PCR analysis. JCV DNA, detectable in CSF or in a brain biopsy, is suggestive of PML.

Brentuximab vedotin dosing must be held if PML is suspected. If PML is confirmed, brentuximab vedotin must be permanently discontinued.

5.1.2 Dose Modifications for Pulmonary Toxicity

Pulmonary toxicity will be defined by grade 3 or 4 dyspnea, pneumonitis, and/or hypoxia that persists for at least three days. There must be no evidence of other etiologies, including left atrial hypertension, congestive heart failure, infection, metabolic abnormalities, or cancer related causes (e.g., malignant pericarditis).

Participants who develop pulmonary toxicity associated with brentuximab vedotin may benefit from treatment with corticosteroids. However, there are no published guidelines to suggest the most appropriate dosing or duration of treatment. Administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses has been reported to improve symptoms in adults with pulmonary toxicity secondary to gemcitabine. The suggested dose for participants who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. Participants who develop pulmonary toxicity meeting the above definition will be taken off protocol therapy (brentuximab vedotin).

5.1.3 Dose Modifications for Febrile Neutropenia

For participants already dosed reduced for reasons other than febrile neutropenia (e.g., neuropathy), dose reduction must start from the level at which the febrile neutropenia occurs.

Table 5-B: Treatment Modification Guidelines for AVD-Brentuximab Vedotin for All Cycles

Episode of Febrile Neutropenia	Action
First Episode of Febrile Neutropenia	Maintain current brentuximab vedotin dose with quinolone prophylaxis, or reduce one dose level (investigator's discretion).
Second Episode of Febrile Neutropenia	Quinolone prophylaxis and reduce one dose level.
Third Episode of Febrile Neutropenia	Quinolone prophylaxis and reduce one dose level.
Fourth Episode of Febrile Neutropenia	Quinolone prophylaxis and reduce one dose level.

Dose Level	Brentuximab Vedotin	AVD
1	1.2 mg/kg	Full dose

-1	0.9 mg/kg	Full dose
-2	0.6 mg/kg	Full dose
-3	0	Full dose
-4	0	0.75

Quinolone prophylaxis: antibacterial therapy is required for all cycles after an initial episode of febrile neutropenia. Suggested regimen can be altered based on availability, allergies, or ANC trends (e.g., levofloxacin **750** mg PO daily, Days 6-13 and Days 20-27). Ciprofloxacin is not preferred due to being a moderate CYP3A4 inhibitor and caution should be exercised due to drug-drug interactions (See Appendix XIII).

Participants who are unable to receive at least 4 doses of brentuximab vedotin will not receive further therapy on study.

See Section 6.1 for a complete listing of potential adverse events and Section 6.1.1 for special precautions and safety issues.

5.2 AVD-Brentuximab Vedotin Dose Modifications (applies to all cycles)

5.2.1 Hematologic Toxicity

Although it is common practice to attenuate doses or delay treatment due to cytopenias alone, recent studies have shown that in the non-HIV setting for cHL patients receiving delays results in suboptimal treatment outcomes[77,78]. Participants will receive full doses of AVD on schedule on Days 1 and 15 of each 28-day cycle without treatment delays, unless neutropenic fever or documented infections are present.

5.2.2 Febrile Neutropenia

See Section 5.1.3 for AVD-brentuximab vedotin dose modification instructions for febrile neutropenia.

5.2.3 Transfusions

Erythrocyte and platelet transfusions will be administered as needed at the discretion of the treating physician.

5.2.4 Severe Infection

Severe infection (NCI CTC Version 5.0, Grade 3 or 4) due to chemotherapy-related neutropenia requires a decrease in the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician.

5.2.5 Impaired Hepatic Function

Please see Table 5-C below for the appropriate dose adjustments based on total bilirubin and AST. In cases of obstruction of the biliary duct by a tumor mass, a biliary drainage stent may be placed prior to chemotherapy. Values must be within protocol eligibility at treatment initiation.

Table 5-C: Total Bilirubin with Appropriate Doxorubicin and Vinblastine Dose Adjustments

Drug[1]	Total Bilirubin: < 1.5 AST: < 60	Total Bilirubin: 1.5 – 3 AST: 60 - 180	Total Bilirubin: 3.1 – 3.5 AST: > 180	Total Bilirubin: > 3.5
Doxorubicin	Administer 100%	Administer 50%	Administer 25%	Safety Not Established
Vinblastine	Administer 100%	Administer 50%	Administer 25%	Safety Not Established

1. If participants are receiving atazanavir, please use **only** the direct bilirubin as an indicator for dose reduction of doxorubicin or vinblastine, following the dose reduction guidance identically as for total bilirubin

5.2.6 Neuropathy

Once brentuximab vedotin has been discontinued, participants experiencing Grade 3 vinblastine-neuropathy (e.g., obstipation, weakness) may continue the study receiving AVD with dose adjustments in vinblastine as clinically necessary, based on the level of neuropathy on the day of treatment. Participants experiencing Grade 4 vinblastine neuropathy will have this drug omitted from all future cycles of AVD.

5.2.7 If a participant's weight has changed more than 10% from baseline or the prior dose, the new BSA must be used on the next cycle. For a weight change of 10% or less, doses may be adjusted according to the BSA or remain the same in conjunction with institutional guidelines.

6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of expected 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}).

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. 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.

A monthly conference call between all participating institutions will be conducted to discuss all adverse events encountered.

6.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) for Brentuximab Vedotin (SGN-35, NSC 749710)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 798 patients.* Below is the CAEPR for SGN-35 (brentuximab vedotin).

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

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
		Colitis[2]	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
		Enterocolitis	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal obstruction[4]	
		Gastrointestinal perforation[5]	
		Gastrointestinal ulcer[6]	
		Ileus	
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Pain		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatotoxicity)[7]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Lung infection		
	Upper respiratory infection		***Upper respiratory infection (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		
	Weight loss		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hyperglycemia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Muscle cramp		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
	Paresthesia		
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 2)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr 2)***
PSYCHIATRIC DISORDERS			
	Anxiety		
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Oropharyngeal pain		
		Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity)[8]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
[2]Colitis may also include the term neutropenic colitis.
[3]Fatal and/or serious gastrointestinal hemorrhages have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower

gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.
[4]Fatal and/or serious gastrointestinal obstructions have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[5]Fatal and/or serious gastrointestinal perforations have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. Lymphoma with preexisting GI involvement may increase the risk of perforation.
[6]Fatal and/or serious gastrointestinal ulcers have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.
[7]Hepatotoxicity may manifest as increased ALT/AST, bilirubin, alkaline phosphatase, and/or GGT.
[8]Pulmonary toxicity, which may manifest as pneumonitis, interstitial lung disease, or adult respiratory distress syndrome (ARDS), has been observed in patients treated in brentuximab vedotin monotherapy trials as well as in combination with bleomycin.

Adverse events reported on SGN-35 (brentuximab vedotin) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that SGN-35 (brentuximab vedotin) caused the adverse event:
BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy)
CARDIAC DISORDERS - Myocardial infarction; Pericardial effusion; Sinus tachycardia
GASTROINTESTINAL DISORDERS - Dyspepsia; Esophagitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Meningitis; Pharyngitis; Sepsis; Shingles; Sinusitis; Skin infection; Soft tissue infection; Thrush; Urinary tract infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; Carbon monoxide diffusing capacity decreased; Creatinine increased; Lipase increased; Lymphocyte count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Myositis; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome

NERVOUS SYSTEM DISORDERS - Dysesthesia; Encephalopathy; Nervous system disorders - Other (demyelinating polyneuropathy); Seizure; Syncope
PSYCHIATRIC DISORDERS - Depression
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (pyelonephritis)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (groin pain)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome[8]; Pleural effusion[8]; Pneumothorax[8]; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (bronchitis)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: SGN-35 (brentuximab vedotin) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.1.1 Special Precautions/Safety Issues

Infusion-Related Reactions

Some patients experienced an infusion-related reaction during or soon after SGN-35 treatment. Symptoms of infusion-related reactions included chills, nausea, cough, itching, and shortness of breath. Two patients experienced a serious allergic reaction (wheezing/difficulty breathing, hives, itching, swelling) that required immediate medical attention and treatment discontinuation.

Peripheral Neuropathy

Some patients who received SGN-35 developed peripheral neuropathy. Symptoms reported by these patients included burning sensation, pain, weakness, numbness and tingling of hands and/or feet, and severe abnormal nerve function that caused difficulty walking.

Neutropenia

Some patients experienced neutropenia that was related to treatment with SGN-35. This could result in an increased risk of infection.

Infection Risk

SGN-35 may cause patients to be less resistant to infections, including severe infections.

Other Important Side Effects

The following important or potentially life-threatening side effects have been reported infrequently in patients treated with SGN-35:

- Serious allergic reaction (wheezing/difficulty breathing, hives, itching, swelling) during or soon after SGN-35 treatment, which requires immediate medical attention and treatment discontinuation

- Severe leukopenia, fever, and possible infection that resulted in death
- Stevens-Johnson syndrome (unexplained widespread skin pain, blisters on skin and mucous membranes, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of skin)
- Tumor lysis syndrome (TLS) is a potentially life-threatening complication. TLS usually occurs within a few days of the start of cancer treatment and may result in metabolic complications. Potential complications may include nausea, vomiting, edema (swelling), shortness of breath, heart rhythm disturbances, and acute renal failure.
- Progressive Multifocal Leukoencephalopathy (PML) is a rare, serious brain infection caused by a certain virus. People with a weakened immune system can experience PML. PML can result in death or severe disability. Care providers should be mindful of confusion or problems thinking, loss of balance or problems walking, difficulty speaking, decreased strength or weakness on one side of your body, blurred vision or loss of vision.

Pregnancy and Breastfeeding

Brentuximab vedotin is pregnancy category D; therefore, participants should not receive SGN-35 if they are pregnant because of the risk to the fetus. SGN-35 affects the testes in animals; therefore, men should not get their partner pregnant while being treated with SGN-35.

- Female study volunteers of reproductive potential (defined as girls who have reached menarche and pre-menopausal women who have not had a sterilization procedure such hysterectomy, bilateral oophorectomy, or salpingectomy) **must** have a negative serum or urine pregnancy test performed within 48 hours before initiating the protocol-specified medication(s). Women are considered menopausal if they have not had a menses for at least 12 months and have a FSH of greater than 40 IU/L or, if FSH testing is not available, they have had amenorrhea for 24 consecutive months.
- All study volunteers, male and female, must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, sperm donation, or in vitro fertilization).
- If participating in sexual activity that could lead to pregnancy, **all** study volunteers must agree to use **two reliable methods of contraception simultaneously** while receiving protocol-specified medication(s) and for 6 months after stopping the medication(s).
- If the female volunteer is not of reproductive potential (defined above) or the man has documented azoospermia, contraception is not required.

Participants who could become pregnant or who have partners who could become pregnant must use birth control during the study and for 6 months after stopping treatment. If a participant or a participant's partner becomes pregnant while taking part in this study or within 6 months after stopping treatment, the participant should inform the study doctor right away. Seattle Genetics will follow the pregnancy to term. In addition, the resultant progeny will be followed for potential side effects for some period of time after birth.

It is not known whether SGN-35 or its breakdown products end up in breast milk. If it does end up in breast milk, it could cause harm to a nursing baby. Therefore, breast feeding is prohibited while on study drug and for 6 months after the last dose of study drug.

Possible Risks in Combination with Other Therapies

Concomitant use of SGN-35 and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial that studied SGN-35 with bleomycin as part of a combination regimen (ABVD), the rate of noninfectious pulmonary toxicity was higher than the historical incidence reported with ABVD. Monotherapy with SGN-35 has not been associated with a clinically meaningful risk of pulmonary toxicity.

An ongoing phase 1 study is investigating the combination of SGN-35 with ABVD or AVD as front-line therapy for HL. Noninfectious pulmonary toxicity was observed in some patients treated with SGN-35 in combination with ABVD. The incidence of pulmonary toxicity in the ABVD + SGN-35 arm of the trial was approximately 40% (10 of 25 patients), compared to an incidence of 10% to 25% most commonly reported in the literature with bleomycin-based regimens[79-81]. Patients presented with cough and dyspnea. Interstitial infiltration and/or inflammation were observed on X-ray and computed tomography of the chest. Five patients had a maximum severity ≥ Grade 3 (3 with Grade 3 and 2 with Grade 4). Most patients responded favorably to corticosteroid therapy.

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

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

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

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

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

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

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

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

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

Definite – The AE is clearly related to the investigational agent.

Probable – The AE is likely related to the investigational agent.

Possible – The AE may be related to the investigational agent.

Unlikely – The AE is doubtfully related to the investigational agent.

Unrelated – The AE is clearly NOT related to the investigational agent.

6.3 Expedited Adverse Event Reporting

6.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System) accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 6.3.3).

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

6.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Protocol Chair, Principal Investigator at the local AMC treating institution and AMC Operations and Data Management Center. CTEP-AERS provides a copy feature for other e-mail recipients.

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

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

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

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

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

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

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

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

- Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
- "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.

- 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 adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the nine-digit AMC participant ID assigned during trial registration on all reports.

6.3.4 Clinical Laboratory Results

Clinical laboratory results that are outside of the institution's reference ranges must be reported as adverse events if they are deemed clinically significant by the investigator(s).

6.3.4.1 A clinical laboratory abnormality should be deemed clinically significant if any one of the following conditions is met:

- The laboratory abnormality is not otherwise proved false by a repeat confirmation test.
- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug(s), close observation, more frequent follow-up assessments, or further diagnostic investigation.

6.3.4.2 In this protocol the following clinical laboratory abnormalities are expected and will not be considered AEs:

- HIV viral load
- T Cell subsets
- LDH

6.4 Routine Adverse Event Reporting

All AEs that require expedited reporting via CTEP-AERS must also be reported in routine study data submissions (Adverse Event Form CRF). Routine reporting of all AEs attributed to therapy (possible, probable or definitely), regardless of grade, should be reported on the Adverse Event Form CRF. Similarly, if participants require radiotherapy, post-treatment AEs related to radiation therapy do not require routine reporting. All Grade 5 events, regardless of attribution to therapy, must be reported in the Adverse Event and Death Forms

in AdvantageEDC^{SM}.

6.4.1 Timeline for routine adverse event reporting

All adverse events will be assessed by the investigator in the study source from the first dose of protocol therapy through the post-treatment discontinuation visit (one month if discontinuing treatment early; 6-8 weeks at scheduled protocol therapy completion). After this evaluation, assessment and reporting of AEs will only be required for all grade 5 AEs and any SAE that the investigator considers related to AMC-085 protocol therapy.

6.5 Secondary Malignancy

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

Acute myeloid leukemia (AML)/Myelodysplastic syndrome (MDS) events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v5.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) MDS, or 3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS report should include the following: tumor pathology; history of prior tumors; prior treatment/current treatment including duration; any associated risk factors or evidence regarding how long the tumor may have been present; when and how the tumor was detected; molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor; and tumor treatment and outcome, if available. These events should be reported for the duration of the study treatment and during the protocol-specified follow-up period.

7.0 PHARMACEUTICAL INFORMATION

7.1 Chemotherapy Medications

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

Doxorubicin will be commercially supplied and please refer to institutional guidelines for administration. Additional information on this medication including all adverse events can be obtained from the approved FDA package insert found at:

http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=13894

7.1.2 Vinblastine

Vinblastine is the salt of an alkaloid derived from Vinca rosea Linn, a common herb known as the periwinkle.

Mechanism of Action: Tissue culture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. A number of studies in vitro and in vivo have demonstrated its stathmokinetic effect and various atypical mitotic figures. Other studies indicate an effect on cell energy production required for mitosis and the interference with nucleic acid synthesis. Reversal of antitumor effect by glutamic acid and tryptophan has been observed.

Leukopenia is the usual dose-limiting side effect, with the nadir falling four to seven days post-injection. Thrombocytopenia and anemia may occur. Gastrointestinal toxicities include nausea, vomiting, diarrhea or constipation, abdominal pain, ileus, peptic ulcer, rectal bleeding and anorexia. Fever and phlebitis have also been seen when the drug is given as an infusion. Extravasation may lead to tissue necrosis. Ten percent of the participants will experience peripheral neuropathy. Alopecia can also occur.

Vinblastine will be commercially supplied and please refer to institutional guidelines for administration. Additional information on this medication including all adverse events can be obtained from the approved FDA package insert found at:

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=17060

7.1.3 Dacarbazine (DTIC)

Three hypotheses have been offered as the mechanism(s) of action of DTIC: inhibition of DNA synthesis by acting as a purine analog, action as an alkylating agent, and/or interaction with SH groups.

Myelosuppression is the dose-limiting toxicity. The predominant side effect observed in humans has been anorexia, nausea, and vomiting. This occurs with maximal intensity on the first day of a five-day course, and in many patients, it is less with each subsequent day. Myelosuppression consisting of thrombocytopenia and leukopenia occurs in approximately one-quarter of patients after a five-day course of 250 mg/m^2. The time course for this myelosuppression is generally maximal approximately three weeks after administration with the period of recovery variable. Other reported side effects include infrequent flu-like syndrome associated with fever and myalgia, phlebitis, liver necrosis, hepatic toxicity, anaphylaxis, photosensitivity, alopecia, and facial flushing. Rarely, DTIC has caused diarrhea.

Dacarbazine is pregnancy category D, please follow the same guidelines stated in Section 6.1.1 under the pregnancy and breastfeeding section.

Dacarbazine will be commercially supplied and please refer to institutional guidelines for administration. Additional information on this medication including all adverse events can be obtained from the approved FDA package insert found at:

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=17060

7.1.4 Brentuximab Vedotin (NSC 749710)

Other Names: Adcetris^{TM}, Brentuximab vedotin

Classification: Monoclonal Antibody

CAS Registry Number: 914088-09-8

M.W.: 153 kDa

Mode of Action: A CD-30 directed antibody-drug conjugate (ADC) consisting of 3 components: (1) the chimeric IgG1 antibody cA10, specific for human CD30, (2) the microtubule disrupting agent monomethyl auristatin E (MMAE), and (3) a protease-cleavable linker that covalently attaches MMAE to cA10. Its cytotoxic activity occurs when ACD binds to the CD-30 expressing cell, forming an ADC-CD30 complex compound and releasing MMAEs via proteolytic cleavage. Subsequently, MMAE binds to tubulin to disrupt the microtubule network within the cells, resulting in cell cycle arrest and apoptosis.

How Supplied: Seattle Genetics supplies and CTEP/DCTD distributes SGN-35 as a single use, preservative free vial containing 50 mg of white to off-white lyophilized powder for Injection. Inactive ingredients are trehalose, sodium citrate, and polysorbate 80. The pH is 6.6 once reconstituted in Sterile Water for Injection.

Preparation: Consists of 2 steps: dilution of the stock solution and dilution of the final solution.

Step 1: To make a 5 mg/mL concentration.

1. Reconstitute the 50 mg lyophilized powder SGN-35 with 10.5 mL Sterile Water for Injection, USP. Final concentration is 5 mg/mL (Note: total volume is 11 mL).
2. Swirl the vial gently. Do not shake.
3. Let the reconstituted vial settle for one minute to eliminate bubbles. The reconstituted solution should be colorless, clear to slightly opalescent and should NOT have visible particulates.
4. Store the reconstituted vial under refrigeration (2° – 8°C), protect from light if not used immediately. Discard after 8 hours.

Step 2: Further dilute the IV solution. Use vials from the same Lot number for each dose.

1. Withdraw the calculated amount of drug from the 5 mg/mL reconstituted vial in step 1.
2. Inject the required amount of drug into a 50 mL to 250 mL of 0.9% NS, Lactated Ringer's Solution, USP, or dextrose 5% in Water (D5W), USP to a final concentration between **0.4 – 1.8 mg/mL**.
3. SGN-35 solution is compatible in polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, or polyethylene.
4. Do not shake. Gently invert the bag.
5. The prepared IV bag is to be stored at 2-8° C and must be used within 24 hours of initial product reconstitution. Protect the prepared IV solution from direct sunlight if not used immediately.
6. Prior to administration, inspect the IV bag for discoloration or floating particulates. Do not use the IV solution if the solution is discolored or/and have particulates.

Storage: Store the intact vials refrigerated at 2-8° C. Protect from direct sunlight.

Stability: The stability testing of the intact vials is ongoing. Reconstituted agent must be diluted and administer within 24 hours.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 8 hours after initial entry.

Route(s) of Administration: Intravenous. Do not administer as an IV Push or bolus.

Method of Administration: Infuse the prepared IV solution over 30 minutes. Do not mix with other medications. Do not use an in-line filter for the IV administration. The IV bag does NOT need light protection during the IV administration.

Potential Drug Interactions: In vitro data, one of SGN-35 active metabolites, monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4 but is not a sensitive substrate nor a strong inhibitor/inducer of CYP3A4. However, participants should be monitored for potential drug-interaction when administered drugs known to be a strong CYP 3A4 inhibitor/inducer with SGN-35. In vitro,

MMAE is a substrate of P-gp transporter and is not an inhibitor of P-gp.

Participant Care Implications:

- New signs and symptoms of CNS system abnormalities may indicate progressive multifocal leukoencephalopathy (PML).
- Tumor lysis syndrome, particularly in participants with highly proliferative tumors or high tumor burden prior to treatment.
- Infusion-related reactions, including anaphylaxis, may occur. Refer to protocol for the management of infusion-related reactions.
- Signs and symptoms of peripheral neuropathy such as tingling or numbness of the hands, feet, or any muscles weakness.
- Steven-Johnson syndrome
- High fever (≥100.5F) or other signs of potential infection.

7.2 Drug Orders, Transfers, Returns, and Accountability

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

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

Seattle Genetics will be responsible for supplying Brentuximab vedotin to all of the LYSA/LYSARC sites in France. Agent orders, transfers, and returns will be conducted according to the agreement between LYSA/LYSARC and Seattle Genetics.

7.3 Reporting Requirements for Concomitant Medications

All medications must be reported in the site's source documents at baseline. All

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

7.3.1 Anti-seizure medications

7.3.2 Prophylactic medications

- Antiviral
- Antifungal
- Quinolone/Antibiotic therapy (See Section 4.4.6)
- Any other medications used for prophylaxis of opportunistic infections

7.3.3 Hepatitis medications

7.3.4 Growth colony stimulation factors (GCSF)

7.3.5 Erythropoiesis Stimulating Agents (ESA)

7.3.6 Anti-retroviral medications. Note: Antiretroviral therapy will be collected in the On Study Form. If the participant remains on the same anti-retroviral medications throughout study participation that have already been reported in the On Study Form, then do not report them in the Concomitant Medications Form. If the participant changes or discontinues anti-retroviral therapy for any reason, then update the Concomitant Medication Form with the start and stop date of the discontinued medication(s) and start date of the new (if applicable) medication(s).

7.3.7 Receipt of disallowed medications (CYP3A4 or P-glycoprotein inhibitors) after study enrollment, as per Appendix XIII

8.0 STUDY PROCEDURES

Schedule of Evaluations is provided in Appendix I.

8.1 Screening/Baseline Evaluations

Unless otherwise specified, the following evaluations must be performed within 6 weeks prior to participant registration:

8.1.1 AIDS and Cancer Specimen Resource (ACSR) Consent for optional donation. It is required that AMC sites present the ACSR donation option to participants. (See Appendix VI for ACSR Informed Consent Form and Appendix V for ACSR Specimen Preparation and Shipping Instructions).

8.1.2 Medical history, history of drug allergies, history of current and past anti-retroviral regimens, if available; and history of any prior AIDS-defining conditions. Date of initial lymphoma diagnosis is required, with a copy of the pathology report in the medical record. Presence of systemic "B" symptoms should be noted, as well as other symptoms of cHL. Current concomitant medication list, including all anti-retroviral, anti-viral, antibiotics, and opportunistic prophylaxis should be obtained.

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

8.1.4 A combined FDG-PET/CT or FDG-PET + CT scan with and without IV contrast is required for this study. If a participant has an allergy to IV contrast, a non-IV contrast CT scan will be permitted. To ensure consistency between all centers, FDG-PET/CT scans at diagnosis should be conducted no more than 28 days before enrollment.

If the CT scan of a PET/CT hybrid is performed with both oral and IV contrast with contrast enhancement in the arterial and/or portal venous phase, with at least a 2-slice CT, and is acquired with at least 80 mAs and CT scans are obtained with contiguous sections (with a maximum of 5 mm slice thickness), then the pre-treatment PET/CT scan alone will suffice for participants enrolled on this trial. If no contrast is used in the FDG-PET/CT, an additional CT scan with contrast is required of the neck, chest, abdomen, and pelvis, see 8.1.5 below.

8.1.5 CT scan of the neck (if palpable lymphadenopathy only), chest, abdomen and pelvis with and without IV contrast will be required. If the CT portions of the FDG-PET/CT combination scan is a non-contrast CT scan, then a separate CT scan with and without IV contrast will be required.

8.1.6 MRI of the brain with and without IV gadolinium contrast, to look for early evidence of PML.

8.1.7 Determination of LVEF by MUGA scan or echocardiogram.

8.1.8 Bone marrow biopsy for histology and determination of percent bone marrow involvement. If bone marrow involvement by lymphoma has already been

documented after bone marrow biopsy performed more than 6 weeks prior to registration, the biopsy does not have to be repeated.

8.1.9 Central pathology review for confirmation of histology of lymphoma specimen: Biopsy material at diagnosis will be sent to confirm HIV-HL and histologic subtype. When possible, biopsy tissue blocks should be sent. If not, one hematoxylin and eosin (H&E) stained slide and ten 5 μm blank (unstained) paraffin sections can be used instead. The tissue block will be returned to the sites. (See Appendix VIII for the acceptable specimens required for central review and for handling instructions).

All specimens will be reviewed by a panel of pathologists and must be submitted within 30 days of study enrollment. **Participants who are found not to have HIV-HL will be withdrawn from the study**

8.1.10 Three 1.0 mm cores from the initial biopsy tissue block will be required to be sent for miRNA analysis. If biopsy block is unavailable, 10 unstained sections at 20 microns can be submitted (See Appendix VIII for the acceptable specimens required for miRNA analysis and for handling and shipping instructions).

8.1.11 Three 1.0 mm cores from the initial biopsy tissue block will be required to be sent for tissue microarray analysis. (See Appendix VIII for the acceptable specimens required for TMA construction and analysis and for handling and shipping instructions).

8.1.12 Laboratory tests, including:

8.1.12.1 CBC with differential and sedimentation rate (within 2 weeks prior to participant registration). Sedimentation rate is only required at screening/baseline.

8.1.12.2 Serum chemistries: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, and phosphorus), glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT (within 2 weeks prior to participant registration).

8.1.12.3 CD4 and CD8 cell count.

8.1.12.4 HIV-1 RNA viral load to be assessed by any FDA-approved viral load assay (evaluated at the local laboratory). This must be performed within 21 days prior to Cycle 1, Day 1. (The HIV viral load assay must detect at minimum viremia > 200 copies/mL to be consistent with the DHHS HIV treatment guidelines).

8.1.12.5 Assessment for Hepatitis C antibody, Hepatitis B core antibody, Hepatitis B surface antigen (HBsAg), and Hepatitis B surface antibody.

8.1.12.6 Serum or urine pregnancy test for women of childbearing potential (within 7 days prior to Cycle 1 chemotherapy). (See Section 6.1.1 under pregnancy and breastfeeding for guidelines on the use of pregnancy category D medications, which includes brentuximab vedotin and dacarbazine.)

8.1.12.7 Blood samples to be taken for EBV tumor DNA studies. See Section 10.0 and Appendix XI for time points needed, sample processing, and shipping instructions. This will be done only in the Phase II portion of the study.

8.1.12.8 Blood samples to be taken for cytokine studies. See Section 10.0 and Appendix X for time points needed, sample processing, and shipping instructions. This will be done only in the Phase II portion of the study.

8.1.12.9 Blood samples will be taken for analysis of latent and HIV reservoirs. See Section 10.0 and Appendix XII for time points needed, sample processing, and shipping instructions. Only for participants who are found to have undetectable plasma HIV-1 RNA by the standard assay performed at the clinical site within 21 days of C1 Day 1.

8.2 Evaluations During Treatment

Evaluations are to occur in both Phase 1 and 2 and all study arms unless otherwise specified.

8.2.1 Update medical history prior to each cycle of chemotherapy. History to include concomitant medication changes and any signs and symptoms. Reportable adverse events must be recorded in AdvantageEDC. To be performed within 48 hours prior to or on first day of each cycle.

8.2.2 Physical examination prior to each cycle of chemotherapy. Examination to include performance status (Appendix III). All participants will be evaluated for clinical response by physical examination prior to receiving treatment on each cycle. The exam should occur within 2 days prior to the start of each cycle but may occur on Day 1 of cycle. Disease measurable by physical examination will be recorded in two dimensions if possible. To be performed within 48 hours prior to or on first day of each cycle.

8.2.3 FDG-PET/CT. Combined FDG-PET/CT or FDG-PET + CT scans with and without IV contrast are required for this study. If a participant has an allergy to IV contrast, a CT scan without contrast will be permitted.

Restaging evaluation by a full body FDG-PET/CT within Day 22-28 of Cycle 2 (i.e., 7-13 days after the Cycle 2 Day 15 doses of AVD-BV). If the CT portion of the PET/CT is a non-contrast CT, an additional CT scan with and without contrast must be obtained. Tumor measurements and SUVs must be documented. A neck CT must be included if palpable neck nodes were present at baseline and a diagnostic CT is being performed.

As the false positive rate of FDG-PET scans may be higher in the HIV population, a biopsy of an unexpected FDG-PET avid lesion is recommended but remains at the discretion of the investigator.

8.2.4 Neuropathy evaluation by completing the FACT/GOG-neurotoxicity questionnaire at the beginning of each cycle. To be performed once within 48 hours prior to or on first day of each cycle (Appendix IV).

8.2.5 CBC with differential within 48 hours of day 1 and 15 of each cycle. Results must

be known prior to treatment.

8.2.6 Serum chemistries within 48 hours of day 1 and 15 of each cycle: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, and phosphorus), glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT. Results do not need to be known prior to treatment unless clinically indicated.

8.2.7 CD4/CD8 count will be performed within 48 hours of cycle 2 and cycle 5 day 1 along with the CBC evaluation.

8.2.8 HIV-1 RNA viral load, to be assessed by any FDA-approved viral load assay (evaluated at the local laboratory). This will be performed within 48 hours of cycle 2 and cycle 5 day 1 along with the CBC evaluation. (The HIV viral load assay must detect at minimum viremia >200 copies/mL to be consistent with the DHHS HIV treatment guidelines).

For participants with undetectable HIV viral at baseline: If the viral load rises above 200 copies per mL, HIV resistance testing will be required. Both viral load and resistance testing information must be shared in real time with the primary HIV provider if different from the protocol investigator. (The HIV viral load assay must detect at minimum viremia >200 copies/mL to be consistent with the DHHS HIV treatment guidelines).

8.2.9 Serum or urine pregnancy test for women of childbearing potential will be performed per institutional guidelines during the study.

8.2.10 Plasma samples to be taken for EBV tumor DNA studies at the end of cycles 1 and 3. See Section 10.0 and Appendix XI for time points needed, sample processing, and shipping instructions. This will be done only in the Phase II portion of the study.

8.2.11 Plasma samples to be taken for cytokine studies. See Section 10.0 and Appendix X for time points needed, sample processing, and shipping instructions. This will be done only in the Phase II portion of the study.

8.2.12 Pharmacokinetic/Immunogenicity studies in select Phase II participants only. See Appendix IX for details on time points, sample processing, and shipping.

8.2.13 Blood samples will be taken for analysis of latent and HIV reservoirs. See Section 10.0 and Appendix XII for time points needed, sample processing, and shipping instructions.

8.3 Post Treatment Evaluation

The studies listed below will be performed post-therapy within 6-8 weeks of the last treatment dose (6-8 weeks after Cycle 6 Day 15; all follow up time points for post-treatment evaluations should be calculated in reference to this treatment discontinuation visit). Studies will then be repeated every 3 months (+/- 7 days) thereafter for 2 years; every 6 months (+/- 7 days) for the third through the fifth years unless otherwise specified. All study participants should be followed for up to 5 years after treatment discontinuation or until death if occurring before 5 years of treatment discontinuation. Participants who discontinue all protocol therapy after a CR or PR are followed for up to 5 years after treatment for recurrence and survival. Participants who discontinue protocol therapy due

to disease progression or other reasons are followed for survival for up to 5 years after treatment discontinuation. No additional studies except follow up for survival are required after disease progression. In those instances in which a third party payer denies payment for some or all of these laboratory analyses, absence of these test results will not be considered a protocol violation.

8.3.1 Medical history.

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

8.3.3 At the conclusion of chemotherapy, a full body FDG-PET/CT scan will be done between 6-8 weeks post the final treatment dose, Cycle 6 Day 15. This will be the final FDG-PET/CT needed for the study. A combined FDG-PET/CT or FDG-PET + CT scans with and without IV contrast are required for the post-treatment scan**.** If a participant has an allergy to IV contrast, a CT scan without contrast will be permitted. As the false positive rate of FDG-PET scans may be higher in the HIV population, a biopsy of an unexpected FDG-PET avid lesion is recommended but remains at the discretion of the investigator.

8.3.4 CT scan with oral/IV contrast every 6 months for 5 years. To begin 6 months from the post treatment FDG-PET/CT scan, obtained 6-8 weeks post the final chemotherapy dose (See Section 8.3.3).

8.3.5 Bone marrow biopsy need only be performed to confirm a CR if positive at baseline (only once, within 8 weeks of the last treatment dose).

8.3.6 CBC with differential.

8.3.7 Serum chemistries: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, and phosphorus), glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT.

8.3.8 CD4 and CD8 cell count beginning with the first follow up visit and every 3 months after treatment completion for one year.

8.3.9 HIV-1 RNA viral load, to be assessed by any FDA-approved viral load assay (evaluated at the local laboratory) beginning with the first follow up visit and every 3 months after treatment discontinuation visit for one year. (The HIV viral load assay must detect at minimum viremia >200 copies/mL to be consistent with the DHHS HIV treatment guidelines).

8.3.10 Plasma samples to be taken for EBV tumor DNA studies at treatment discontinuation visit and 3, 6, and 12 months after treatment discontinuation visit. See Appendix XI for time points, sample processing, and shipping instructions. This will only be performed on the Phase II portion of the study.

8.3.11 Plasma samples to be taken for and cytokine studies. See Appendix XI for time points needed, sample processing, and shipping instructions. This will only be performed on the Phase II portion of the study.

8.3.12 Pharmacokinetic/Immunogenicity studies in select Phase II participants only. See Section 10.1 and Appendix IX for time points and sample processing post therapy.

8.3.13 Blood samples will be taken for analysis of latent and HIV reservoirs. See Section 10.0 and Appendix XII for time points needed, sample processing, and shipping instructions.

8.4 Early Discontinuation of Therapy

8.4.1 Participants discontinuing therapy early (i.e., PD or stable disease, administrative reasons, participant non-compliance, etc.) will have a medical history update and complete physical examination. The examination will include performance status and blood drawn for the following studies within 1 month after treatment discontinuation, unless otherwise noted. See Section 4.7 for a list of reasons for study termination. Participants will be followed for survival only for 5 years after the last date of treatment:

8.4.1.1 CBC with differential.

8.4.1.2 Serum chemistries: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, and phosphorus), glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT.

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

8.4.1.4 HIV-1 RNA viral load to be assessed by any FDA-approved viral load assay (evaluated at the local laboratory, do not repeat if done within 1 month from removal from treatment).

8.4.1.5 Pharmacokinetic/Immunogenicity studies in select Phase II participants only. See Section 10.1 and Appendix IX for time points and sample processing.

8.4.1.6 Blood samples will be taken for analysis of latent and HIV reservoirs. See Section 10.0 and Appendix XII for time points needed, sample processing, and shipping instructions (do not repeat if done within 1 month from removal from treatment).

8.4.1.7 Plasma samples to be taken for EBV tumor DNA studies. See Appendix XI for sample processing and shipping instructions. This will only be performed on the Phase II portion of the study.

8.4.1.8 Plasma samples to be taken for and cytokine studies. See Appendix XI for sample processing and shipping instructions. This will only be performed on the Phase II portion of the study.

9.0 EFFICACY AND SAFETY MEASUREMENTS

9.1 Efficacy Measurements

All participants will be evaluated for clinical response by physical examination prior to receiving treatment on each cycle. The exam should occur within 3 days prior to the start of each cycle, but may occur on Day 1 of cycle.

All participants will be evaluated for clinical response by imaging studies after by FDG-PET/CT at the completion of cycle 2 and at the completion of therapy (See Section 5.0).

9.2 Response Assessment

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

Definition of Response:

The response definitions used for this study are the 2007 Cheson criteria. A major distinction in the 2007 criteria is that PET/Gallium studies are used to facilitate the distinction between persistent tumor and scar/fibrosis.

Complete Response (CR):

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: In participants with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: In participants without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry.

Partial Response (PR) Requires all of the Following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at

least two perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Participants who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, participants should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for a participant with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: if a pretreatment PET scan was negative, CT criteria should be used.

Stable Disease (SD) is Defined as the Following:

1. A participant is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]) below.
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD):

1. Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes 1.0 x 1.0 cm will not be considered as abnormal for relapse or progressive disease.
2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In participants with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis. At least a 50% increase in the long est.

diameter of any single previously identified node more than 1 cm in its short axis. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

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

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

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

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

Safety Measures

All AE will be monitored by ongoing review of reported adverse events by the protocol chair and the AMC Operations and Data Management Center, and will be discussed during the monthly investigators' Lymphoma Working Group conference calls (see Section 4.7 for rules for early study termination).

10.0 CORRELATIVE STUDIES

For this protocol, we propose three correlative studies: miRNA analysis (see Section 10.2 and Appendix VIII), Tissue Microarray Studies (TMA) (see Appendix VIII), and Pharmacokinetic studies (PK) (see Section 10.1 and Appendix IX). We will collect either the paraffin blocks or Cores from these tissue and multiple unstained slides as a requirement for study entry to perform the miRNA and the TMA studies in addition to central pathology diagnosis confirmation. We will then correlate findings with the outcomes of participants enrolled on this trial in addition to their HIV infection characteristics. Please see Section 10.1 and Appendix IX for a detailed description of the PK studies to be performed in this clinical trial using serum isolated from participants during therapy.

In addition, upon acquisition of funding, we propose 3 more correlative studies. 1) We will analyze the Granzyme B to FoxP3 ratio on paraffin sections, to determine if these values, which have been reported to be prognostic indicators in non-HIV associated cHL, also correlate with outcome in HIV-HL[62] (see Appendix VIII). 2) We will also screen participant's plasma for molecules associated with immune activation and inflammation, specifically sCD30, CXCL13, IL-6 and IL-10. In a prior study in the AMC, we also assessed the effect of treatment for AIDS-associated NHL on plasma levels of these biomarkers, finding that treatment resulted in a marked decrease in many of these molecules, and that pre-treatment initiation plasma levels of CXCL13, IL-6 and IL-10 were predictive of subsequent CR to treatment[63,64]. In fact, in multivariate analysis, CXCL13 levels proved to be better predictors of subsequent clinical response that IPI or other established prognostic markers[63,64]. We will confirm if these molecules are prognostic in HIV-HL as well as these molecules were also found to be elevated in these participants[65,66] (see Appendix X). 3) As HIV-HL is co-infected with EBV, an attempt will be made to detect levels EBV derived tumor DNA in the plasma and use this as a tumor marker and a prognostic one. To do these last two studies, we will also collect plasma samples over time throughout therapy and post therapy to see how these biomarkers change over time (see Appendix XI).

10.1 Pharmacokinetic/Immunogenicity Studies

Chemotherapy-HAART interactions have become more pronounced in the transition from single agent HIV therapies to the era of cART as protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRT) are potent inhibitors (i.e., ritonavir) or inducers (i.e., efavirenz) of the cytochrome P450 system, in particular CYP3A4. As described in Section 7.1.4, brentuximab vedotin is an ADC whose conjugate MMAE is also metabolized via CYP3A4. As pharmacokinetic interactions between HAART and brentuximab vedotin are unknown, these interactions will be carefully monitored. Drug levels will be determined by assaying brentuximab vedotin, total antibody, and the free drug MMAE concentration over time. The formation of anti-brentuximab vedotin antibodies will be also assessed at the time points summarized below in Appendix IX. As the use of most potent inhibitor of CYP3A4 (i.e., ritonavir) is prohibited in this study, the pharmacokinetic data will compare two patient populations, those taking chemotherapy with concurrent efavirenz and non-efavirenz-based HAART. The pharmacokinetic data of 6 participants from each group will be assessed in the phase II portion of the clinical trial, once the maximum tolerated dose has been determined. Please see Appendix IX for a

detailed description of sample processing, time points that need to be assayed, shipping, and the assays involved.

10.2 Micro RNA Analysis of HIV-Associated Hodgkin Lymphoma

Mature microRNAs (miRNAs) are small non-coding RNAs that act as negative regulators of protein synthesis by covalently binding to the single stranded mRNA[67-71.] Once bound, the RNA-induced silencing complex (RISC) is formed[67-71]. Over 800 miRNAs have been identified in humans. These miRNAs play important roles in every cell function including cell proliferation/differentiation and can act as tumor suppressor and/or oncogenes[72,73]. Viruses also encode miRNA, and interactions between viral and host miRNAs affect host protein expression in specific manners to either promote viral replication or, in certain instances, cellular transformation1-4. The most common viruses identified to play a role in HIV-associated cancer tumorigenesis, HHV-8, HPV, and EBV together express over 40 miRNAs[67,68]. Viral miRNAs transform cells by various mechanisms. MiR-BHRF1-1 and miR-BART1, EBV expressed miRNAs, inhibit the tumor suppressor p53 and activate BCL-2 (an anti-apoptotic protein), respectively[67,68]. These miRNA combinations found in profile analysis are so specific that they define specific cancers as precisely as mRNA gene profiling[74]. Since many of the targets of the miRNAs are known, clues into the mechanisms of transformation and potential targets for therapy can be obtained[67-70]. Unfortunately, little data exist on the miRNA profiles on HIV-associated lymphoma, and no data exist on HIV-HL. It is known that hRS cell, can be co-infected in non-HIV participants, hRS cells are co-infected in 30-40% of the cases[15,17,18]. In HIV-HL the infection rate of the hRS cells with EBV range from 80-100[%15,17,18.] The molecular basis of transformation is unclear. In HIV-HL, the lymphocytic depleted histologic subtype of HL is more common than the non-HIV or the non-HIV EBV-associated HL. HIV-HL also is the most aggressive form of HL, imparting the worst prognosis. MiRNA profiling of HL in non-HIV-infected population identified unique molecular signatures so specific that just looking at the miRNA profile, a 100% correlation was made as to which tumors were infected with EBV[75]. Which types of EBV miRNA are expressed in HIV-HL vs. non-HIV HL and whether HIV effects the expression of different miRNAs in HL have never been assessed. **Because the clinical course and histology differ from classic HL and EBV-associated HL in non-HIV infected individuals, we speculate that HIV-associated Hodgkin Lymphoma has a different molecular signature.**

To this end, as a correlative study in this clinical trial, we will analyze the miRNA profiles of the paraffin-embedded tumor samples of the study participants. This analysis will be performed using high throughput sequencing to comprehensively define the miRNA expression, as described previously. As controls, reactive lymph nodes from HIV-infected and uninfected participants, as well as non-HIV HL samples that are EBV positive will be used.

We will also correlate miRNA expression with overall survival, tumor response to therapy, histologic subtype of HIV-HL, and HIV disease characteristics to identify miRNAs that could act as prognostic and diagnostic markers.

Please see Appendix VIII for a detailed description of specimens required, sample processing, and shipping.

10.3 Effects of AVD-Brentuximab Vedotin on T-cell Subsets *in vivo*

Brentuximab vedotin has the potential to destroy all cells that are CD30 positive as seen in the HRS cell. Heiser *et al.* investigated the distribution of CD30 expression across all T-cell subsets and demonstrated CD30 expression was identified mostly in the T-regulatory cells.[93] While these cells have many roles, one of their main functions is to suppress CD8 and CD4+ T-cell proliferation. When CD8+ and FOX-P3+ T-Regulatory cells were co-incubated in vitro, brentuximab vedotin challenge resulted in a decrease in T-regulatory T-cell number, and an increase in CD8+ T-cells number.[93] Preliminary data from AMC-085 identified that CD4+ T-cells as well as CD8+ T-cells increased about 1 month after AVD-BV treatment in nearly all subjects enrolled to date (unpublished data).

To see if this was a brentuximab vedotin effect, we compared data with 54 patients with HIV-associated Hodgkin Lymphoma treated with ABVD alone at County Hospital in Chicago (unpublished data). To exclude the possibility that uncontrolled HIV was a cause for a drop in the CD4+ T-cell counts in these subjects, patients with undetectable viral loads were identified. In this ABVD comparison group, 80% of the subjects had drops in CD4+ T-cell counts about 1-2 months post chemotherapy, the opposite of the effect seen in AMC 085. Additionally, when CD8+ T-cell counts were analyzed in subjects treated with ABVD, 100% had drops in CD8+ T-cell counts.

The fact that patients with **ABVD** had drops in CD8 and CD4+ T-cell counts while trial participants receiving **AVD**-BV had elevations suggests brentuximab vedotin is the causative agent of the elevation, possibly due to T-regulatory T-cell destruction. **The hypothesis of this correlative study is that brentuximab vedotin achieves T-regulatory T-cells destruction causing CD8 and CD4+ T-cell count elevation The purpose of this correlative study is to evaluate whether this is the mechanism seen *in vivo* in participants with HIV-associated cHL.**

To prove this mechanism, we will use cytokine analysis via multiplex, flow cytometry and CyTOF (cytometry by time of flight) to confirm which cytokines and T-cell subsets are altered over time. Cytokine analyses will be performed on all participants enrolled at Dr. Otto Martinez-Maza's laboratory (AMC Core Biomarkers Laboratory), on existing samples for cytokine analysis. The T-cell subset and cytokine assays performed by CyTOF and flow cytometry will be performed by Dr. Robert Baiocchi's laboratory (Ohio State University AMC site) for up to 10 participants. The cells required will be aliquots from blood samples already collected from participants in the optional HIV viral reservoir studies in Appendix XII, who have also consented for the additional use of his/her specimens in future research by the ACSR. **Please see Appendix XIV for a detailed description of sample processing, time points that need to be assayed, shipping, and the assays involved.**

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

This multicenter, Phase I/II open label study will determine the safety and tolerability of participants with stage II/IV HIV-associated Hodgkin Lymphoma and evaluate the treatment effect of AVD in addition to brentuximab vedotin (SGN-35). The primary objective of the Phase I portion of the study is to identify the maximal tolerated doses of brentuximab vedotin when combined with the AVD chemotherapy regimen in HIV participants with advanced stage Hodgkin lymphoma. The primary objective of the Phase II portion of the study is to establish an estimate of the two-year progression-free survival for participants using brentuximab vedotin plus AVD regimen with HIV-associated advanced stage Hodgkin lymphoma.

Secondary objectives include:

1. To evaluate toxicity of AVD and brentuximab vedotin with HAART.
2. To estimate the partial response (PR) rate, complete response (CR) rate, overall survival (OS), event free survival at 2 and 5 years.
3. To evaluate effect of AVD and brentuximab vedotin on CD4 and CD8 counts after cycle 1, 4, at the end of therapy, and every 3 months after treatment completion for one year.
4. To investigate the prognostic value of FDG-PET/CT scans at baseline, after cycle 2, and at treatment completion, with respect to 2-year progression free survival.
5. To evaluate HAART status at baseline and to correlate this with tumor response to therapy and OS and PFS.
6. To characterize the histologic subtypes in HIV-HL in the highly active antiretroviral therapy (HAART) era.
7. To assess the neurotoxicity of HAART in combination with AVD and brentuximab vedotin.
8. To evaluate effect of AVD and brentuximab vedotin on viral load after cycles 1, 4, at completion of therapy, and every 3 months after treatment completion for one year.
9. To perform pharmacokinetic and immunogenicity studies to determine drug levels during therapy (see Section 10.0 and Appendix IX).
10. To perform miRNA profile analysis on the HIV-HL tumor specimens and to correlate miRNA expression with OS, PFS, tumor response to therapy, histologic subtype of HIV-HL, and HIV disease characteristics (see Section 10.0 and Appendix VIII).
11. To perform tissue microarray analysis on HIV-HL tumor specimens and to correlate the markers studied with OS, PFS, and tumor response to therapy (see Section 10.0 and Appendix VIII).
12. To identify EBV associated tumor derived DNA in the plasma of study participants, and to correlate these levels during therapy with disease response and OS (see Section 10.0 and Appendix XI). This objective will only be performed in the Phase II portion of the study.
13. To identify cytokines in the plasma of participants during therapy, that can be used as tumor and prognostic markers. (see Section 10.0 and Appendix X). This objective will be done only in the Phase II portion of the study.

14. To assess latent and expressed HIV reservoirs before, during, and post chemotherapy. To understand how cytotoxic chemotherapeutic agents effect HIV expression (see Section 10.0 and Appendix XII).

The Phase I portion of the clinical trial is a de-escalation design evaluating 3 doses of brentuximab vedotin (1.2mg/kg, 0.9 mg/kg, and 0.6mg/kg) given every 2 weeks with AVD in a 28-day cycle. Three to six participants will be enrolled at dose level 0. If > 1 DLT are encountered, an additional three to six participants will be enrolled at the next lowest dose level. If no more than 1/6th of the participants at the 0 dose level encounter a DLT, this dose (1.2 mg/kg) will be used in the phase II portion. If dose de-escalation is required, we will follow the algorithm presented in Table 4-A in Section 4.1.1.

The primary objective of the Phase I portion of the study is to identify the maximal tolerated doses of brentuximab vedotin when combined with the AVD chemotherapy regimen in HIV participants with advanced stage Hodgkin lymphoma. No formal statistical hypothesis testing is planned for the primary analysis on the Phase I safety parameters; results will be presented descriptively. Continuous data will be summarized for each cohort using descriptive statistics (N, mean, median, standard deviation, minimum, maximum, geometric mean, and percentage coefficient of variation [CV]). Categorical data will be summarized for each cohort using frequency tables (frequencies and percents).

The primary endpoint of the phase II portion will estimate the two-year progression-free survival for AVD-brentuximab vedotin which will be done using a one sample nonparametric survival analysis.

11.2 Sample Size/Accrual Rate

No formal statistical hypothesis testing is planned for the primary analysis of the Phase I portion of the study. In the Phase II portion of the study, 51 participants will be enrolled to estimate the 2-year progression free survival. Sample size calculation is based on providing an estimate of the PFS with a 95% confidence interval ±10% under the hypothesis that 2-year PFS is 85%.

If there are no DLTs in the Phase 1 portion of the study, and if 100% of the Phase 1 participants are treated identically to those in the Phase 2, data from the Phase 1 and 2 portions can be combined to complete the phase 2 portion of the study.

The primary endpoint of the phase II portion will be to estimate the two-year progression-free survival for AVD-brentuximab vedotin which will be done using Kaplan-Meier estimates and corresponding 95% confidence intervals based on standard errors using Greenwood's formula.

11.3 Stratification Factors

No stratification is planned for this study.

11.4 Analysis of Secondary Endpoints

Descriptive summaries and exploratory analyses for secondary objectives will be conducted. Significance for comparisons will be at the $p<0.05$ level.

Secondary objectives include:

1. To evaluate toxicity of AVD and brentuximab vedotin with HAART.

2. To estimate the partial response rate, complete response rate, overall survival (OS), event free survival at 2 and 5 years. To evaluate effect of AVD and brentuximab vedotin on CD4 and CD8 counts after 2 cycles, 6 cycles, and every 3 months after treatment completion for one year.
3. To evaluate effect of AVD and brentuximab vedotin on viral load after 2 cycles, 6 cycles, and every 3 months after treatment completion for one year
4. To investigate the prognostic value of FDG-PET scans at baseline and after 2 cycles in participant with HIV and HL with respect to 2 year progression free survival.
5. To evaluate HAART status at baseline for difference in outcome.
6. The characterization of histologic subtypes in HIV-HL in the HAART era.
7. To assess additional neurotoxicity in combination with HAART and AVD and brentuximab vedotin.

The frequency of AEs and their severity will be tabulated to evaluate tolerance of AVD and brentuximab vedotin with HAART. Further, binomial probabilities and their 95% confidence intervals will be used to estimate the response rates (i.e., partial response rate, complete response rate, overall response rate) and event free survival at 2 and 5 years of AVD and brentuximab vedotin for a treatment of participants with stage III/IV HIV-associated Hodgkin Lymphoma.

Repeated measures analysis of variance (ANOVA) models will be used to evaluate the effect of AVD and brentuximab vedotin on CD4 counts, CD8 counts and viral load after 1, 4, and 6 cycles, and every 3 months after treatment completion for one year.

Log-rank analysis will be used to investigate the prognostic value of FDG-PET scans at baseline, after 2 cycles and post-therapy in participants with HIV and HL with respect to progression free survival.

After cycle 2 and post-therapy, progression-free survival will be estimated for participants whose FDG-PET findings were negative and those whose findings were positive using Kaplan-Meier estimates and corresponding 95% confidence intervals based on standard errors using Greenwood's formula. Positive predictive value after 2 cycles and post-therapy will be estimated as the proportion of PET-positive participants who progress or die before two years; negative predictive value after 2 cycles and post-therapy will be estimated as the proportion of PET-negative participants who are progression-free and alive at two years. Sensitivity of FDG-PET at cycle 2 and post-therapy will be estimated as the proportion of participants who progressed or died prior to year 2 whose FDG-PET was positive. Specificity of FDG-PET at cycle 2 and post-therapy will be estimated as the proportion of participants who are alive and progress-free at 2 years whose FDG-PET was positive. Exact two-sided 95% confidence intervals will be used for all estimates.

Log-rank analysis will be used to evaluate HAART status at baseline for difference in outcome in terms of overall survival and progression free survival. The frequency and proportion of different histologic subtypes will be calculated.

The frequency of neurotoxicity in participants taking AVD and brentuximab vedotin in combination with/without HAART will be tabulated. A binomial test of proportions will be used to test the difference in additional toxicity between those participants taking AVD

and brentuximab vedotin on HAART vs. those participants not on HAART.

12.0 ROLE OF DATA MANAGEMENT

12.1 CRF Instructions

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

12.2 Data Quality

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

12.3 Data Monitoring

This study will be monitored in compliance with AMC policies and by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and participant-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

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

13.0 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master data files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

13.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Appendix VII). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the participants. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the participants (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

13.3 IRB Approval and Informed Consent

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

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

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

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

as required by regulation. A copy of the consent form will be given to the participant to keep.

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

13.4 Research Authorization

Each institution should insert the appropriate research authorization sections into the informed consent document.

13.5 Participant Confidentiality

In order to maintain participant privacy, all data capture records, drug accountability records, participant number. The Investigator will grant monitor(s) and auditor(s) from Seattle Genetics, AMC or the NCI and regulatory authorities (FDA) access to the participant's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The participant's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.6 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authorities. Changes to the protocol will require approval from CTEP and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The Investigator will submit all protocol modifications to Seattle Genetics and the regulatory authorities in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

13.7 Changes to the Protocol

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

13.8 On-site Audits

Regulatory authorities, the IEC/IRB, the AMC ODMC, and/or Seattle Genetics clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

13.9 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 assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

Table 13-A: Accrual Targets

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	1	+	2	=	3
Not Hispanic or Latino	3	+	45	=	48
Ethnic Category: Total of all participants	4	+	47	=	51
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	1	+	1	=	2
Black or African American	1	+	10	=	11
Native Hawaiian or other Pacific Islander	0	+	1	=	1
White	2	+	35	=	37
Racial Category: Total of all participants	4	+	47	=	51
	(A1 = A2)		(B1 = B2)		(C1 = C2)

14.0 REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed. 4th). Lyon, France: IARC Press; 2008.
2. Hodgkin T (1832). On some morbid experiences of the absorbent glands and spleen. Med Chir Trans 17: 69–97.
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008: 57; 43-66.
4. Kuppers R, Rajewsky K, Zhao M et al. Hodgkin disease: Hodgkin and Reed-Sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from B cells at various stages of development. Proc Natl Acad Sci USA 1994; 91:10962.
5. Hummel M, Ziemann K, Lammert H et al. Hodgkin's disease with monoclonal and polyclonal populations of Reed-Sternberg cells. N Engl J Med 1995; 333:901.
6. Kanzler H, Küppers R, Hansmann M-L et al. Hodgkin and Reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. J Exp Med 1996; 184:1495
7. Marafioti T, Hummel M, Anagnostopoulos I et al. Origen of nodular lymphocyte-predominant Hodgkin's disease from a clonal expansion of highly mutated germinal-center B cells. N Engl J Med 1997; 337:459.
8. Carbone A, Gloghini A, Gaidano G et al. Expression status of BCL-6 and syndecan-1 identifies distinct histogenetic subtypes of Hodgkin's disease. Blood 1998; 92:2220.
9. Shiels MS, Pfeiffer RM, Gail MH et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011; 103(9):753-62.
10. Patel, P., D. L. Hanson, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med 2008; 148: 728-36.
11. Levine A. HIV-associated Hodgkin's disease. Hematol Oncol Clin North Am 1996; 10; 1135-48.
12. Skinnider BF, Mak TW. The role of cytokines in classical Hodgkin lymphoma. Blood. 2002; 99:4283-4297.
13. Levine AM. Hodgkin lymphoma: to the HAART of the matter. Blood 2006; 108; 3630.
14. Biggar RJ, Jaffe ES, Goedert JJ et al. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood 2006; 108: 3786-91.
15. Spina M, Carbone A, Gloghini A, Serraino D, Berretta M, Tirelli U. Hodgkin's Disease in Patients with HIV Infection. Adv Hematol. 2011;!doi:10.1155/2011/402682.
16. Hasenclever D. and Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998; 19:1506-14.
17. Ambinder RF. Epstein-Barr virus and Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2007:204-9.
18. Keegan TH, Glaser SL, and Clarke CA et al. Epstein-Barr virus as a marker of survival after Hodgkin's lymphoma: a population-based study. J Clin Oncol. 2005; 23: 7604-1.
19. Carbone A, Gloghini A, Larocca LM et al. Human immunodeficiency virus-associated Hodgkin's disease derives from post-germinal center B cells. Blood. 1999; 93: 2319-26.

20. Powles T and Bower M. HIV-associated Hodgkin's Disease. Int J STD AIDS 2000; 11, 492-4.
21. Gerard L, Galicier L, Boulanger E, et.al Improved survival in HIV-related Hodgkin's lymphoma since the introduction of highly active antiretroviral therapy. AIDS. 2003 Jan 3; 17(1):81-7.
22. Hentrich M, Maretta L, Chow KU et al. Highly active antiretroviral therapy (HAART) improves survival in HIV-associated Hodgkin's disease: results of a multicenter study. Ann Oncol. 2006; 17: 914-9.
23. Spina M, Gabarre J, Rossi G et al. Stanford V regimen and concomitant HAART in 59 patients with Hodgkin disease and HIV infection. Blood. 2002; 100:1984-8.
24. Xicoy B, Ribera JM et al. Results of treatment with doxorubicin, bleomycin, vinblastine and dacarbazine and highly active antiretroviral therapy in advanced stage, human immunodeficiency virus- related Hodgkin's Lymphoma. Haematologica 2007; 92: 191-198.
25. Spina M, Rossi G, Antinori A et al. VEBEP regimen and highly active antiretroviral therapy (HAART) in patients with HD and HIV Infection (HD-HIV). Blood 2005; 106:100a.
26. Hartmann P, Rehwald U, Salzberger B et al. BEACOPP therapeutic regimen for patients with Hodgkin's disease and HIV infection. Ann Oncol. 2003; 14:1562-9.
27. Levine A M, Li P, et al. Chemotherapy consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine with granulocyte-colony-stimulating factor in HIV-infected patients with newly diagnosed Hodgkin's disease: a prospective, multi-institutional AIDS clinical trials group study (ACTG 149). J Acquir Immune Defic Syndr. 2000; 24(5): 444-50.
28. Errante D, Gabarre J, Ridolfo AL et al. Hodgkin's disease in 35 patients with HIV infection: an experience with epirubicin, bleomycin, vinblastine and prednisone chemotherapy in combination with antiretroviral therapy and primary use of G-CSF. Ann Oncol. 1999; 10:189-95.
29. Errante D, Tirelli U, Gastaldi R et al. Combined antineoplastic and antiretroviral therapy for patients with Hodgkin's disease and human immunodeficiency virus infection: a prospective study of 17 patients. Cancer 1994; 73: 437-444.
30. Gastaldi R, Martino P, Gentile G et al. Hodgkin's disease in HIV-infected patients: report of eight cases usefully treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) plus granulocyte colony-stimulating factor. Ann. of Oncol 2002; 13: 1158-1160.
31. Tirelli U. Errante D, Vaccher E et al. Hodgkin's disease in 92 patients with HIV infection: The Italian experience. Ann Oncol 1992; 3: S69-72.
32. Andrieu JM, Roithmann S, Tourani JM et al. Hodgkin's disease during HIV-I infection: The French registry experience. Ann Oncol 1993; 4: 635-41.
33. Berenguer J, Miralles P et al. Characteristics and outcome of AIDS-related Hodgkin lymphoma before and after the introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2008; 47: 422-8.
34. Francisco JA, Cerveny CG, Meyer DL, et al. cAC10-vcMMAE, an anti-CD30–monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood 2003; 102: 1458-1465.
35. Wahl AF, Klussman K, Thompson JD, Chen JH, Francisco LV, Risdon G, Chace DF, Siegall CB and Francisco JA (2002). The anti-CD30 monoclonal antibody SGN-30 promotes

growth arrest and DNA fragmentation in vitro and affects antitumor activity in models of Hodgkin's disease. Cancer Res 62: 3736-42.

36. Younes A, Forero-Torres A, Bartlett NL, et al. Multiple complete responses in a phase 1 dose-escalation study of the antibody-drug conjugate SGN-35 in patients with relapsed or refractory CD30-positive lymphomas. Blood (ASH Annual Meeting Abstracts) 2008. 112:1006.
37. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010; 363: 1812-21
38. Chen, Gopal A, Smith SE, Ansell SM, Rosenblatt JD, Klasa R, Connors JM, Engert A, Larsen EK, Kennedy D, Sievers E and Younes A**.** Results of a Pivotal Phase 2 Study of brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 283.
39. Advani RH, Shustov AR, Brice P, et al. Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma: A Phase 2 Study Update. American Society of Hematology 2011. Abstract 443.
40. Forero-Torres A, Berryman RB, Advani RH et al. Prolonged Treatment with brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL). American Society of Hematology 2011. Abstract 3711.
41. Younes A, Connors J, Park S, et al. Frontline Therapy with brentuximab Vedotin Combined with ABVD or AVD in Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma. American Society of Hematology 2011. Abstract 955.
42. Hoskin PJ, Lowry L, Horwich A, et al. Randomized Comparison of the Stanford V Regimen and ABVD in the Treatment of Advanced Hodgkin’s Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2011 Nov 10; 29(32):4227-33.
43. Ngeow J, Tan IB, Kanesvaran R, Tan HC, Tao M, Quek R, Lim ST. Prognostic impact of bleomycin-induced pneumonitis on the outcome of Hodgkin's lymphoma. Ann Hematol. 2011 Jan; 90(1):67-72.
44. Pizzolo G, Vinante F, Morosato L, Nadali G, Chilosi M, Gandini, G, Sinicco A, Raiteri R, Semenzato G, Stein H, and Perona G. High serum level of the soluble form of CD30 molecule in the early phase of HIV-1 infection as an independent predictor of progression to AIDS. AIDS 1994. 8: 741–745.
45. Rizzardi GP, Barcellini W, Tambussi G, Lillo F, Malnati M, Perrin L, and Lazzarin A. Plasma levels of soluble CD30, tumour necrosis factor (TNF)- § and TNF receptors during primary HIV-1 infection: correlation with HIV-1 RNA and the clinical outcome. AIDS 1996. 10:45-50.
46. Pizzolo, G., Vinante, F., Nadali, G., Krampera, M., Morosato, L., Chilosi, M., Raiteri, R. and Sinicco, A., High serum level of soluble CD30 in acute primary HIV-1 infection. Clin. Exp. Immunol. 1997. 108: 251–253.
47. Maggi E, Annunziato F, Biagiotti R, Giudizi MG, Ravina A, Almerigogna F, Boiani N, Alderson M, Romagnani S. Activation of HIV expression by CD30 triggering in CD4 + T cells from HIV infected individuals. Immunity 1995; 3:251–255.

48. Brew BJ, Davies NW, Cinque P, Clifford DB and Nath A. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. Nat Rev Neurol 2010; 6: 667-79.
49. Koralnik IJ, Schellingerhout D, Frosch MP. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 14-2004. A 66-year-old man with progressive neurologic deficits. N Engl J Med. 2004; 350(18):1882.
50. Cinque P, Koralnik IJ, Gerevini S, Miro JM, and Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. Lancet Infect Dis. 2009 Oct; 9(10):625-36.
51. Engsig FN, Hansen AB, Omland LH et al. Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIV-infected patients during the highly active antiretroviral therapy era: a nationwide cohort study. J Infect Dis. 2009; 199(1):77.
52. Khanna N, Elzi L, Mueller NJ et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. Clin Infect Dis. 2009 May 15; 48(10):1459-66.
53. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. Annu Rev Med. 2010; 61:35-47.
54. FDA Drug Safety Communication, New Boxed Warning and Contraindication for Adcetris (brentuximab vedotin) 1/13/2012. http://www.fda.gov/Drugs/DrugSafety/ucm287668.htm.
55. Antoniou T and Tseng AL. Interactions Between Antiretrovirals and Antineoplastic Drugs. Clin Pharmacokinet 2005; 44: 111-145.
56. Rubinstein PG, Braik T, Jain S et al. Ritonavir Based Highly Active Antiretroviral Therapy (HAART) Correlates with Early Neurotoxicity When Combined with ABVD Treated HIV Associated Hodgkin Lymphoma but Not Non-Hodgkin Lymphoma. A Retrospective Study. American Society of Hematology 2010. Abstract # 2807.
57. Sandu S, Gupta S, Itokazu G et al. Suspension of Ritonavir and Zidovudine Prevents Adverse Events During the Treatment of HIV Associated Hodgkin Lymphoma. ASCO 2012, abstract #8085.
58. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J. Clin. Oncol. 25:3746-52, 2007.
59. Hutchings M, Loft A, Hansen M, et. al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma Blood, 1 January 2006, Vol. 107, No. 1, pp. 52-59.
60. Wedgwood A.R, Fanale A, Fayad L.E, et al. Rituximab + ABVD Improves Event-Free Survival (EFS) in Patients with Classical Hodgkin Lymphoma in All International Prognostic Score (IPS) Groups and in Patients Who Have PET Positive Disease after 2–3 Cycles of Therapy. Blood (ASH Annual Meeting Abstracts) 2007 110: Abstract 215.
61. Brust D, Polis M, Davey R, et al. Fluorodeoxyglucose imaging in healthy subjects with HIV infection: impact of disease stage and therapy on pattern of nodal activation. AIDS 2006, Vol 20 No 7.

62. Kelley T, Pohlman B, Elson P, et al. The ratio of FOXP3+ regulatory T cells to granzyme B+ cytotoxic T/NK cells predicts prognosis in classical Hodgkin lymphoma and is independent of bcl-2 and MAL expression. Am J Clin Pathol 128:958-65, 2007.
63. Epeldegui M, Lee JY, Martinez AC, Widney DP, Magpantay L, Regidor D, Mitsuyasu R, Sparano JA, Ambinder RF and Martínez-Maza O. Serum levels of several molecules associated with B cell activation and inflammation are elevated in AIDS-NHL and predict response to treatment. In preparation.
64. Epeldegui, M. D. P. Widney, A. C. Martínez, D. Regidor, L. Magpantay, R. Mitsuyasu, J. A. Sparano, J. Y. Lee, R. F. Ambinder, O. Martínez-Maza. 2011. Serum levels of several molecules that are associated with B cell activation and inflammation are elevated in AIDS-associated non-Hodgkin's lymphoma (AIDS-NHL) and predict response to treatment. International Conference on Malignancies in AIDS and Opportunistic Infections (ICAMOI). Abstract. Bethesda, MD.
65. Levin, L., E. C. Breen, B. Birmann, J. J. Kasperzyk, L. Magpantay, R. F. Ambinder, N. Mueller and O. Martínez-Maza. Elevated serum levels of soluble CD30, IL-6 and IL-10 precede the diagnosis of Hodgkin lymphoma. In preparation.
66. Levin, L., E. C. Breen, C. Kitchen, D. Widney, B. Kim B, A. Marrogi, R. Krampf, L. Magpantay, and O. Martínez-Maza. 2010. Elevated Serum Levels of CXCL13 Precede the Diagnosis of B Cell Non Hodgkin Lymphoma (NHL). AACR Special Conference on The Future of Molecular Epidemiology: New Tools, Biomarkers, and Opportunities. Abstract. Miami, FL.
67. Yeung ML, Bennasser Y, LE SY, Jeang KT. siRNA, miRNA and HIV: promises and challenges. Cell Res. 2005; 15(11-12):935-46.
68. Qi P, Han JX, Lu YQ, Wang C, Bu FF. Virus-encoded microRNAs: future therapeutic targets? Cell Mol Immunol. 2006; 3(6):411-9.
69. Visone R, Croce CM. MiRNAs and Cancer. Am J Pathol. 2009; 174(4):1131-8.
70. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009; 136 (2): 215–33.
71. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004; 116 (2): 281–97.
72. Bentwich I, Avniel A, Karov Y et al. Identification of hundreds of conserved and nonconserved human microRNAs. Nat. Genet. 2005; 37 (7): 766–70.
73. Homo sapiens miRNAs in the miRBase at Manchester University.
74. Lu J, Getz G, Miska EA, et al. MicroRNA expression profiles classify human cancers. Nature 2005; 435:834-838.
75. Navarro A, Gaya A, and Martinez A et. al. MicroRNA expression profiling in classic Hodgkin lymphoma. Blood 2008; 111: 2825-2832
76. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009 Sep; 50(3):1-36.
77. Boleti E and Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. Ann Oncol 18:376-80, 2007.
78. Evens A, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 137:545-52, 2007.

79. Duggan DB, Petroni GR, Johnson JL, Glick JH, Fisher RI, Connors JM, Canellos GP and Peterson BA. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease. Report of an intergroup trial. J Clin Oncol; 2003 21: 607-14.
80. Martin WG, Ristow KM, Habermann TM, Colgan JP, Witzig TE and Ansell SM. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol; 2005 23: 7614-20.
81. Hoskin PJ, Lowry L, Horwich A, Jack A, Mead B, Hancock BW, Smith P, Qian W, Patrick P, Popova B, Pettiti A, Cunningham D, Pettengell R, Sweetenham J, Linch D and Johnson PW. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol 2009; 27: 5390-6.
82. Glaser, S.L., et al., Population-based patterns of human immunodeficiency virus-related Hodgkin lymphoma in the Greater San Francisco Bay Area, 1988-1998. Cancer, 2003. 98(2): p. 300-9.
83. Keegan, T.H., et al., Epstein-Barr virus as a marker of survival after Hodgkin's lymphoma: a population-based study. J Clin Oncol, 2005. 23(30): p. 7604-13.
84. Hohaus, S., et al., The viral load of Epstein-Barr virus (EBV) DNA in peripheral blood predicts for biological and clinical characteristics in Hodgkin lymphoma. Clinical Cancer Research: an official journal of the American Association for Cancer Research, 2011. 17(9): p. 2885-92.
85. Gandhi, M.K., et al., Plasma Epstein-Barr virus (EBV) DNA is a biomarker for EBV-positive Hodgkin's lymphoma. Clinical cancer research: an official journal of the American Association for Cancer Research, 2006. 12(2): p. 460-4.
86. Kanakry, J.A., Plasma viral DNA as a marker of tumor response in EBV(+) Hodgkin lymphoma in a phase III study (E2496). Journal of clinical oncology, 2012. 30.
87. Chan, K.C., et al., Molecular characterization of circulating EBV DNA in the plasma of nasopharyngeal carcinoma and lymphoma patients. Cancer research, 2003. 63(9): p. 2028-32.
88. Lin, L., et al., Effects of chemotherapy in AIDS-associated non-Hodgkin's lymphoma on Kaposi's sarcoma herpesvirus DNA in blood. J Clin Oncol, 2009. 27(15): p. 2496-502.
89. Shamay, M., et al., CpG methylation as a tool to characterize cell-free Kaposi sarcoma herpesvirus DNA. J Infect Dis, 2012. 205(7): p. 1095-9.
90. Kasamon, Y.L., et al., Multicenter phase II study of rituximab-ABVD in classic Hodgkin lymphoma (cHL). ASCO Meeting Abstracts, 2011. 29(15_suppl): p. 8039.
91. Meignan M, Barrington S, Itti E, Gallamini A, Haioun C, Polliack A. Report on the 4th International Workshop on Positron Emission Tomography in Lymphoma held in Menton, France, 3-5 October 2012. Leuk Lymphoma. 2013 Jun 14. [Epub ahead of print]
92. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma. 2009 Aug; 50(8):1257-60.

93. Heiser RA, Grogan BM, Manlove LS, Gardai SJ. Abstract 1789: CD30+T regulatory cells, but not CD30+CD8 T cells, are impaired following brentuximab vedotin treatment in vitro and in vivo. Cancer Res July 1 2018 (78) (13 Supplement) 1789.

APPENDIX I: SCHEDULE OF EVALUATIONS

Evaluations	Eligibility (Baseline)[a]	Cycle 1-6 Day 1	Cycle 1-6 Day 15	Cycle 2 Day 1	Cycle 2 Day 22-28	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Post-Treatment	Early Treatment Discontinuation[j]
Informed consent	X									
ACSR consent and donation (optional)	X									
Medical history and physical examination	X	X[g]							X[b]	X
FDG-PET/CT or FDG-PET + CT	X[o]				X				X[r]	
CT scan with oral/IV contrast	X[n]								X[i]	
MRI of brain with and without IV gadolinium contrast	X									
MUGA or echocardiogram	X									
FACT-GOG-neurotoxicity questionnaire		X[g]								
Bone marrow biopsy	X[c]								X[d]	
Central pathology review	X									
Paraffin Cores for miRNA and Tissue Microarray Analysis	X									
CBC with diff	X[e]	X[h]	X[h]						X[b]	X
Sedimentation rate	X[e]									
Serum chemistries: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, phosphorus), glucose, BUN, creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT	X[e]	X[g]	X[g]						X[b]	X
CD4/CD8 cell count	X			X[g]				X[g]	X[q]	X[k]
HIV-1 RNA viral load	X[p]			X[g]				X[g]	X[q]	X[k]
Hepatitis C antibody, Hepatitis B core antibody, Hepatitis B surface antigen (HBsAg), and Hepatitis B surface antibody	X									
Serum or urine pregnancy test	X[f]									

Evaluations	Eligibility (Baseline)[a]	Cycle 1-6 Day 1	Cycle 1-6 Day 15	Cycle 2 Day 1	Cycle 2 Day 22-28	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Post-Treatment	Early Treatment Discontinuation[j]
Pharmacokinetic studies (select Phase II participants only)		X[l]	X[l]						X[l]	X[l]
EBV/Immunogenicity Studies (Phase II only)	X[m]	X[m]							X[m]	X[m]
HIV Reservoir Studies	X[s]					X[t]			X[u]	X[k]

A. Screening to be completed within 6 weeks prior to participant registration unless otherwise specified.
B. Post-treatment evaluation to occur within 6-8 weeks of the last treatment dose and then every 3 months thereafter (+/- 7 days) for 2 years; every 6 (+/- 7 days) months for the third through fifth years unless otherwise specified.
C. Does not have to be repeated if bone marrow involvement by lymphoma already documented after bone marrow biopsy more than 6 weeks prior to registration.
D. Only need to perform to confirm CR is positive at baseline (only once, within 8 weeks of last treatment dose).
E. Must be completed within 2 weeks prior to participant registration.
F. To be performed within 7 days prior to Cycle 1, Day 1.
G. To be performed within 48 hours prior to or on first day of each cycle, where required for a given visit.
H. To be performed within 48 hours of day 1 and 15 of every cycle. Results must be known prior to treatment.
I. Every 6 months after end of treatment for 5 years, to begin 6 months from the post treatment FDG-PET/CT scan, obtained 6-8 weeks post the final chemotherapy dose
J. To be performed within 1 month after treatment discontinuation.
K. Do not repeat if done within 1 month from removal from treatment.
L. In select Phase II participants only. See **Section 10.1** and **Appendix IX** for details on time points and sample processing.
M. In Phase II participants only. After study entry, samples will be collected at the end of Cycles 1 and 3, treatment discontinuation, and at 3, 6, and 12 months post treatment discontinuation. See **Section 10.1** and **Appendix XI** for details on time points and sample processing.
N. To be done if the CT portion of the PET/CT is without contrast.
O. To be performed no more than 28 days before enrollment.
P. To be performed within 21 days prior to Cycle 1, Day 1.
Q. To be performed at 6-8 weeks following protocol therapy completion and every 3 months thereafter for one year.
R. To be done once at the completion of the study, at the 6-8 week follow up after the final treatment dose at Cycle 6 Day 15.
S. To be done, 1 week before cycle 1 day 1 (+/- 3 days) and again 24 hours prior or on the day of cycle 1 day 1. Only for participants who are found to have undetectable plasma HIV-1 RNA by the standard assay performed at the clinical site within 21 days of C1 Day 1.
T. To be done, 48 hours prior to or on the first day of Cycle 3 and /or at the Early Treatment Discontinuation Visit if indicated.
U. To be done within 6-8 weeks following the last cycle and at the 12 months follow up visit.
V. Cytokine studies required of all participants (**Appendix X**). T-cell subsets required for consented participants per Appendix XIV (no additional samples collected beyond those required for HIV viral reservoirs per **Appendix XII**).

APPENDIX II: COLLABORATIVE RESEARCH AGREEMENT

The agent, brentuximab vedotin, supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between Seattle Genetics (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator"

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a participant or participant's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

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

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

   Email: ncicteppubs@mail.nih.gov

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

APPENDIX III: PERFORMANCE STATUS SCALES

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

APPENDIX IV: FACT-GOG-NEUROTOXICITY QUESTIONNAIRE V4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days. **ADDITIONAL CONCERNS**	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands…….	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

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

A. GENERAL

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

NOTE: Specimens MUST BE SHIPPED **Monday** through **Thursday** as an OVERNIGHT PRIORITY shipment. Specimens are **NOT ACCEPTED ON SATURDAYS, OR SUNDAYS** in the GWU/ACSR Lab. When sending to the ACSR, please be certain to create a shipment, assign specimens, and send the shipment in Global Trace prior to shipping the specimens to the ACSR. Include the FedEx Tracking number in Global Trace shipment information.

B. SPECIMEN PREPARATION, PACKAGING, AND SHIPMENT

Blood Specimens

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

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

Specimen Shipment

1. Seal the tops of the two 8.5 cc yellow tops with parafilm.
2. Place the two sealed tubes into bubble wrap (provided in STP-210 kit).
3. Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
4. Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and “self-seal.”
5. Place poly-bag containing tubes into the white TYVEK bag and seal.
6. Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Include a shipment manifest form Global Trace. Then seal the cardboard shipper with clear packing/shipping tape.
7. Affix the FED-EX airbill on blank side of the shipper making sure that it is marked “FED-EX PRIORITY OVERNIGHT.”

8. Mark “OTHER” in the airbill under “Packaging.” Please use the FedEx number provided on the AMC members’ only website.
9. Under airbill section “Special Handling,” indicate “YES-SHIPPERS DECLARATION NOT REQUIRED.”
10. Place “From/To” information onto areas provided on the shipper.

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

    Dr. Sylvia Silver
    George Washington University Medical Center
    2300 I St, NW
    Room 118
    Washington, DC 20037
    Tel: (202) 994-2945
    Fax: (202) 994-5056
    Email: ssilver@gwu.edu
    amc-bio@emmes.com
11. Make certain that shipper is already either pre-labeled with the “UN#3373” stamp, or make a paper label with “UN#3373” and affix it to the shipper.
12. Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in mL and affix to the shipper.
13. Affix airbill to shipper so that the ‘UN’ and ‘VOLUME’ labels are visible.
14. RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
15. Place the box in the FedEx pickup area at your site or call to request a package pickup.

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

INSTRUCTIONS FOR BLOOD SPECIMENS COLLECTED ON THURSDAY OR FRIDAY:

Preparation of Plasma and Mononuclear Cells

It is preferable that separation occurs as soon as possible. If necessary, whole blood in ACD (yellow top tubes) can be held at room temperature for no more than 24 hours. Plasma and PBMC should be separated according to the AMC Biorepository’s SOP on Separation of Plasma and Mononuclear Cells, available on the AMC Operations web site.

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

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

Preparation of Tissue Samples

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

Tissue specimens for donation may be batched for shipping after storage in -80ºC freezer. Allowable shipment days are Monday through Thursday. Shipping frozen tissue requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

TISSUE specimens should be shipped by overnight express to:

Dr. Sylvia Silver
George Washington University Medical Center
2300 I St, NW
Room 118
Washington, DC 20037
Tel: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@gwu.edu
amc-bio@emmes.com

C. 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.

APPENDIX VI: ACSR INFORMED CONSENT

INFORMED CONSENT FORM
RESEARCH STUDY
AIDS AND CANCER SPECIMEN RESOURCE (ACSR)

A. INTRODUCTION

You are being asked to donate blood and/or tissue for research. Before you decide to donate to this research project you need to understand the risks and benefits. This consent form provides information about the research project. The medical team will explain it to you and answer questions. If you agree to donate samples you will be asked to sign this consent form. This is known as informed consent.

Your decision is entirely voluntary. You are free to choose if you want to donate or not.

B. PURPOSE AND BACKGROUND

The National Cancer Institute (NCI) has set up the AIDS and Cancer Specimen Resource (ACSR). The ACSR collects, stores, and gives out human biological specimens (biospecimens) from persons who have HIV-related medical conditions, including HIV-related cancers. Scientists use these biospecimens for research purposes only. Scientists use the biospecimens to study cancers and other diseases associated with HIV disease. They hope to better understand the causes of these diseases and to develop better treatments. If you agree to take part, we will ask you to provide a blood sample and to donate some leftover tissue biopsy material to the ACSR.

Why is this being done?

The ACSR collects and stores biospecimens from people with and without HIV-related diseases and cancers. The ACSR makes the specimens available to researchers for use in research studies. These studies aim to increase our understanding of biological, molecular, and genetic factors that cause or increase risk for HIV-related diseases and cancers. The information may help to identify those who are at increased risk and those who may benefit from targeted treatment and screening. In turn, this could reduce the development of these diseases or improve the outcomes for patients with HIV diseases.

Currently, scientists are working to identify where cancer-causing genetic changes occur, if you agree we would like to make available for future studies the genetic material from your cancer tissue and compare it to the material from your normal tissue (blood) to try to find the differences that exist. From these results, it may be possible to identify many of the changes that are associated with diseases such as cancers. It may also help us to understand how patients respond to treatment. With such knowledge, treatments could potentially become more tailored to a patient's unique genetic make-up and/or to the genetic markers of the tumors.

C. PROCEDURES

If you agree to donate biospecimens to the ACSR, the following will happen:

1. The medical team will draw about 2 tablespoons of blood to give to the ACSR (this takes about 10 minutes). These samples may be studied to explore how genetic factors may be related to HIV-infection, AIDS and cancer. Please see the “Biologic studies” section of this consent form for more information.

2. If you agree, leftover tissue biopsy material will be donated to and stored by the ACSR. Your specimens may be used for a wide variety of tests. Scientists may study how genetic factors are related to HIV-infection, AIDS and cancer. However, we cannot tell you at this time what those tests will be. Please see the "Biologic studies" section of this consent form for more information.
3. Some of your clinical information will be released to the ACSR and entered into their database. The information given to the ACSR will not have any information which could personally identify you. We may give your specimens and certain clinical information to scientists or researchers who have approved research projects. The ACSR's independent research panel has approved these scientists/researchers to do research studies using specimens collected and stored by the ACSR.
4. Biologic Studies: A sample of your blood or tissue biopsy that is collected and is not required for routine diagnosis or treatment may be provided by the ACSR in the future for research studies. The samples may be studied in combination with hundreds or thousands of other samples to explore how genetic factors may be related to HIV-related diseases and cancer. The information might help doctors in the future to identify who will or will not benefit from treatment. The sample may be used to learn more about how HIV-related diseases and cancers develop. The sample may also lead to new tests or discoveries.
5. You will not need any extra study procedures to donate your samples to the ACSR. You are free to decide if you want to donate your samples to the ACSR. You are not required to donate your samples to take part in any AMC clinical trial. If you donate your samples to the ACSR, your blood or tissue sample may be used for future research that includes genetic testing. If genetic tests are done, the results will not be put in your health records or provided to your doctor. The information will be combined with the results of others to help determine the causes of HIV-related diseases and cancers. The research will not change the care you receive. You will not receive the results of genetic tests because the tests are done for research and not for diagnostic purposes.
6. Your sample will be labeled with a unique number. Your clinical information (for example your diagnosis, sex) may be given with your sample to researchers and added to a government health research database. Your name, address or other information that could identify you will not be given out. The ACSR will not be able to link your samples to you. Your blood or tissue sample will be stored until it is used up or destroyed. If you later decide you do not want your specimens and information to be used for future research, you may contact your AMC study coordinator. The coordinator can ask in writing that your sample be removed from research use and that any identifiable sample and information still in their possession be destroyed. However, if any research has already been done using some of your biospecimens, the data will be kept and analyzed as part of those studies. Please tell us whether we may use your samples for future research by initialing one of the lines at the end of this consent form.

D. RISKS/DISCOMFORTS

If you choose to participate:

- Blood Draw: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and, rarely, infection.
- Biopsy: The risks of biopsy include possible need for stitches depending on the size of the biopsy. There may be swelling, slight pain and a small amount of blood loss. There is also a chance of infection at the site of the biopsy.
- Confidentiality: The ACSR will receive study samples with code numbers. There will be no personal identifiers on the samples. Then the samples will be relabeled with a bar-code scan. Samples will be stored in groups of samples for future testing.

E. ALTERNATIVES

If you decide not to donate, it will not affect your participation in the AMC clinical study. You may decide not to join or withdraw your biospecimens from the ACSR at any time. However, if any research has already been done using portions of the biospecimens, the data will be kept and analyzed as part of those research studies.

F. POSSIBLE BENEFITS

There may be no direct benefit to you by allowing the ACSR to have portions of your biopsies and biological fluids. However, this research may help us learn more about how to prevent and treat HIV-associated cancers and diseases in the future.

G. COSTS

There will be no cost to you for donating your biospecimens to the ACSR.

H. PAYMENT FOR INJURY OR HARM

If you agree to donate specimens to the ACSR, there is a chance of injury or harm to you. If you require immediate medical care, you should go to an emergency room. Otherwise, the doctor in charge of the study will take care of you or help you get the care you need. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization. However, you are not giving up your right to seek to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

I. PRIVACY

To protect your privacy, the AMC does not keep identifying information that links study participants to specific samples. As a result, the AMC and ACSR will not be able to link the results from studies that use your samples back to you. Further, the ACSR has obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify the participant, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

Thus, information including genetic information, that may be obtained by studies that use your biospecimens cannot be linked to you, placed in, or linked to your medical record. However, some clinical and basic information obtained confidentially from the AMC will

be attached with these data. It is possible that findings may one day help, for example, people of the same race or sex as you. It also is possible that genetic factors might come to be associated with people who have HIV and cancer through these kinds of studies.

There is a new federal law called the Genetic Information Nondiscrimination Act (GINA). It makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This means that:

- Health insurance companies and group health plans may not request the genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use the genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

This new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

J. PAYMENT

You will not receive any payment for donating your samples to the ACSR. If any discovery or new treatment results from studies that use your specimens you will not receive any payment.

K. QUESTIONS

If you have any questions about this research study, you should contact the AMC Investigators, Dr. (_____) at ***(Phone Number)*** or, ***(_____)***, the study coordinator, at ***(Phone Number)***. If you have any questions about your rights as a as a donor and volunteer in a research project, you should call or write *(IRB Representative)*, in *(Institution)* Office of Human Research at (_____). *(IRB Representative)* is your representative and is not employed by the individuals conducting the study.

L. CONSENT

You have been given copies of this consent form and the Research Participant's Bill of Rights to keep.

Participation in research is voluntary. You have the right to decline to donate your biospecimens or to withdraw your biospecimens at any time without affecting your medical care. Your participation or nonparticipation will in no way affect the treatment you receive from any medical center now or in the future. You may choose to donate blood, biopsy tissue or both.

Please read each sentence below and indicate your choice by putting your initials next to "Yes" or "No."

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

   YES **NO**

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

   YES **NO**

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

   YES **NO**

4. **I agree to donate some of my tissue biopsy material that is not required for my treatment or diagnosis to the ACSR for future research that my include genetic testing to learn about, prevent, diagnose or treat HIV-related diseases and cancer.**

   YES **NO**

M. SIGNATURES

I understand that, where appropriate, the NCI may inspect the records held by the ACSR. I understand that my donation will remain confidential.

I am free to withdraw my consent and donation at any time after written notification to the AMC collecting site. The AMC site will immediately notify the ACSR to destroy any remaining identifiable specimens and information. However, if any research has already been done using my specimens, the data will be kept and analyzed as part of those research studies without prejudicing any involvement with the AMC.

I understand that signing this form, beyond giving consent, I am not waiving any legal rights that I might otherwise have, and I am releasing the investigator, the sponsor, the institution, or its agents from any legal liability for damages that they might otherwise have.

_____	_____
Donor	Date
_____	_____
Professional Obtaining Consent	Date
_____	_____
Witness	Date

APPENDIX VII: AMC DATA AND SAFETY MONITORING PLAN

(Version 6.0 • March 21, 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 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 preventative action plan. 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 VIII: CENTRAL PATHOLOGY REVIEW

Handling of Tissues:

Institutions should submit:

- A paraffin block

  OR

- 1 hematoxylin and eosin stained slide and 10 blank tissue sections at 5 microns for pathology review;
- 10 blank tissue sections at 20um for miRNA analysis; and
- 3 cores of the paraffin tissue block for TMA production and analysis.

The block or the sections and cores involved by lymphoma should be sent to the AMC Biorepository housed at George Washington University

(www.ncbi.nlm.nih.gov/pubmed/20949389).

AMC Biorepository:
Dr. Sylvia Silver
George Washington University Medical Center
2300 I St, NW
Room 118
Washington, DC 20037
Tel: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@gwu.edu
amc-bio@emmes.com

Specimen Labeling

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

- Protocol #: AMC-085
- 9-digit Participant ID #
- Visit #
- Date and time of specimen collection
- Specimen Type: “Tissue (tissue block),” “Tissue (unstained slide/section),” “H&E stained slide”
- Purpose: “Central Pathology Review”

The AMC Biorepository will send the following specimens in batch to the following address:

For Central Pathology Review

Each tissue block or 1 hematoxylin and eosin stained slide and 10 blank tissue sections at 5 microns per participant will be sent to Dr. Cesarman for pathology confirmation to the following address:

Julio Cordero
Research Coordinator
Laboratory of Hematopathology
Department of Pathology and Laboratory Medicine
Weill Cornell Medical College/The New York Presbyterian Hospital
Starr-702
525 East 68th Street
New York, New York 10065
Tel (212) 746-6357
Fax (212) 746-2009
juc9045@med.cornell.edu

For HIV-HL miRNA Analysis

3 cores/participant or 10 unstained sections at 20 µm each for miRNA analysis

Dirk P. Dittmer, Ph.D.
University of North Carolina at Chapel Hill
CB# 7290, 715 Mary Ellen Jones Bldg
Chapel Hill, NC 27599-7290
Phone (lab): (919) 966-7962
Fax: (919) 966-6153
Email: dirkdittmer@me.com

For TMA for HIV-HL Construction and Analysis

3 cores/participant on study for TMA construction and analysis.

Amy Chadburn, MD
Feinberg Pavilion 7-210
Northwestern Memorial Hospital
251 E. Huron
Chicago, IL 60611

Handling of Tissues:

The submitting Pathology Laboratory is also asked to provide the tissue block from representatively involved tissues; a total of 5-7 1.0 mm tissue cores from the block will be taken by the Immunopathology Laboratory for the miRNA studies and for inclusion in a tissue microarray, in addition to sections for diagnosis confirmation. The tissue block will be returned to the submitting laboratory one month after pathology review. If the submitting Pathology Department does not agree to submission of the block, we will accept, instead, 1 hematoxylin and eosin stained slide and 10 blank tissue sections at 5 microns for immunohistochemistry studies and diagnosis confirmation, ten unstained sections at 20 microns for the miRNA studies and three, 4mm punches for tissue micro array.

Specimens should be sent to Dr. Sylvia Silver (see above) within 30 days of enrollment. The handling procedures and shipping requirements are described below.

Specimen Accessioning:

Upon receipt from the AMC Biorepository, each specimen from an AMC participant will be identified by an Immunopathology Laboratory accession number which will be sequential with

the other the specimens, including clinical specimens, received in the laboratory. This will avoid delays in processing specimens belonging to the AMC. AMC will be stated under "Clinical Information," and therefore, can be easily identified and tracked by Dr. Cesarman and her team. A report will be issued by Dr. Cesarman or a member of her team within two weeks of receipt, with a description and preliminary diagnosis based on the microscopic review of H&E-stained sections, results of immunohistochemistry, and in situ hybridization for EBV (EBER). All the reports will be sent by FAX to the Operations Center as well as to the submitting physician if the information is provided, and hard copies to both will follow.

Tissue Microarrays and MiRNA Analysis:

Tissue microarrays will be constructed from formalin-fixed paraffin-embedded tissues from all the cases for which blocks are received. A Beecher tissue microarray instrument (Beecher instruments Inc., Sun Prairie, WI) will be used. Six 1.0 mm tissue cores will be obtained from representative lesional areas from each block. Controls will include a variety of benign and malignant lymphoid tissue appropriate for the studies to be done and will be provided from patients outside the trial. Once all the patients are recruited and all trial specimens are received, 3 cores will be made available for complete miRNA analysis and 3 for tissue microarray construction and analysis.

Pathology Review:

Specimens received from AMC will undergo histopathologic diagnosis and classification, immunostaining and in situ hybridization for EBV EBER. Pathologic evaluation will be performed by Dr. Cesarman's team; all interesting, atypical and unusual cases will also be reviewed by Dr. Knowles. Specifically, cases will be processed as follows:

1. Histopathology- Pathologist review of H&E stained slide with tumor classification.
2. Immunohistochemistry for HL will include the following antibodies as necessary for HL diagnosis CD45, CD20, CD3, CD30, CD15, and in situ hybridization for EBER.
3. If funding is available, Dr. Cesarman will immunostain for CD68, for the number of macrophages, as well as for Granzyme B and FoxP3, to determine the Granzyme B to FoxP3 ratio to determine if these values, which have been reported to be prognostic indicators in non-HIV associated cHL, also correlate with outcome in HIV-HL.

Record of Specimens:

The specimens will be tracked via GlobalTrace^{SM}, a component of the AMC AdvantageEDC^{SM} system. The GlobalTrace^{SM} shipment manifest must accompany all specimen shipments.

AMC BIOREPOSITORY DISTRIBUTION OF SAMPLES

Upon receipt from a site, slides for central pathology review will be sent to Dr. Cesarman. The AMC Biorepository will cut slides from the tissue block as required.

Upon a final decision on the participant's eligibility from the central pathology review, the AMC Biorepository will cut cores and slides as needed for tissue microarray and miRNA analysis for batch shipment at the end of the study. Materials for ineligible cases will be returned to the submitting site.

APPENDIX IX: PHARMACOKINETIC/IMMUNOGENICITY STUDIES

BACKGROUND AND PROCEDURES

Since pharmacokinetic interactions between HAART and brentuximab vedotin are unknown, these interactions will be carefully monitored. Drug levels will be determined by assaying brentuximab vedotin, total antibody, and the free drug MMAE concentration over time. The formation of anti-brentuximab vedotin antibodies will be also assessed at the time points summarized below in Table App IX-A. The pharmacokinetic data of participants from both groups (efavirenz and non-efavirenz- based HAART) for a total of 12 participants will be assessed in the phase II portion of the clinical trial once the maximum tolerated dose has been determined. Equal group sizes may not be analyzed given infrequent use of efavirenz-based HAART in the U.S. **Participants taking any azole-based therapy should not be approached for participation in the pharmacokinetic studies.** However, participants with protocol deviations for concurrent medications with sufficient samples for the PK analysis may be analyzed with the protocol chair's approval.

The study coordinator will be informed of which arm the participant enrolled will be assigned to.

Sensitive, validated assays will be used to measure concentrations of brentuximab vedotin, total antibody, ATA in serum, and free MMAE in plasma. These assays will include enzyme-linked immunosorbent assays (ELISA) and LC/MS/MS assays. Other assays may be utilized if required to further characterize pharmacokinetics. These assays will be performed at Covance, Inc. Each assay will have a positive control and a pre-infusion serum sample will serve as the negative control. These data will provide unique insight in how we use this drug in participants receiving anti-HIV therapy.

RELEVANT PRECLINICAL DATA

Little to no data exists on the dosing of 1.3mg/kg of brentuximab vedotin to be used in this study, and no information exists on its interactions with anti-HIV medications. The data summarized below were obtained using 1.8mg/kg.

Pharmacokinetic parameters for individual patients were determined using concentrations of serum brentuximab vedotin ADC, plasma MMAE, serum TAb, and actual sampling times relative to the start of the infusion. The maximum concentrations for the serum PK of brentuximab vedotin ADC following an IV dose of 1.8 mg/kg were typically observed at the end of infusion. A multi-exponential decline in ADC serum concentrations was observed with a terminal half-life (t1/2) of approximately 4 to 6 days. Exposures were approximately dose proportional. After administration of multiple doses of brentuximab vedotin, steady-state was achieved by 21 days, consistent with the t1/2 estimate. Minimal to no accumulation was observed with multiple doses with the q3wk regimen, and ADC exposure did not decrease with subsequent doses.

The plasma PK profile of MMAE following an IV dose of 1.8 mg/kg brentuximab vedotin appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. Tmax ranged from approximately 1 to 3 days. Exposures were linear and approximately dose proportional with MMAE exposures decreasing after multiple doses with approximately 50% to 80% of the exposure of the first dose observed at subsequent doses. After administration of multiple doses of brentuximab vedotin, MMAE steady-state was achieved by 21 days, similar to ADC. Total antibody exposures were approximately dose proportional and higher than brentuximab vedotin ADC exposures while Tmax was similar.

TIME POINT OF SPECIMEN COLLECTION

Table App IX-A: Pharmacokinetic Time Point and Immunogenicity Sampling Time Points

Cycle	Study Day	Time	Window	Relative Time	PK (ADC & fMMAE)	ATA
1	Day 1	Pre-dose	within 2 hrs of **BV infusion**	start of **BV** infusion	X	X
		0 min	within 5 min post end of infusion	End of **BV** infusion	X	
	Day 3	At Clinic Visit			X	
	Day 15	Pre-Dose	within 2 hrs of **BV infusion**	start of **BV** infusion	X	
2nd and Subsequent Cycles	Day 1	Pre-dose	within 2 hrs of **BV infusion**	start of **BV** infusion	X	X
Post-Treatment Evaluation	6-8 weeks after Cycle 6 Day 15	At Clinic Visit			X	X
Early Discontinuation	Within 1 month after treatment discontinuation	At Clinic Visit			X	X

PK (Includes assay for Brentuximab vedotin and Free MMAE) ATA (Anti-Therapeutic Antibody)

SPECIMEN COLLECTION AND PROCESSING INSTRUCTIONS

Antibody Drug Conjugate (ADC) - Serum PK Specimen Collection & Processing:

☐ 5.0 mL of whole blood will be collected in a gold-top serum separator tube.

☐ Sample will be allowed to clot for 30 minutes at room temperature.

☐ Centrifuge sample for 15 minutes at approximately 1500 x g at room temperature.

☐ Serum will be aliquotted into two 3 mL cryovials, and frozen at -20ºC or -80ºC preferably as soon as possible. **Do not use liquid nitrogen to flash freeze the specimen.**

For Free MMAE (fMMAE) Specimen Collection and Processing:

☐ 2.5 mL of whole blood will be collected in a 2.7 mL Na Citrate tube (blue top) tube.

☐ Immediately after the blood draw, carefully mix the blood with the anticoagulant by gently inverting the tube 8-10 times. DO NOT SHAKE.

☐ Immediately after mixing the specimen, place the vacutainer tube into a container with cold water and ice for 1-2 minutes. If your site does not a have a refrigerated centrifuge, leave the specimen in the ice mixture for 5-6 minutes before processing. The samples should be processed within 1 hour of collection.

☐ Centrifuge blood at 800-1000 g for 15 minutes to separate the plasma from blood cells.

☐ Transfer the plasma into one appropriately labeled 2 mL cryogenic vial. Be careful not to include any of the separated cells.

☐ Samples must be frozen and stored immediately at -20ºC or -80ºC preferably. **Do not use liquid nitrogen to flash freeze the specimen.** If it is impossible to place the specimen immediately at >-20ºC, it may be refrigerated up to 8 hours prior to storage at > -20ºC.

Antitherapeutic Antibody (ATA) Specimen Collection & Processing:

☐ 2.5 mL of whole blood will be collected in a gold-top serum separator tube.

☐ Sample will be allowed to clot for 30 minutes at room temperature.

☐ Centrifuge sample for 15 minutes at approximately 1500 x g at room temperature.

☐ Serum will be aliquotted into one 3 mL cryovial, and frozen at -20ºC or -80ºC preferably as soon as possible. **Do not use liquid nitrogen to flash freeze the specimen.**

Store all serum and plasma samples at -80°C if not able to ship within the month to the AMC Biorepository.

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

- Protocol #: AMC-085
- 9-digit Participant #
- Date and time of collection
- Specimen type: "Plasma," "Serum"
- Sample Volume
- Specimen purpose: Indicate which analyses should be performed on each tube (i.e., "Antibody Drug Conjugate (ADC) - PK/Immuno Studies," "free MMAE (fMMAE) - PK/Immuno Studies," or "Antitherapeutic Antibody (ATA) - PK/Immuno Studies").
- Nominal Timepoint

SPECIMEN SHIPMENT

Specimens are accepted **MONDAY** through **FRIDAY**. All specimens should be shipped to the AMC Biorepository housed at George Washington University

(www.ncbi.nlm.nih.gov/pubmed/20949389) within one month of collection.

AMC Biorepository:
George Washington University Medical Center
2300 I St, NW
Room 118
Washington, DC 20037
Tel: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@gwu.edu
amc-bio@emmes.com

The AMC Biorepository will send the following specimens in batch to the following addresses upon direction from the AMC ODMC:

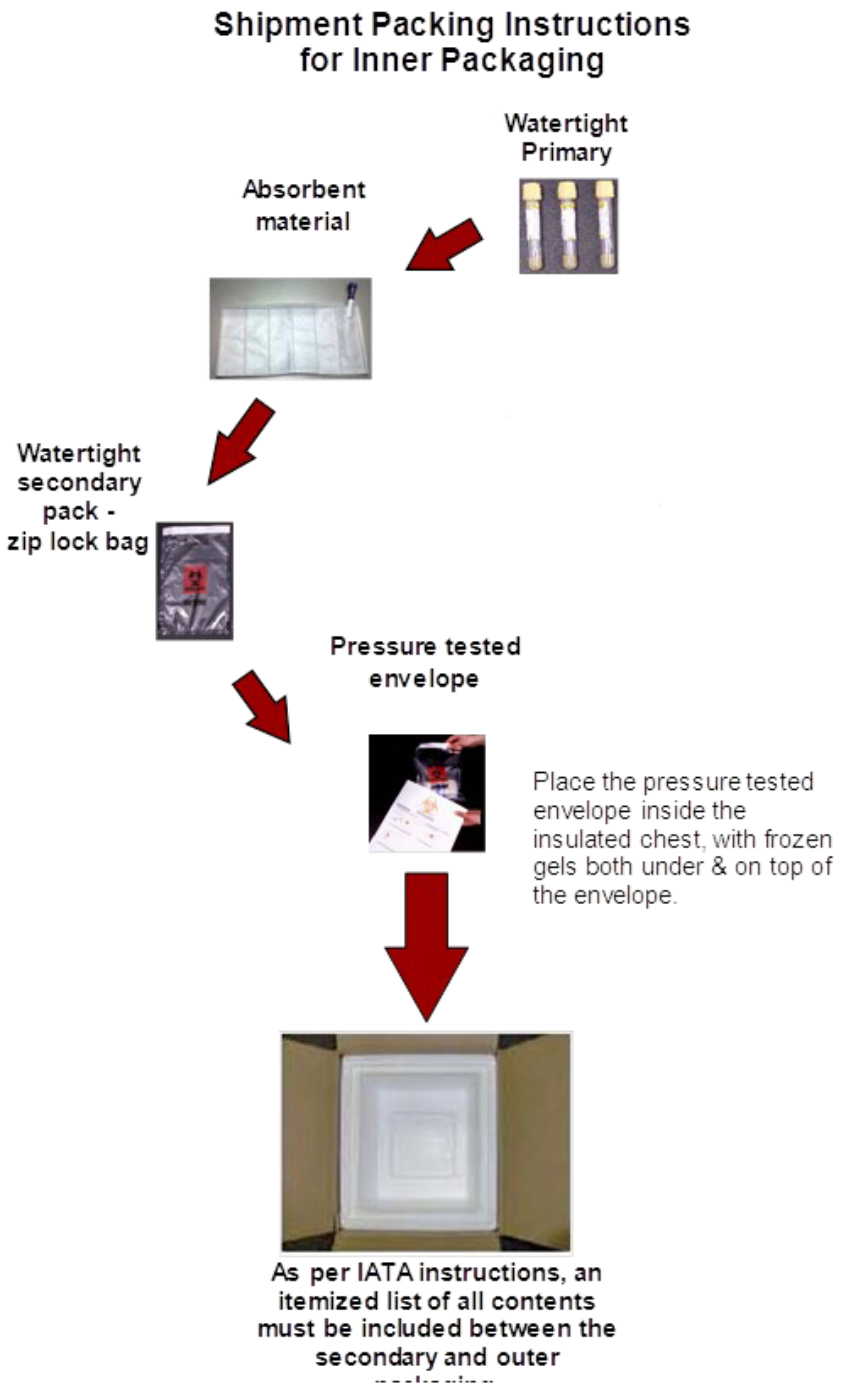
ADC and ATA serum samples should be sent to:
Covance Chantilly:
Attn: Reena Pappachen
3635 Concorde Pkwy, Suite100
Chantilly, VA, 20151
MMAE Plasma samples should be sent to:
Covance Madison:
Attn: Sample Management – Bioanalytical (Rm 131D 1S)
3301 Kinsman Blvd
Madison, WI 53704-2523

SHIPPING INSTRUCTIONS

To ship to Covance, remember to include the following information for samples:

- Sample matrix (plasma, serum, etc.)
- Analyte (which analyses should be performed on each tube)
- Sample volume
- Sample draw date
- Sample draw time
- Participant identifier
- Nominal time point

1) Put the serum or plasma tube in the inner biohazard bag with absorbent material and seal
2) Put the biohazard bag in the outer therapak envelope and seal well per instructions on the packaging
3) Envelope goes in the provided dry ice shipper, surround with dry ice
4) Close foam inner box, and place the requisite and any other relevant sample documentation in a ziplock bag on top of the foam inner box.
5) Seal the outer cardboard, add appropriate hazard stickers for the blood product and dry ice (not provided).
6) Ship to Covance following the instructions below



To order the shippers:

Biohazard bags from Fisher: 95kpa catalog #22-130-020

Shipping boxes from VWR: thermosafe 11x14.5x9, catalog #14100-414

Contact Covance's contacts for technical questions (below) prior to using alternate shippers.

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

handling and shipping of hazardous goods. (IATA Packing Instruction 650 is located on the AMC web site.)

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

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

Billing

Bill the FedEx number provided on the AMC members’ only website. This number is supplied by the AMC Operations and Data Management Center. It is only to be used for billing shipment of specimens to the lab where the sample is processed and/or stored.

Record of Specimens

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

Technical Questions

For Free MMAE:
Glenn Hanson
Senior Principal Investigator
Bioanalytical Chemistry
Covance Laboratories, Inc.
3301 Kinsman Boulevard
Madison, WI 53704-2523
E-mail: glenn.hanson@covance.com
Tel: 608-242-2640
Fax: 608-242-2735
Available hours: Monday-Friday (9AM-5PM EST)

For ADC, and ATA:
Reena Pappachen
Principal Investigator
Immunochemistry Services
Covance Laboratories, Inc.
Chantilly, VA
E-mail: reena.pappachen@covance.com
Tel: 703-889-9482

APPENDIX X: ASSESSMENT OF CIRCULATING LEVELS OF PRO-INFLAMMATORY AND ANGIOGENESIS-ASSOCIATED MOLECULES STUDY PLAN

1.0 OBJECTIVES

The aims of this proposed pilot study are:

1.1 To determine if pre-treatment plasma levels of cytokines and/or biomarkers associated with inflammation and immune activation are elevated in persons with HL;

1.2 To evaluate the effect of brentuximab-containing AVD therapy on plasma levels of these biomarkers following 1 cycle of therapy, following 3 cycles of therapy, at the conclusion of therapy, and at 3, 6 and 12 months after the conclusion of therapy, to identify the clinical correlates with regard to tumor response and disease-free survival.

2.0 BACKGROUND

We have seen that elevated serum/plasma levels of several molecules associated with immune activation and inflammation, including sCD30, CXCL13, IL-6 and IL-10, occur preceding the diagnosis of AIDS-associated NHL, as well NHL, and HL in presumably immunocompetent persons[63-66]. These studies were all done using specimens obtained from several prospective longitudinal cohort studies. In a prior study in the AMC, we also assessed the effect of treatment for AIDS-associated NHL on plasma levels of these biomarkers, finding that treatment resulted in a marked decrease in many of these molecules, and that pre-treatment initiation plasma levels of CXCL13, IL-6 and IL-10 were predictive of subsequent CR to treatment[63-66]. In fact, in multivariate analysis, CXCL13 levels proved to be better predictors of subsequent clinical response that IPI or other established prognostic markers (8, 9). Therefore, biomarkers, including sCD30, IL-6 and IL-10 are known to be elevated preceding HL and NHL, and levels of these molecules may be associated with subsequent response to treatment in AIDS-NHL. However, little is known about these biomarkers in HIV infection-associated HL.

3.0 RATIONALE

HIV-driven inflammatory cytokine production has the potential to contribute to the growth of AIDS-associated cancers, including HL, and enhanced production of these and other B cell-stimulatory molecules may contribute to the genesis and/or growth of HL. Additionally, dysregulated infection with EBV may contribute to immune activation and inflammation. However, there is little information available on the effect of treatment of AIDS-associated HL with brentuximab on serum levels of these biomarkers, nor on the prognostic significance of such biomarkers.

The recent availability of multiplexed immunometric assays has made possible the simultaneous assessment of several of these immune activation and inflammation-associated factors, using small volumes (<500 μl) of serum or plasma.

The results of this study will provide information on immune activation/inflammation-associated biomarker plasma levels in HIV-associated HL, and on effects of AVD-BV

therapy for HL on these biomarkers, as well as on the prognostic value of such biomarkers in those receiving AVD-BV treatment.

4.0 EVALUATIONS

Plasma levels of cytokines and inflammation-associated molecules will be determined at the following study visits: pre-treatment (entry), and following 1 cycle of therapy, following 3 cycles of therapy, at the conclusion of therapy (6-8 weeks post treatment discontinuation), and at 3, 6 and 12 months after the treatment discontinuation visit.

5.0 ANALYSES

The working hypothesis that will be tested is that participants who will achieve clinical CR will have plasma levels of sCD30, IL-6 and IL-10 that fall within the normal range, following the conclusion of therapy.

Levels of cytokines and inflammation-associated biomarkers will be determined using two Luminex-based panels. The first is a high-sensitivity cytokine panel that can detect human IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNFα, VEGF, GM-CSF, IFNγ. The second is a soluble receptor/inflammatory cytokine panel: BAFF/BLyS, sCD14, sIL-6R, sgp130, sIL-2R, sTNF-R2, CXCL13, sCD30 (or sCD27). Both of these panels are produced by R&D Systems, and have been used by us extensively in prior epidemiologic studies. The cytokine panel has yielded results that compare well to ELISA results for IL-6 and IL-10. The soluble receptor/inflammation panel yields detectable results for these biomarkers in the majority of persons tested.

2 mL of plasma in 1 mL aliquots should be sent in batch at the end of the study to the Martinez-Maza laboratory.

6.0 SHIPPING INSTRUCTIONS AND SAMPLE PROCESSING

A. General

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

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

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

B. Specimen preparation, packaging, and shipment

Draw two 6 cc (mL) lavender top [EDTA] tubes from study participant. Seal the tops of the tubes with parafilm. Place the two sealed tubes into bubble wrap (provided in STP-210

kit). Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break. Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and "self-seal." Place poly-bag containing tubes into the white TYVEK bag and seal. Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.

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

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

Dr. Sylvia Silver
George Washington University Medical Center
2300 I St, NW
Room 118
Washington, DC 20037
Tel: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@gwu.edu
amc-bio@emmes.com

Specimen Labeling

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

- Protocol #: AMC-085
- 9-digit Participant ID #
- Visit #
- Date and time of specimen collection
- Specimen Type: "Plasma"
- Purpose: "Cytokine Assays"

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

Billing

Bill the FedEx number provided on the AMC members' only website. This number is supplied by the AMC Operations and Data Management Center. It is only to be used for billing shipment of specimens to the lab where the sample is processed and/or stored.

Contact for Site Questions (9AM-5PM Pacific Time)
Lab Manager: Larry Magpantay (lmagpantay@mednet.ucla.edu)
Lab phone: 310-206-6846

Otto Martinez-Maza's office phone: 310-825-2542

7.0 AMC BIOREPOSITORY INSTRUCTIONS ONLY

The AMC Biorepository will separate plasma, aliquot the plasma into as many 1.0 mL aliquots until the sample is used as per AMC Biorepository SOPs, and store at -80°C. Specimens should be sent in batch at the end of the study to:

Larry Magpantay
BSRB 173
UCLA AIDS Institute
615 Charles Young Drive
Los Angeles, CA 90095-7363
Tel: 310-206-6846
Fax: 310-206-5387
Email: lmagpantay@mednet.ucla.edu

APPENDIX XI: ASSESSMENT OF EBV DNA IN PLASMA

1.0 OBJECTIVES

The aims of this proposed pilot study are:

1.1 To determine if pre-treatment levels of EBV DNA in plasma from HL participants prior to treatment are prognostic indicators

1.2 To determine if following the initiation of treatment EBV DNA in plasma serves as a tumor marker

1.3 to determine whether measurement of methyl CpG EBV DNA in plasma is a prognostic indicator at baseline or a tumor marker at follow up.

2.0 BACKGROUND

Approximately 90% of HL in HIV patients is associated with the presence of EBV in the malignant cells as assessed by in situ hybridization or immunohistochemistry of diagnostic biopsies[82]. In other populations the association is less common[83]. Several groups have reported that detection of EBV DNA in plasma or serum correlates with the presence of EBV in tumor cells in HL[84,85]. In a recent study we have seen that in non-HIV patients in North America with HL, pretreatment plasma copy number had an excellent concordance rate with in situ hybridization (95%) and was a prognostic factor in multivariate analysis for failure-free survival that superseded the international prognostic score (IPS)[86]. Furthermore, failure to clear EBV DNA from plasma after the initiation of therapy was associated with a very poor failure-free survival (44% at 3 years, p=0.0001). In immunocompetent patients without HIV infection, detection of EBV DNA in plasma of patients with EBV-associated tumors reflects mainly release of viral DNA from latently infected tumor cells[87].

In contrast, in HIV patients, plasma copy number for EBV and KSHV are often elevated. Copy number measurements often fail to distinguish between patients with virus associated malignancy and patients without virus-associated malignancy[88]. The explanation is that HIV patients are often viremic i.e., whereas viral DNA in other settings is mainly that released from tumor cells, in HIV patients EBV and KSHV virions are also present in plasma. Because the virion coat provides protection from DNase digestion, resistance to such digestion has been used to distinguish virion DNA from viral DNA released from tumor or other cells that was not encapsidated. However, the approach is difficult to standardize and not readily applied to clinical trials specimens. We have developed a technique to distinguish virion DNA from cell viral DNA which is straightforward and quantitative. The technique involves measurement of copies of methylCpG KSHV or EBV DNA[89]. Virion DNA is never CpG methylated, whereas cellular EBV DNA is usually CpG methylated.

3.0 RATIONALE

Detection of EBV DNA in plasma is very useful in EBV-associated malignancies in non-immunocompromised patients including nasopharyngeal carcinoma and Hodgkin lymphoma. It has not been carefully studied in HIV HL before, but we suspect that as in other HIV settings, tumor-derived DNA will be obscured by virion DNA. By comparing measurements of viral DNA and methylCpG viral DNA, we expect to test our hypothesis, that methylCpG DNA will be much more useful as a tumor marker.

4.0 EVALUATIONS

Plasma levels of EBV DNA and methyl CpG EBV DNA will be determined at the following study visits: pre-treatment (entry), and following 1 cycle of therapy, following 3 cycles of therapy, at the treatment discontinuation visit, and at 3, 6 and 12 months after the post treatment evaluation. At each required time point, participants will have two 6 cc (mL) lavender top [EDTA] tubes of blood drawn at ambient temperature.

5.0 ANALYSES

We will analyze baseline EBV DNA and methylCpG EBV DNA for prognostic value. We will also measure serial changes in these values with therapy.

For detection of EBV DNA in plasma we used standard PCR-based real time techniques[90]. For detect of methyl CpG EBV DNA, we fractionate DNA extracted from plasma using DNA methylbinding protein 2 magnetic beads as described[90]. Methyl CpG DNA is eluted from the beads in high salt and then assayed by standard PCR as above.

6.0 SHIPPING AND SAMPLE PROCESSING

Preparation and Shipping Instructions

A. General

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

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

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

B. Specimen Preparation, Packaging, and Shipment

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

Affix the FED-EX airbill on blank side of the shipper making sure that it is marked "FED-EX PRIORITY OVERNIGHT." Mark "OTHER" in the airbill under "Packaging." Under airbill section "Special Handling," indicate "YES-SHIPPERS

DECLARATION NOT REQUIRED." Place "From/To" information onto areas provided on the shipper.

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

Dr. Sylvia Silver
George Washington University Medical Center
2300 I St, NW
Room 118
Washington, DC 20037
Tel: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@gwu.edu
amc-bio@emmes.com

Specimen Labeling

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

- Protocol #: AMC-085
- 9-digit Participant ID #
- Visit #
- Date and time of specimen collection
- Specimen Type: "Plasma"
- Purpose: "EBV Load"

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

Billing

Bill the FedEx number provided on the AMC members' only website. This number is supplied by the AMC Operations and Data Management Center. It is only to be used for billing shipment of specimens to the lab where the sample is processed and/or stored.

7.0 AMC BIOREPOSITORY INSTRUCTIONS ONLY

The AMC Biorepository will separate cells in blood sample, aliquot the plasma into as many 0.5 mL aliquots until the sample is used as per AMC biorepository SOPs, and store at -80°C. At least four 0.5 mL plasma aliquots are required per collection time point. Specimens should be sent in batch at the end of the study to Dr. Ambinder's laboratory at Johns Hopkins University.

APPENDIX XII: ASSESSEMENT OF HIV LATENT AND EXPRESSED HIV RESERVOIRS

1.0 BACKGROUND AND RATIONALE

The effect of intensive chemotherapy on the HIV reservoirs is not well understood. The model of AIDS-related malignancies provides an opportunity to define alterations in HIV reservoirs resulting from cytoreductive cancer chemotherapy. In the current study, we propose to better characterize HIV reservoirs (HIV-1 DNA and RNA) prior to, during, and after treatment of HIV-related Hodgkin lymphoma by sensitive measurement of HIV-1 DNA and RNA in plasma and peripheral blood mononuclear cells using quantitative PCR assays (qPCR). In patients with plasma HIV-1 RNA level below the limit of detection by standard commercial assays (typically <50 copies/mL), qPCR assays with single copy sensitivity (SCA) can detect HIV-1 RNA in plasma and in PBMC from most patients. The origin of this viremia has not been identified, but may be either from latently-infected that are triggered to produce virus, from virus-producing cells that are long-lived, from ongoing low-level virus replication and spread, or some combination of these possibilities. Cytoreductive chemotherapy may impact HIV reservoirs by killing latently-infected cells or those expressing HIV-1 RNA or producing virus, at least temporarily. Such an impact can be readily detected by qPCR assays of HIV-1 RNA in plasma and HIV-1 DNA and RNA blood mononuclear cells. The magnitude of the effect of chemotherapy on reservoirs and whether it is temporary or sustained are important questions that can be answered in this study.

2.0 HYPOTHESIS

We hypothesize that treatment of AIDS-related malignancies using cytotoxic chemotherapy in participants will result in a substantial reduction in the size of the HIV reservoirs and thereby reduce low-level viremia and the number of HIV-infected cells expressing HIV-1 RNA. This study will apply the use of qPCR to assess viremia and cellular reservoirs in participants receiving three de-escalating doses of brentuximab vedotin in conjunction with standard, fixed doses of doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 (AVD). Blood samples will be obtained at two time points prior to Cycle 1, Day 1 (baseline samples), at one time point during treatment, and then at completion of therapy and at one year post treatment.

3.0 SAMPLE REQUIREMENTS

Single Copy HIV Assays (Plasma and Peripheral Blood Mononuclear Cells (PBMCs))

As stated below, **as a requirement, the samples MUST be processed within 4 hours of blood collection. Only sites able to comply with this requirement will be permitted to participate in this correlative.**

Time points for sample collection:

- *Pre-Treatment:* at 1 week (+/- 3 days) prior to Cycle 1 Day 1 and again 24 hours prior or on the day of Cycle 1 Day 1. Only for participants who are found to have undetectable plasma HIV-1 RNA by the standard assay performed at the clinical site within 21 days of C1 Day 1.

- *Treatment Phase:* Within 48 hours prior to or on the first day of Cycle 3 and/or at the Early Treatment Discontinuation Visit if indicated.

Post-Treatment: 6-8 weeks following the last treatment dose only for those participants who are found to have undetectable plasma HIV-1 RNA by the standard assay performed at the clinical site on the Cycle 3 Day 1 sample.

A subsequent 30 mL sample will be obtained 12 months (+/- 14 days) following the treatment discontinuation visit for participants who are found to have undetectable plasma HIV-1 RNA by standard assay performed at the clinical site.

Sample preparation:

A 30 mL peripheral blood sample will be collected in three (3) 10 mL EDTA-containing tubes. Gently mix the blood with EDTA by inverting the tubes 8-10 times. Store the tubes at room temperature **for up to four hours** prior to on-site processing to plasma and PBMCs at a local laboratory.

4.0 SPECIMEN PROCESSING

Plasma

Blood samples MUST be processed within 4 hours of collection. **If samples cannot be processed within the 4 hours, sites will be able to opt out of this correlative study.** Centrifuge blood at 400 x g for 10 minutes in a table top centrifuge. Remove plasma very carefully without disturbing the buffy coat and/or mixing cells into the plasma. To prevent contamination of the plasma with cells, leave about 0.5 mL of plasma behind above the cell layer. This is very important. Re-centrifuge plasma at 1350 x g for 15 min. Again, leave about 0.5 mL of plasma behind to prevent potential cell contamination. Save all cells for processing to cryopreserved PBMC as described below.

Freeze at least 5 x1.5 mL aliquots and as many additional 1.5 mL aliquots as possible at -70°C or colder and ship on dry ice to the AMC Biorepository.

Peripheral Blood Mononuclear Cells (PMBCs)

Blood samples MUST be processed within 4 hours of collection. **If samples cannot be processed within the 4 hours, sites will be able to opt out of this correlative study.** Dilute the cells and plasma left behind from above to the original blood volume with Dulbecco's phosphate buffered saline. Isolate and cryopreserve PBMC as described in HANC Cross-Network PBMC processing SOP

(https://www.hanc.info/labs/labresources/procedures/Pages/pbmcSop.aspx). Store at least 5 aliquots of 5 million PBMC per vial at -70°C or colder and ship on dry ice to the AMC Biorepository.

5.0 SPECIMEN SHIPMENT

To ship frozen specimens to the AMC Biorepository, please follow the instructions in Appendix V. Shipping will require the use of packaging acceptable for dry ice and Class 9 label with the weight of dry ice indicated on the package.

Available aliquots will be periodically shipped from the AMC Biorepository to the designated project laboratory at the University of Pittsburgh for testing. **IF SPECIMENS**

CAN NOT BE SHIPPED ON MONDAY THROUGH THURSDAY, STORE SAMPLES AT -70°C UNTIL THE FOLLOWING MONDAY.

Specimens should be shipped by overnight express to:

Dr. Sylvia Silver
George Washington University Medical Center
2300 I St, NW
Room 118
Washington, DC 20037
Tel: (202) 994-2945
Fax: (202) 994-5056
Email: ssilver@gwu.edu
amc-bio@emmes.com

Specimen Labeling

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

- Protocol #: AMC-085
- 9-digit Participant ID #
- Visit #
- Date and time of specimen collection
- Specimen Type: "Plasma," "PBMC"
- Purpose: "HIV latent reservoir"

6.0 BILLING

Bill the FedEx number provided on the AMC members' only website. This number is supplied by the AMC Operations and Data Management Center. It is only to be used for billing shipment of specimens to the lab where the sample is processed and/or stored.

7.0 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.

8.0 AMC BIOREPOSITORY INSTRUCTIONS ONLY

Batches of specimens will be sent from the AMC Biorepository to the Mellors Laboratory by overnight express on dry ice:

The first shipment should be sent when the first 5 participants have completed the study and all the samples are received at the AMC Biorepository. Subsequent shipments will be batched when an additional 5 participants' complete the study and their samples are available at the AMC Biorepository.

Dianna Koontz/Virology Support Laboratory (Mellors)
University of Pittsburgh
3550 Terrace Street
S816 Scaife Hall

Pittsburgh, PA 15261
Tel: (412) 624-8509
Email: zonarich@pitt.edu

APPENDIX XIII: PROHIBITED AND USE WITH CAUTION MEDICATIONS THAT ARE P-GLYCOPROTEIN AND CYP3A4 INHIBITORS

Strong CYP3A inhibitors and P-glycoprotein inhibitors must be discontinued 7 days prior to therapy. Moderate CYP3A4 inhibitors should be Used with Caution but are not excluded. If 2 moderate CYP3A4 inhibitors are used concurrently, one must be discontinued at least 7 days prior to chemotherapy.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

P-Glycoprotein Inhibitors	Strong CYP 3A4 Inhibitors	Moderate CYP 3A4 Inhibitors
Antiretrovirals	**Antiretrovirals**	**Antiretrovirals**
Lopinavir and ritonavir	Cobicistat	Atazanavir
	Indinavir	
Other Agents	Nelfinavir	**Other Agents**
Amiodarone	Ritonavir	Aprepitant
Azithromycin*	Saquinavir	Amprenavir
Captopril		Amiodarone
Carvedilol	**Other Agents**	Ciprofloxacin
Clarithromycin	Boceprevir	Dronedarone
Conivaptan	Clarithromycin	Erythromycin
Cyclosporine	Itraconazole	Diltiazem
Diltiazem	Ketoconazole	Fluconazole
Dronedarone	Mibefradil	Fosamprenavir
Erythromycin	Nefazodone	Grapefruit juice
Felodipine	Posaconazole	Seville orange juice
Itraconazole	Suboxone	Verapamil
Ketoconazole	Telithromycin	Voriconazole
Quercetin	Telaprevir	
Quinidine	Troleandomycin	
Ranolazine		
Tacrolimus		
Verapamil		

* See Section 4.4.4 for guidance on azithromycin use in MAC prophylaxis.

APPENDIX XIV: ANALYSIS OF T-CELL SUBSETS AND CYTOKINES OVER TIME IN SUBJECTS TREATED WITH AVD-BV

1.0 OBJECTIVES

The aims of this exploratory correlative study are to study the T-cell subsets and cytokine levels over time to understand CD4+ and CD8+ T-cell elevations identified in AMC-085:

1.1 To determine what changes from pre-treatment plasma levels of cytokines are associated with CD8 and CD4 + T-cell function. The cytokine analysis will be performed pretreatment, following cycle 1, cycle 3, and at the conclusion of therapy. Analysis will also be performed at 3, 6, and 12 months post therapy

1.2 We will also evaluate and attempt to identify changes in pretreatment T-cell subsets and cytokines in up to 10 participants via cytometry by time of flight (Cy-TOF) on subjects pre-treatment, following cycle 3, and at the conclusion of therapy.

2.0 BACKGROUND

Brentuximab vedotin has the potential to destroy all cells that are CD30 positive, as seen in the HRS cell. Heiser et al. attempted to understand the distribution of CD30 expression across all T-cell subets.[93] There data demonstrated that CD30 expression was identified mostly in the T-regulatory cells. While these cells have many roles, one of their main functions is to suppress CD8+ and CD4+ T-cell proliferation. In co-incubation experiments in vitro, it was demonstrated that when CD8+ and FOX-P3+ T-regulatory cells were co-incubated, as T-regulatory T-cells decreased in number CD8+ T-cells also increased in number when challenged with brentuximab vedotin.[93]

Preliminary data from this study realized in an interim analysis identified that CD4+ T-cells as well as CD8+ T-cells increased in just about 1 month after AVD-BV treatment in essentially all subjects enrolled to date (unpublished data). To see if this was an effect of brentuximab vedotin, 54 patients with HIV-associated Hodgkin Lymphoma were identified at County Hospital in Chicago. To exclude the possibility that uncontrolled HIV was a cause for a drop in the CD4+ T-cell counts in subjects, patients with undetectable viral loads were identified. Of the patients with undetectable viral loads treated with ABVD, 80% of the subjects had drops in CD4+ T-cell counts about 1-2 months post chemotherapy. Additionally, when CD8+ T-cell counts were analyzed in subjects treated with ABVD, 100% had drops in CD8+ T-cell counts (unpublished data). Based on the interim analysis of AMC-085, the increase in CD4 T cell counts was observed only in patients that were treated with AVD-BV but not with ABVD.

The fact the in subjects with **ABVD** had drops in CD8 and CD4+ T-cell counts while subjects with **AVD**-BV had elevations, points to brentuximab vedotin as the causative agent of the elevation. Combining this data with the data presented by Heiser and colleagues, points to the cause of the elevation as T-regulatory T-cell destruction. **We hypothesize that brentuximab vedotin achieved T-regulatory T-cells destruction, thereby causing total CD8+ and total CD4+ T-cell count elevation. The purpose of this correlative study is to prove that this is the mechanism seen in vivo in subjects with HIV-associated cHL.**

3.0 RATIONALE

The results of this study will provide information on immune activation/inflammation-associated biomarker plasma levels in HIV-associated HL, and on effects of AVD-BV therapy for HL on these biomarkers, as well as on the prognostic value of such biomarkers in those receiving AVD-BV treatment.

4.0 EVALUATIONS

Plasma levels of cytokines will be determined as described in Appendix X at the AMC Biomarkers Core Laboratory (Otto Martinez-Maza). The cytokine analysis will be performed pre-treatment, following cycle 1, cycle 3, and at the conclusion of therapy. Analysis will also be performed at 3, 6, and 12 months post therapy. T-cell subsets and further cytokine analysis will be examined pre-treatment, following cycle 3, and at the conclusion of therapy (6-8 weeks post-treatment discontinuation). The PBMC utilized for the CyTOF portion of this study will rely on aliquots of cells received for the HIV viral reservoirs correlative study utilized in Appendix XII, provided that the participant has consented to the additional use of his/her specimens in future research by the ACSR. The T-cell subset and cytokine assays performed by CyTOF and flow cytometry will be performed by Dr. Robert Baiocchi's laboratory (Ohio State University AMC site). **No additional blood draws** will be required for this correlative study.

5.0 ANALYSES

The working hypothesis that will be tested is that participants who will achieve clinical CR will have plasma levels of sCD30, IL-6 and IL-10 that fall within the normal range, following the conclusion of therapy.

Levels of cytokines and inflammation-associated biomarkers will be determined using two Luminex-based multiplex assay panels. The first is a high-sensitivity cytokine panel that can detect human Granzyme B, IFN-alpha, IFN-beta, IFN-gamma, IL-1 beta, IL-2, IL-4, IL-5, IL-7, IL-12 p70, IL-13, IL-15, IL-17A. The second is a soluble receptor/inflammatory cytokine panel: CCL17/TARC, CCL22/MDC, CCL24/Eotaxin-2/MPIF-2, CD163, SDF-1 alpha/CXCL12, IL-6 R alpha, IL-18.

Both of these panels are produced by R&D Systems, and have been used by the Martinez-Maza laboratory extensively in prior epidemiologic studies. Both of these cytokine assays will be added on to the assay already described in Appendix X, prospectively and for all other U.S. participants previously enrolled on AMC-085.

The T-cell subset and cytokine assays performed by CyTOF and flow cytometry will be performed by Dr. Robert Baiocchi's laboratory (Ohio State University AMC site) for up to 10 participants. The cells required will be aliquots from blood samples already collected from participants in the optional HIV viral reservoir studies in Appendix XII, who have also consented for the additional use of his/her specimens in future research by the ACSR.

Cy-TOF will be used to identify changes in T-cell subsets as described above looking at Live/dead dye, CD3, CD4, CD8, CCR7, CD45RA, CCR6, CXCR3, CD30, CD25, CD127, HLA-DR, CD38, and CCR4. We will also assay, KI 67, FoxP3, GATA3, and TBET (markers for TH1, TH2, and T-regulatory T cells). We will use CyTOF to also validate the cytokine portion of the correlative study, assaying pre, during, and post therapy levels

6.0 SHIPPING INSTRUCTIONS AND SAMPLE PROCESSING

No additional samples will be collected for these correlative studies. Samples will be designated for this study as noted above under item 4 (Evaluations).

7.0 AMC BIOREPOSITORY INSTRUCTIONS ONLY

The AMC Biorepository will send all plasma aliquots available for cytokine analysis in batch at the end of the study to as stated in Appendix X, for performance of these assays.

For the T-cell subset analysis, cytokine, and CyTOF of PBMCs collected not utilized for the viral reservoir studies will be designated for this study. For up to 10 participants meeting the consent requirements for the HIV viral reservoirs study and for future use of residual study specimens by the ACSR, the AMC Biorepository will send 2 aliquots of PBMCs containing 5 million PBMCs each pre, end of cycle 3, and post therapy will be sent to the Baiocchi laboratory at Ohio State University. These aliquots will be apportioned from samples that are collected as described in Appendix XII.

APPENDIX XV: AMC-085 LYSARC PROTOCOL

To expand international collaborations in the AMC and facilitate recruitment goals, participation in the phase II portion of the AMC-085 study was extended to The Lymphoma Study Association (LYSA), and being conducted by The Lymphoma Academic Research Organisation (LYSARC) in France. The content of the LYSA/LYSARC AMC-085 protocol does not vary from the original AMC-085 protocol. The AMC-085 protocol version that was approved by the French regulatory authority has been added as an appendix for reference in U.S. regulatory submissions.

The protocol provided in this appendix applies only to the participating LYSA sites. Accrual at all LYSA sites concluded on 30 November 2017.

INTERGROUP STUDY: AMC-085

A Pilot Trial of AVD and Brentuximab Vedotin (SGN-35) in the treatment of stage III-IV HIV- associated Hodgkin Lymphoma

A STUDY SPONSORED BY: LYSARC

THE LYMPHOMA ACADEMIC RESEARCH ORGANISATION

Centre Hospitalier Lyon Sud - Secteur Sainte Eugénie – Pavillon 6D 69495 Pierre Bénite Cedex– France

COORDINATING GROUP: AMC (AIDS MALIGNANCY CONSORTIUM)

Cet essai, soutenu par l'Institut National du Cancer, est réalisé dans le cadre de la collaboration entre le National Cancer Institute américain et l'Institut National du Cancer.

COORDINATING INVESTIGATOR **CO- COORDINATING INVESTIGATOR**	Pr. Caroline BESSON Pr. Nicolas MOUNIER
PROTOCOL CHAIR **PROTOCOL CO-CHAIR**	Dr. Paul G. RUBINSTEIN Dr. Ariela NOY
STATISTICAL COORDINATOR	Milan Bimali, AMC Statistical Center
PATHOLOGICAL COORDINATOR	Pr. Sophie Prevot (Hopital Beclere) and Dr. Bettina Fabiani (Hopital Saint Antoine)
COORDINATION CENTER	LYSARC
REGISTRATION	**SEE SECTION 11.1**
AE AND SAE REPORTING	**SEE SECTION 13**

Version and date of Protocol: 6.0 final on 15/04/2019

EudraCT number: 2014-003678-18 **ClinicalTrials.gov ID**: 02298257

CONFIDENTIALITY STATEMENT

The information contained in this document is the property of The Lymphoma Academic Research Organisation (LYSARC) and therefore is provided to you in confidence for review by you, your staff, an applicable Ethics Committee/Institutional Review and regulatory authorities. It is understood that the information will not be disclosed to others without prior written approval from the Lymphoma Academic Research Organisation (LYSARC), except to the extent necessary to obtain informed consent from those persons to whom the medication may be administered.

PROTOCOL SIGNATURE PAGE
AMC-085

A PILOT TRIAL OF AVD AND BRENTUXIMAB VEDOTIN (SGN-35) IN THE TREATMENT OF STAGE III-IV HIV-ASSOCIATED HODGKIN LYMPHOMA

LYSARC

Name: Pascal DESCHASEAUX	Date Title: General Manager

COORDINATING INVESTIGATORS

Name: Dr Caroline BESSON Title: Coordinating Investigator	Date
Name: Prof Nicolas MOUNIER Title: Co-Coordinating Investigator	Date

1.0 SYNOPSIS

Study ID **Eudract N°**	AMC-085 2014-003678-18
Title of the study	A Pilot Trial of AVD and Brentuximab Vedotin (SGN-35) in the treatment of stage III-IV HIV-associated Hodgkin Lymphoma
Development phase of the study	Phase II
Investigational product	Brentuximab Vedotin
Protocol version	1
Sponsor	LYSARC
Coordinating investigator **Co- coordinating investigator**	Pr Caroline BESSON Pr Nicolas MOUNIER
Centres	7 centers
Study Objectives and endpoints	**Primary objective:** • To establish an estimate of the two-year progression-free survival (PFS) for patients with HIV-associated stage III-IV Hodgkin lymphoma when treated using brentuximab vedotin plus the AVD chemotherapy regimen. See paragraph 6.1 **Secondary objectives:** • To evaluate the toxicity of AVD and brentuximab vedotin with highly active antiretroviral therapy (HAART). • To estimate the partial response (PR) rate, complete response (CR) rate, overall survival (OS), and event free survival (EFS) at 2 and 5 years. • To evaluate the effect of AVD and brentuximab vedotin on CD4 and CD8 counts after cycle 1, 4, at the end of therapy, and every 3 months after treatment completion for one year. • To investigate the prognostic value of FDG-PET/CT scans at baseline, after cycle 2, and at treatment completion, with respect to 2-year progression free survival. • To evaluate HAART status at baseline and to correlate this with tumor response to therapy and OS and PFS. • To characterize the histologic subtypes in HIV-HL in the HAART era. • To assess the neurotoxicity of HAART in combination with AVD and brentuximab

	vedotin. • To evaluate effect of AVD and brentuximab vedotin on viral load after cycle 1, 4, at the completion of therapy, and every 3 months after treatment completion for one year. See paragraph 6.2
Study design	This study is a multicenter, phase II trial. See paragraph 7
Duration of the study	Patients will receive brentuximab vedotin 1.2 mg/kg in conjunction with standard, fixed, doses of doxorubicin 25 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² on days 1 and 15 of a 28-day cycle for 6 cycles. Patients will be followed for a total of 5 years, every 3 months for the first 2 years and every 6 months for years 3 to 5 of follow up. Patients who discontinue all protocol therapy after having a CR or PR are followed for up to 5 years after treatment for recurrence and survival. Patients who discontinue protocol therapy due to disease progression or other reasons (Section12) are followed for survival only for up to 5 years after treatment or until death, whichever occurs first. Patients who cross over to non-protocol therapy (if PR or stable disease at physician discretion), or other reasons will be followed for survival for up to 5 years after treatment. Participants removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Duration of recruitment : 24 months Duration of treatment per patient: 6 cycles of 4 weeks = 24 weeks Duration of follow up: 5 years
Number of patients	20 patients in France among 51 patients in protocol developed by AMC The title of the AMC study is AMC PROTOCOL #085: A Pilot Trial of AVD and Brentuximab Vedotin (SGN-35) in the treatment of stage II-IV HIV-associated Hodgkin Lymphoma.
Inclusion criteria	1. Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of brentuximab vedotin in combination with AVD in patients <18 years of age, children are excluded from this study. 2. HIV-1 positive. Documentation of HIV-1 infection by means of one of the following:

	3. Documentation of HIV diagnosis in the medical record by a licensed health care provider; 4. Documentation of receipt of ART by a licensed health care provider; 5. HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating > 1000 RNA copies/mL; 6. Any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed assay such as a HIV-1 Western blot confirmation or HIV rapid multispot antibody differentiation assay. 7. Histologic diagnosis of CD30-positive classical HL as defined by the 2008 WHO Classification of Hematological diseases. Nodular lymphocyte predominant Hodgkin Lymphoma is not eligible. 8. Stage III or IV disease as defined by the Ann Arbor Staging System. 9. Participants must have previously untreated HIV-cHL, with the exception of up to 14 consecutive days of steroids, emergency radiation, or 1 prior cycle of cyclophosphamide to reduce tumor burden and improve hyperbilirubinemia in the setting of lymphoma related liver involvement. 10. Normal baseline cardiac ejection fraction ≥ 50%. 11. Serum creatinine of ≤ 1.5 mg/dL. If creatinine >1.5 mg/dL (133 micromol/L), creatinine clearance must be ≥ 60 mL/minute according to MDRD/Cockroft-Gault formula. 12. ANC ≥ 1000/μL and platelets ≥ 75,000/μL unless related to bone marrow involvement by HIV-cHL. 13. Total bilirubin must be < 1.5x the upper limit of normal, unless the elevation of bilirubin is thought to be seconday to Gilbert's syndrome or cART. • If, however, the elevated bilirubin is felt to be secondary to antiretroviral therapy, the total bilirubin must be ≤ 3.5 mg/dL (60 μmol/L), provided that the direct bilirubin is normal and the AST and ALT ≤ 3 x the upper limit of normal. • If the elevation of bilirubin is thought to be secondary to Gilbert's syndrome, the total bilirubin must be ≤ 3x the upper limit of normal or the direct bilirubin must be ≤ 1.5x the upper limit of normal. • Also, if the elevated bilirubin is thought to be secondary to cHL the same criteria for

	hyperbilirubemeimia should be applied; however 1 prior cycle of cyclophosphamide is permitted in attempt to make the participant eligible (see section 8.1.5). Patients should not be excluded from study participation unless dosing cannot be safely established per Section 10.6.2. 14. Female subjects must have a negative pregnancy test within 1 week of enrollment and all subjects must agree to use two reliable methods of contraception simultaneously if conception is possible during the study. 15. Should a woman subject become pregnant or suspect she is pregnant while the subject is participating in this study, she should inform her treating physician immediately. The patient will then be removed from protocol therapy. 16. Subjects who father a child while participating in the study will be permitted to continue with the protocol. The subject, however, is required to notify the investigator if he fathers a child. 17. Ability to understand and the willingness to sign a written informed consent document. 18. Karnofsky performance status > 30% (given the aggressiveness of this disease and the often severely debilitated nature of the patients at initial presentation). See Appendix 20.5. 19. Measurable or non-measurable (evaluable) tumor parameter(s). Nonmeasurable tumor parameters will be defined as not having bi-dimensional measurements (i.e., gastric or marrow involvement) but can be followed for response by other diagnostic tests such as gallium, PET imaging and/or bone marrow biopsy. 20. Patients already receiving erythropoietin or GCSF for treatment of HIV-related cytopenia are eligible. 21. CD4 count ≥ 100 cells/µl and serum HIV viral load <50copies/ml. 22. Subjects are required to be on antiretroviral regimens that are in accordance with the current International AIDS Society guidelines concurrently with chemotherapy. Use of experimental antiretroviral agents or those containing zidovudine (including Combivir and Trizivir) or ritonavir (includes Norvir® or Kaletra®), cobicistat, or Didanosine (Videx® or Videx EC®), or similar potent CYP3 inhibitors

	are prohibited, as explained in Section **Error! Reference source not found.**. In order to be eligible, patients taking zidovudine or ritonavir or didanosine, or cobicistat or Didanosine, or other CYP3 inhibitors must change to a different regimen 7 days prior to therapy initiation. Subjects must be on HAART for at least 7 days prior to therapy. See section 10.3 23. Patients will be required to obtain a pulmonary function test, despite the exclusion of bleomycin from protocol regimen. The subject's diffusing capacity of the lung for carbon monoxide (DLCO) adjusted for hemoglobin must be greater than 70% predicted to enter the study and to continue with brentuximab vedotin. 24. Negative for Hepatitis B, or if infected with Hepatitis B, receiving anti- Hepatitis B therapy. All subjects will be required to be screened for Hepatitis B. Per IDSA and AASD guidelines, those subjects that show no immunity, defined by the lack of Hepatitis B surface antibody, and show evidence of chronic infection (i.e., HBsAg+, HBcore+, HBsAB-) will be required to be on anti-Hepatitis B therapy during the study in order to be eligible. Patients will be permitted to enroll in the study provided normal liver function tests (see Section 9.3) and no evidence of cirrhosis. The exact Hepatitis B therapy will be at the discretion of the infection disease specialist or investigator. However all patients who present with acute hepatitis B or show normal transaminases and are HBsAg+ and IgM+ for Hepatitis core antigen will not be eligible for trial enrollment. 25. Patients diagnosed with Hepatitis C who are Hepatitis C antibody positive, whether Hepatitis C RNA level is measurable or not, must have no evidence of cirrhosis and have liver function tests that conform to Section 9.3. 26. Brentuximab vedotin is partially metabolized via the CYP3A4 pathway and is cleared from the cells via the P-glycoprotein pump. Therefore, participants must discontinue use of the following agents at least 7 days prior to therapy as per Appendix 20.9. 27. Strong CYP 3A4 inhibitors that treat HIV, see 8.1.16. 28. Other strong CYP3A inhibitors.

	29. Moderate CYP3A4 inhibitors should be used with Caution but are not excluded. If 2 moderate CYP3A4 inhibitors are used concurrently, one must be discontinued at least 7 days (1 week) prior to the initiation of chemotherapy. 30. P-glycoprotein inhibitors. 31. If patients are taking any of these excluded medications, they must be discontinued at least 7 days (1 week) prior to the initiation of chemotherapy. All concomitant medications must be reviewed by the study chair or co-chair prior to enrollment by email. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of. See paragraph 8.1
Exclusion criteria	Patients who do not fulfill the criteria as listed in Section 8.1, are ineligible. Additionally, the presence of any of the following conditions will exclude a subject from study enrollment: 1. Patients with prior anthracycline therapy will be excluded. 2. Female subjects who are pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum b-human chorionic gonadotropin (b-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women. 3. Medical illness unrelated to HL, which in the opinion of the study physician will preclude administration of chemotherapy safely. This includes patients with uncontrolled infection (including opportunistic), chronic renal failure, myocardial infarction (MI) within the past 6 months, unstable angina, or cardiac arrhythmias other than chronic atrial fibrillation. 4. Prior malignancy within 5 years of enrolment other than curatively treated cutaneous basal cell or squamous cell carcinoma, carcinoma in situ of the cervix, anal intraepithelial neoplasia, or cutaneous Kaposi's sarcoma (KS). 5. Grade 2 or greater peripheral neuropathy. 6. Evidence of PML identified on the pretreatment

<table>
<tr><td></td><td>MRI.
7. Central nervous system disease.
8. Patients with history of JC Virus identified in the CSF or previous history of PML will be excluded from the study.
9. Cirrhosis secondary to any cause will be excluded.

See paragraph 8.2</td></tr>
<tr><td>Study treatment</td><td>AVD dosing, in conjunction with brentuximab vedotin will be as described in Table 2. Drugs will be given on days 1 and 15 on a 28-day cycle for a total of 6 cycles. Brentuximab Vedotin will be administered after AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2).
<table>
<tr><th>Doxorubicin</th><th>Vinblastine</th><th>Dacarbazine</th><th>Brentuximab Vedotin</th></tr>
<tr><td>Day 1, 15
Of 28-day cycle</td><td>Day 1, 15
Of 28-day cycle</td><td>Day 1, 15
Of 28-day cycle</td><td>Day 1, 15
Of 28-day cycle</td></tr>
<tr><td>25 mg/m^2</td><td>6 mg/m^2</td><td>375 mg/m^2</td><td>1.2 mg/kg
Maximal dose=120 mg.</td></tr>
</table>
See paragraph 10</td></tr>
<tr><td>Assessment schedule</td><td>See paragraph 9

See flowchart 20.2</td></tr>
<tr><td>Statistical consideration</td><td><u>Sample size calculation</u>

In the Phase II portion of the study, 51 patients worldwide will be enrolled to estimate the 2-year progression free survival. Sample size calculation is based on providing an estimate of the PFS with a 95% confidence interval ±10% under the hypothesis that 2-year PFS is 85%.

<u>Analysis plan</u>

The primary endpoint of the phase II portion will be to estimate the two-year progression-free survival for AVD-brentuximab vedotin which will be done using Kaplan-Meier estimates and corresponding 95% confidence intervals based on standard errors using Greenwood’s formula.

Descriptive summaries and exploratory analyses for secondary objectives will be conducted. Significance</td></tr>
</table>

	for comparisons will be at the $p<0.05$ level. See paragraph 15

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
ABVD	Adriamycin (=Doxorubicin), Bleomycin, Vinblastine, Dacarbazine
ADC	Antibody-Drug Conjugate
AdvantageEDCSM	AMC Internet Data Entry System
AE	Adverse Event
AIDS	Acquired ImmunoDeficiency Syndrome
AJCC	American Joint Committee on Cancer
ALCL	Anaplastic Large Cell Lymphoma
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
AMC	AIDS Malignancy Consortium Clinical Trials
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplant
AST (SGOT)	ASpartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
AVD	Adriamycin (= Doxorubicin), Vinblastine, Dacarbazine
AVD-BR	Adriamycin, Vinblastine, Dacarbazine-BRentuximab vedotin
AZT	Zidovudine
BCSAP	B-cell Specific Activator Protein
βHCG	beta-Human Chorionic Gonadotropin
BSA	Body Surface Area
cART	Combined Antiretroviral Therapy
CBC	Complete Blood Cell
CFR	Code of Federal Regulations
cHL	Classical Hodgkin Lymphoma
cm	centimeter
CR	Complete Response
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP	AERS CTEP Adverse Event Reporting System
DARF	Drug Accountability Record Form
DCTD	Division of Cancer Treatment and Diagnosis
DDI	Didanosine
DFS	Disease Free Survival
DHHS	Department of Health and Human Services
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DTIC	Dacarbazine
DSUR	Development Safety Update Report

EBV..... Epirubicin, Bleomycin, Vinorelbine
EBVP .....Epirubicin, Bleomycin, Vinorelbine, Prednisone
ECOG..... Eastern Cooperative Oncology Group
EFS.....Event Free Survival
ELISA ..... Enzyme Linked Immunosorbent Assay
ESA .....Erythropoiesis Stimulating Agents
FDA.....Food and Drug Administration
FDG-PET ..... Fluorodeoxyglucose-Positron Emission Tomography
GCP.....Good Clinical Practice
GCSF..... Granulocyte Colony-Stimulating Factor
HAART..... Highly Active Antiretroviral therapy
HBV .....Hepatitis B Virus
HIV .....Human Immunodeficiency Virus
HL .....Hodgkin Lymphoma
HRS.....Reed Stemberg Cell
IDMC.....Independent Data Monitoring Committee
IDSA .....Infectious Diseases Society of America
IP .....Investigational Product
IPI..... International Prognostic Index
IPS..... International Prognostic Score
IV ..... IntraVenous
JCV .....John Cunningham Virus
kg.....kilogram
LDH ..... Lactic DeHydrogenase
LVEF..... Left Ventricular Ejection Fraction
LYSA ..... The Lymphoma Study Association
LYSARC.....The Lymphoma Academic Research Organisation
miRNA.....Mature microRNA
MMAE .....Monomethyl Auristatin E
MRI ..... Magnetic Resonance Imaging
MUGA .....Multiple Gated Acquisition scan
NADC .....Non-AIDS Defining Cancer
NCCN .....National Comprehensive Cancer Network
NCI.....National Cancer Institute
NHL ..... Non-Hodgkin Lymphoma
NLPHL.....Nodular Lymphatic Predominant Hodgkin Lymphoma
NNRT.....Non-nucleoside Reverse Transcriptase Inhibitors
NSC.....National Service Center
ODMC.....Operations and Data Management Center
OS ..... Overall Survival
PD .....Progressive Disease
PET .....18F-FDG Positon Emission Tomography
PCR.....Polymerase Chain Reaction

PFS ..... Progression Free Survival
PFT ..... Pulmonary Function Test
PK ..... PharmacoKinetics
PML ..... Progressive Multifocal Leukoencephalopathy
PO ..... Per oral [by mouth]
PR ..... Partial Response
RNA ..... Ribose Nucleic Acid
SAE ..... Serious Adverse Event
SD ..... Stable Disease
SPD ..... Sum of the Product of the Diameters
SPM ..... Second Primary Malignancy
SUSAR ..... Suspected Unexpected Serious Adverse Reaction
SUV ..... Standardized Uptake Values
TMA ..... Tissue Micro Array
ULN ..... Upper Limit of Normal
WHO ..... World Health Organization

4.0 RESPONSIBILITIES

4.1 Sponsor and Program Coordination Center

4.1.1 Sponsor

LYSARC (the Lymphoma Academic Research Organisation)
✉: Centre Hospitalier Lyon Sud – Secteur Sainte Eugénie - Pavillon 6D F-69495 Pierre Bénite Cedex
☎: +33(4) 72 66 93 33 Fax: +33(4) 72 66 93 71
Email: amc-085@lysarc.org

4.1.2 Coordinating Investigators

Pr Caroline BESSON
✉: Service d'hématologie et oncologie
CENTRE HOSPITALIER DE VERSAILLES
177, rue de Versailles - 78150 LE CHESNAY
France
☎💻 0145212577
Email : caroline.besson@bct.aphp.fr

Prof Nicolas Mounier
✉💻 CHU de Nice
Service d'Onco-Hématologie - 151 route St Antoine de Ginestière 06202 Nice
FRANCE
☎💻 04 92 03 58 41
Email : mounier.n@chu-nice.fr

4.1.3 Protocol Chair

Protocol Chair

Paul G. Rubinstein, MD
John H. Stroger Jr. Hospital of Cook County (Cook County Hospital)
Section of Hematology/Oncology
Administration Building
1900 W. Polk Street, Suite 755
Chicago, IL 60612
Tel: 312-864-7277
Fax: 312-864-9002
Email:
prubinstein@cookcountyhhs.org

Protocol Co-Chair

Ariela Noy, MD
Memorial Sloan-Kettering Cancer Center Lymphoma Service
1275 York Avenue
New York, NY 10065
Tel: 212-639-7423
Fax: 646-422-2284
Email: noya@mskcc.org

4.1.4 Program Coordination Center

Protocol Statistician	**Data Management/Operations**
Milan Bimali, PhD AMC Statistical Center University of Arkansas for Medical Sciences 4301 West Markham Street Little Rock, AR 72205 Tel: 501-686-8204 Fax: 501-526-6729 Email: mbimali@uams.edu	AMC Operations and Data Management Center The Emmes Corporation 401 N. Washington Street, Suite 700 Rockville, MD 20850 Tel: 301-251-1161 Fax: 240-238-2842 Email: amcpm@emmes.com
Project Manager Ombeline Vérité **Clinical Project Managers** ✉💻 Centre Hospitalier Lyon Sud Secteur Sainte Eugénie - Pavillon 6D 69495 PIERRE-BENITE Cedex – FRANCE ☎💻 +33 (0) 4 72 66 93 33 Fax: +33 (0) 4 72 66 38 57 Email: ombeline.verite@lysarc.org	

4.1.5 Biological/Pathological coordinator

Nadine VAILHEN, Director of Biological and Histopathological Operations
✉ CHU Henri Mondor - 51, av. du Maréchal de Lattre de Tassigny 94010 CRETEIL – FRANCE

Pathological coordinator:

Dr. Bettina FABIANI
✉💻 Hôpital Saint Antoine -Service d'Anatomie Pathologique - 184, rue du Fg Saint Antoine -75012 Paris – FRANCE
☎💻 +33 (0)1 49 28 21 76
Fax : +33 (0)1 49 28 28 78
Email:bettina.fabiani@sat.ap-hop-paris.fr

Biological coordinator:

Dr. Yassine TAOUFIK
✉💻 CHU Bicêtre - Service d'hématologie-immunologie biologiques 78, rue du Général Leclerc 94275 LE KREMLIN BICETRE
☎💻 01 45 21 35 94
Email: yassine.taoufik@bct.aphp.fr

4.2 Investigators

All participating LYSA centers from France may include patients in this study. Before any inclusion, each center must be declared to the Ethical Committee and national competent authority according to each country regulations and have had the initiation visit/call. To be declared as a participating center, the principal investigator must send to the LYSARC all administrative documents required for regulatory submission (e.g., Curriculum vitae, for France the affiliation medical association number [e.g., CNOM, RPPS] etc.).

4.3 Laboratory Sites

Laboratories of each study center must provide their normal values and an updated accreditation for quality control.

5.0 BACKGROUND AND STUDY RATIONALE

5.1 Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a lymphoid neoplasm first described by Thomas Hodgkin in the 1890s[2]. The disease presents with or without splenomegaly, fevers, night sweats, weight loss and occasionally pruritus. In 2008, 8,220 new cases of HL were diagnosed resulting in 1,350 deaths[1,3]. The transformed cell that defines classic Hodgkin lymphoma (cHL) is the Reed Sternberg cell (HRS), a large multinuclear cell expressing surface antigens CD15 and CD30 without B or T cell surface antigens[1]. The cell of origin was unclear until the mid-1990s, when it was shown that the tumor originated from germinal B cell lymphocytes, as demonstrated by the expression of PAX 5, B-cell Specific Activator Protein (BCSAP), and B cell clonality based on single cell PCR of the IgH gene[4-8]. Based on these data, the World Health Organization (WHO) changed the name from Hodgkin disease to Hodgkin lymphoma1. The four histological subtypes of cHL recognized by the WHO are mixed cellularity, nodular sclerosis, lymphocytic depletion, and lymphocyte predominant HL[1]. Nodular lymphocytic predominant HL (NLPHL) is quite different from cHL in that HRS present in NLPHL expresses mature B cell antigens, CD20, CD79a, does not express CD15 or CD30, and has a slow progressive course[1]. This trial will only include patients with HIV infection and cHL (HIV-cHL) in light the lack of CD30 expression, differences in disease biology, and the rarity of NLPHL in the HIV-positive population.

5.2 Hodgkin Lymphoma in HIV Patients

HIV-cHL is one of the most common non-acquired immunodeficiency syndrome (AIDS)-defining tumors[9]. Multiple large database studies of linked cancer and HIV/AIDS registries from 1992-2005 in the United States showed that HL represents the second to third most common non-AIDS defining cancer (NADC)[9,10]. One of these studies showed that the risk for HIV-cHL was 68% higher in 1996-2002, the post HAART era (SIR 13.6), than in 1990-1995 (SIR 8.1)[10]. In a comparative study conducted from 1992 to 2003, the trend over time in cancer rates for the HIV- cHL was elevated despite stable rates of HL in the general population[11]. Studies on HRS microenvironment in non- HIV associated HL showed that the HRS were surrounded by B and CD4 cells, eosinophils, macrophages, and fibroblasts, all of which affect its survival and disease course[12,13]. This trophic effect, due in part to CD4 cells, has been postulated to explain the increase in incidence of HIV-cHL in the post HAART era[12-14]. In addition, many observational studies consistently showed that HIV-HL patients present with higher CD4 counts compared to other HIV-associated lymphoproliferative disorders, with the exception of Burkitt's lymphoma[9-14].

As a population, patients with HIV have a 10-25 fold increase risk of developing HL, and they present with many high-risk characteristics that distinguish it from non-HIV cHL[15]. The differences are seen in patient presentation, histology, immunohistochemistry, molecular changes, and overall outcome[15]. The International Prognostic Score (IPS) for patients with advanced non HIV-HL defined the following adverse risk factors: age over 45 years, male gender, stage IV disease, low albumin, anemia, lymphopenia, and leukocytosis[16]. Eighty percent of patients with HIV-cHL present with stage III/IV disease, and 70-96% presents with B symptoms[15]. B symptoms, defined as one of the following: 1) drenching night sweats, 2) fever of over 100.4°F / 38°C for 3 consecutive days, and 3) a weight loss exceeding 10% of body weight in 6 months. These are also poor prognostic signs in stage I/II non-HIV HL. The two most aggressive histological forms of HL, mixed cellularity and lymphocytic depletion are predominate in HIV- cHL compared to the non-HIV population[15]. In

addition, histologically, the HRS is found in much higher concentrations in HIV-cHL than non HIV-cHL[15]. HIV-cHL is associated in 80-100% of the cases with EBV co-infection of the HRS, though in the non-HIV cHL patients this occurs only with a frequency of 30-40%[15,17,18]. The expression of the Epstein-Barr Virus (EBV) has been identified by both single cell polymerase chain reaction (PCR) and co-immunohistochemical analysis of the HRS in HIV-infected patients [15,17,18]. The HRS in non-HIV patients are derived from germinal center B cell lymphocytes, on the other hand, the origin of HIV-associated HRS have been linked to post germinal lymphocytes [19]. It is interesting to note that diffuse large B-cell lymphoma derived from non-germinal center have a worse prognosis than germinal cell derived large cell lymphoma in most studies. It is unclear the role each factor plays in disease outcome (i.e., HRS origin, EBV co-infection status, presentation, and histology) but it is clear that outcomes for patients with HIV-cHL are inferior to HIV-negative patients.

For HIV-cHL, the median complete remission rate is about 58% with a median survival 8-20 months in the pre HAART era, which is substantially lower than the median complete remission rate of approximately 90% with a median survival of 7 years for HIV-negative patients [15,20,21]. Retrospective data showed improved overall survival in the post HAART compared to treatment without HIV therapy [21,22]. Both studies showed an improved 2 year overall survival while taking HAART, ranging from 16 to 42% depending on the study [21,22]. Similarly, of the four HIV-HL trials completed while utilizing combined antiretroviral therapy (cART), the overall survival has varied from 86% at 2 years to 51% at 3 years, an improvement compared to the historical controls in the pre HAART era, but still lagging behind historical controls of non-HIV infected patients [23-26]. Explanations for poorer survival are likely multifactorial, including treatment-related toxicity, EBV status, HRS non-germinal cell of origin, tumor biology, histology, and presentation. More prospective trials and newer treatments are needed to improve on the outcomes of HIV-positive patients to where they are comparable to the HIV-negative population.

5.3 Current treatment for HIV-related HL

Currently, no standard of care exists for the upfront treatment of HIV-cHL. Outcomes of clinical trials for HIV-cHL in the pre- and post-HAART era are summarized in Table 1. In the pre-HAART era, the AIDS Clinical Trials Group (ACTG 149) performed a prospective multi-institutional clinical trial of ABVD with supportive GCSF[27]. Antiretroviral therapy was not used. Among 21 patients enrolled between 1992 and 1996, 90% had B symptoms at presentation, and 67% had stage IV disease. Complete remission (CR) was attained in only 9 patients (43%; 95% CI: 24%-63%), a partial remission (PR) in 4 subjects (19%), resulting in a 2 year OS was 48%[27]. Even with routine GCSF use, 10 patients developed severe neutropenia and opportunistic infections (OIs) occurred in 6 patients (29%) during the study. A similar study with EBVP utilizing only zidovudine (AZT) or didanosine (DDI) as HIV therapy showed an equivalent 2 year OS of 40% [28].

Retrospective data showed a positive effect of HAART on OS, disease free survival (DFS), and infectious complications, though these benefits have been limited to studies implementing HAART. As illustrated above, the difference between no HAART and single agent antiretroviral therapy is minimal [27, 28]. Comparing sequential HIV- cHL studies with ABVD with cART and without HAART, the OS improved from 48% at 2 years to 76% at 5 years. [27, 24]

In the post HAART era, only 5 prospective studies have been completed all with cART

[23-26,30]. A study of therapy with ABVD regimen in patients with advanced stage HIV-HL assessed the outcome in 62 patients (1996-2005) with advanced stage HL from multiple centers in Spain[24]. Six patients died during induction, 54 (87%) achieved CR and 2 had resistant disease. After a median follow up of 39 and 47 months, 5 year EFS probability was 71% and OS was 76% [24]. An immunological response was observed in 56% and a virological response in 68%. The immunological response to HAART had a positive impact on OS and EFS[24].

The VEBEP, Stanford V, and BEACOPP standard studies included all stages of HIV-cHL, and despite the inclusion of earlier stages, OS in each study did not compare well to ABVD, (see Table 1) [23-33]. The BEACOPP regimen did show an improved CR rate compared to ABVD (100% vs. 87%), but only 66% of subjects were able to tolerate the 6 courses of BEACOPP compared to 82% in the ABVD trial. Also, 3 of the 12 participants in the BEACOPP trial died during chemotherapy (25%). Thus, based on OS, adverse events, and PFS, ABVD currently is the most promising regimen studied for advanced stage HIV-cHL [23-30].

Table 1: Summary of Retrospective and Prospective Trials of HIV-cHL

Regimen	Trial Type	HAART	# Patients	Year	Stage III/IV%	OS% (Months)
MOPP or ABVD or MOPP/ABVD +/- RT 31	Retrospective	Pre-HAART	71	1992	80%	Median Survival (14)
MOPP or ABVD or MOPP/ABVD +/- RT 32	Retrospective	Pre-HAART	45	1993	75%	Median Survival (20)
MOPP or ABVD or MOPP/ABVD +/- RT 28	Retrospective	Pre-HAART	46	1994	89%	Median Survival (15)
MOPP or ABVD or MOPP/ABVD +/- RT 28	Retrospective	Pre-HAART	24	1991	92%	Median Survival (15)
MOPP or ABVD or MOPP/ABVD +/- RT 28	Retrospective	Pre-HAART	23	1991	74%	Median Survival (8)
MOPP/ABVD +/- RT 28	Retrospective	Pre-HAART	13	1988	92%	Median Survival (14)
EBV 29	Prospective	No-HAART	17	1994	88%	11 months
ABVD 27	Prospective	No-HAART	21	1992-6	67%	48% (24)
EBVP 28	Prospective	AZT or DDI	35	1993-7	66%	40% (24)
ABVD 30	Prospective	HAART	8	2002	75%	43 Months
Stanford V 23	Prospective	HAART	56	2005	71%	59% (60)
BEACOPPstd 26	Prospective	HAART	12	2002	92%	75% (36)
VEBEP 25	Prospective	HAART	28	1996-05	71%	69% (24)
ABVD 24	Prospective	HAART	62	2007	100%	76% (60)

Regimen abbreviations: ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), VEBEP (vinorelbine, epirubicin, bleomycin, cyclophosphamide, prednisone), EBVP (epirubicin, bleomycin,

vinorelbine, prednisone), EBV (epirubicin, bleomycin, vinorelbine), BEACOPPstd (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), and RT (radiation therapy).

5.4 Rationale for the use of brentuximab vedotin in HIV-cHL

Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components:

(a) the antibody cAC10, specific for human CD30, (b) the highly potent anti-microtubule agent, monomethyl auristatin E (MMAE), and (c) a protease-cleavable linker that covalently attaches MMAE to cAC10[34]. The biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage [34]. Binding of MMAE to tubulin prevents its polymerization, thus disrupting the microtubule network within the cell, inducing cell cycle arrest, and apoptotic death of the CD30-expressing tumor cell[34]. MMAE was found to be a quasi-irreversible, mechanism- based CYP3A inhibitor, and, to the limited extent that metabolism occurred, the primary metabolites were formed by CYP3A4 [34,35]. CD30, a member of the TNF-receptor (TNF-R) super family, is a transmembrane glycoprotein receptor normally found on the surface of activated T cells but present on a variety of cell types of hematopoietic origin. The CD30 antigen has a very low expression on normal cells but is found on the HRS cells of HL, anaplastic large cell lymphoma (ALCL), and other T cell lymphoproliferative disorders. While the function of CD30 has not been clearly defined, CD30 has been implicated both in cell death and proliferation [34,35]. The utility of CD30 as a diagnostic marker for malignancies (including HL and ALCL), its limited normal tissue expression profile, and its apoptosis-inducing characteristics have led to the investigation of this antigen as a target for immunotherapy. Brentuximab vedotin has been studied and is FDA approved in the relapsed/refractory setting for ALCL and non- HIV cHL [36-40]. In the frontline setting, a phase I study is currently ongoing with brentuximab vedotin for non-HIV-cHL in combination with AVD [41].

A phase 1 study of brentuximab vedotin was performed in relapsed and refractory CD30 positive malignancies, including ALCL and HL. Patients had a median of 3 prior chemotherapy regimens (range 1-7) with 73% of patients having previously received an autologous stem cell transplant (ASCT) [36]. The brentuximab vedotin dose levels ranged from 0.1 to 3.6 mg/kg (2-hr outpatient IV infusion) every 3 weeks. Brentuximab vedotin was generally well- tolerated in the study. The most common adverse events, which occurred in 20% of patients or more, were fatigue, pyrexia, nausea, and diarrhea. The neutropenia observed appeared to be dose-related. The maximum tolerated dose was 1.8 mg/kg every 3 weeks. One patient treated at 3.6 mg/kg developed febrile neutropenia and presumed sepsis, and died 14 days after the first dose of brentuximab vedotin. Neuropathy was also observed in some patients, especially after repeated dosing. Approximately 75% of patients reporting B symptoms at baseline experienced symptom resolution while on study. Despite a median 3 prior chemotherapy regimens per patient including 75% with prior ASCT, 88% of the patients in the study experienced tumor reductions. The objective response rate (CR+PR) was 46% (n=13), with a CR rate of 25% (n=7). Two additional PRs were observed in the 0.6 mg/kg cohort. Median response duration to date was 22 weeks (range, 0.1+ to 38+ weeks) [39-41].

A phase 2 study of brentuximab vedotin (SGN-35) studied 102 patients with relapsed

or refractory HL post autologous stem cell transplant [41]. Patients received brentuximab vedotin every three weeks at a dose of 1.8 mg/kg. The median duration of brentuximab vedotin treatment was 27 weeks (range 3-54). The most common treatment-related adverse events (AEs) of any grade in >15% of patients were peripheral sensory neuropathy (43%), fatigue (40%), nausea (35%), neutropenia (19%), diarrhea (18%), and pyrexia (16%). Most events were Grade 1 or 2. The Grade 3 treatment-related AEs reported in more than 1 patient were neutropenia (14%), peripheral sensory neuropathy (5%), thrombocytopenia and hyperglycemia (3% each), and fatigue (2%). The only Grade 4 treatment-related events were neutropenia (4%), and thrombocytopenia, abdominal pain, and pulmonary embolism (1% each). There we no related Grade 5 events. Eighteen patients discontinued treatment due to an adverse event[41]. While no interim analysis was presented with respect to overall response rate, there was a 95% reduction of tumor size and an 83% resolution of B symptoms [41].

5.5 Rationale for substitution of brentuximab vedotin for bleomycin in ABVD regimen

Bleomycin is associated with significant pulmonary toxicity, particularly in the setting of radiation involving lung fields as is typically prescribed in the context of bulky mediastinal Hodgkin lymphoma. There are no large studies addressing the incidence of bleomycin-associated pneumonitis in the setting of HIV-HL. Outside of HIV, the incidence of bleomycin-associated pneumonitis with ABVD in HL has been reported in the range 10-15%. A randomized trial comparing ABVD to Stanford V (25% of the bleomycin dose) reported a 10% versus 2% incidence of pulmonary toxicity, respectively, requiring early discontinuation of bleomycin in 20/23 subjects [42,80]. A separate, single institution retrospective study demonstrated a 15% incidence in bleomycin pneumonitis in 184 HL patients treated with ABVD [43]. In this study, low albumin and use of GCSF were the factors most predictive of bleomycin toxicity. These factors are both likely to occur with high incidence in the HIV HL population where more advanced HL presentation is typical and the increased risk of marrow suppression with chemotherapy, use of GCSF is often required to maintain or approximate optimal chemotherapy dose density in the setting of HIV and aggressive lymphomas.

The substitution of brentuximab vedotin for bleomycin is being explored in the general HL population. A phase 1, open-label, multicenter study is currently underway to evaluate the safety of brentuximab vedotin when administered in combination with standard therapy with AVD (ClinicalTrials.gov #NCT01060904) as the combination with ABVD had intolerable pulmonary toxicity[41]. Patients have received doses of 0.6, 0.9, or 1.2 mg/kg brentuximab vedotin with standard doses of ABVD or 1.2 mg/kg brentuximab vedotin with AVD, depending upon cohort assignment. The combination regimens were administered on Days 1 and 15 of each 28-day cycle for up to 6 cycles of therapy. Each regimen evaluated a dose limiting toxicity (DLT) period, defined as any Cycle 1 toxicity requiring a delay of ≥7 days in standard ABVD or AVD therapy[41]. This is the first trial to dose brentuximab vedotin every two weeks and in combination with multi-agent chemotherapy. Interim data of the first 31 patients treated were recently presented[41]. Six patients received 0.6 mg/kg, 13 received 0.9 mg/kg, and 6 received 1.2 mg/kg with ABVD; 6 patients received 1.2 mg/kg with AVD. Patient baseline characteristics included: Stage IV, 55%; IPS score ≥4, 29%; male, 77%; median age, 35 years (range, 19-59). The combination of chemotherapy and brentuximab vedotin treatment had no DLT observed up to 1.2 mg/kg in either regimen[41]. AEs reported in ≥45% of patients, regardless of severity, were nausea and neutropenia (77% each); peripheral sensory neuropathy (48%); and fatigue (45%).

Infusion-related reactions occurred in 23% of patients. Grade 3/4 AEs observed in >10% of patients were neutropenia (74%), febrile neutropenia (16%), and anemia (13%). No Grade 5 AEs were observed. Overall, 6 patients discontinued combination treatment due to an adverse event. In the ABVD cohorts (n=25), AEs of pulmonary toxicity, dyspnea, and interstitial lung disease that could not be distinguished from bleomycin toxicity led to discontinuation of bleomycin in 7 patients. Five of these 7 patients continued treatment with AVD and brentuximab vedotin[41]. The expansion cohort of approximately 20 patients is currently enrolling at the 1.2 mg/kg brentuximab vedotin dose combined with AVD therapy [41]. An international phase III study comparing ABVD versus AVD in combination with brentuximab vedotin is currently under development. This AMC trial will help define more clearly how this regimen can be used in the HIV-infected population.

While it is desirable to replace bleomycin with a less toxic alternative in the general HL population, the argument is even more compelling in the HIV-HL population with a higher prevalence of risk factors associated with bleomycin toxicity, i.e., intercurrent infection, and a higher prevalence of tobacco use. In replacing bleomycin, risk of reduced efficacy exists. Given this, as well as the preliminary efficacy data of brentuximab vedotin + AVD in the general HL population, a dose de-escalation design is chosen for this study to maximize anti-tumor activity of the regimen for each cohort.

5.6 Considerations regarding progressive multifocal leukoencephalopathy associated with HIV, brentuximab vedotin, and HIV-cHL

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the lytic replication of the John Cunningham Virus (JCV). It typically occurs in immunocompromised individuals and is nearly uniformly fatal [48-54]. In a clinical study conducted by Koralnik et al, 80% of reported PML patients had AIDS, 13% had hematologic malignancies, 5% were transplant recipients, and 2% had chronic inflammatory diseases [49]. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%) [48]. The onset of neurological deficits may occur over weeks to months[48]. In a retrospective study, data showed the incidence of PML in patients with NHL is 8 per 100,000 patient years, though the incidence in cHL or HIV-cHL is not known. In the onset of the HIV epidemic, the incidence of the PML was 3.4 per 1000 patient years at risk with HIV [50,51]. But in the era of HAART, the incidence has decreased to 1.3 patients per 1000 patient years[51]. In a Swiss HIV cohort study, a multivariate analysis showed that of the 226 patients diagnosed with PML from 1998 to 2007, HAART was associated with a hazard ratio of 0.22 ($p<0.01$). A trend was seen for decreased incidence with elevated CD4 counts[52]. Compared to patients with CD4 counts below 50 cells/µl, the hazard ratio for patients with CD4 counts above 100 cells/µl was 0.75 ($p<0.38$)[52].

Recently PML has been reported in HIV negative patients receiving antibody based immunomodulatory therapies for lymphoma, multiple sclerosis, and collagen vascular diseases treated with antibodies rituximab, efalizumab, and natalizumab [53]. To date 3 patients treated with brentuximab vedotin have developed PML, each in the relapsed refractory setting, with 3 to 6 chemotherapeutic regimens before treatment with brentuximab vedotin[54]. To curtail the risk of PML in this study, no patients with a CD4 count below 50 cells/µl will be permitted on study, all participants will be required to take HAART, and MRI scans pre-study will be required. In addition, we will incorporate stopping rules should any patient develop PML with a CD4 count > 50 at

the time of PML diagnosis.

5.7 Rationale for use of concurrent HAART with HL treatment

The improvement in outcomes of HIV-cHL patients to standard treatment in the HAART era is partially related to the HAART therapy itself. Given this and concerns above regarding HIV viremia with CD30 perturbation and PML, we will require patients to be on HAART. Chemotherapy-HAART interactions have become more pronounced in the transition from single agent HIV therapies to the era of cART as protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRT) are potent inhibitors or inducers of the cytochrome p450 system [55]. In early studies with HIV-cHL treated with EBVP, where only AZT or DDI was used as antiviral therapy, 1% neurotoxicity all grades, 7% Grade 3/4 leukopenia, and 3% G3/4 anemia were observed. However, in a single institution retrospective study of 23 patients treated with ABVD, while taking HAART, 31% were found to have neuropathy (all grades), 68% G3/4 neutropenia, and 57% G3/4 anemia [56]. Correlations were then made comparing all adverse events with HAART therapy. Of the patients with neuropathy, 13% had grade 3 sensory neuropathy and each developed the symptoms before cycle 2 of ABVD. Many had symptoms years after therapy. One hundred percent of the patients with neuropathy were taking ritonavir based HAART[56]. Similarly, 75% of the patients who were taking ritonavir based HAART developed G3/4 neutropenia, as opposed to only 21% taking non- ritonavir based HIV-therapy. Lastly, it was noted that 82% of the patients with Grade 3/4 anemia were taking ritonavir and or AZT in some combination. Based on these data, at this institution made a policy to utilize only non- ritonavir and non-AZT based HAART regimens during treatment for HIV-cHL57. Twelve patients were subsequently treated, and neuropathy, febrile neutropenia, G4 neutropenia, and G4 anemia had decreased by 100%, 100%, 20%, and 15% respectively [57].

One concern to be managed in the current study is the overlapping toxicities of brentuximab vedotin and vinblastine, both of which have been shown to cause neuropathy and neutropenia. To prevent potentiating any adverse events, we will require subjects' HAART regimens to exclude ritonavir or AZT. Cobisistat, another potent inhibitor of the CYP 3A4 enzyme system, will also be excluded from the study. Any new forthcoming CYP 3A4 inhibitors will be excluded.

Despite these changes, many of the HAART drugs undergo metabolism by and can induce or inhibit various CYP450s enzyme systems. Therefore, all patients will be closely monitored for AEs throughout the entire study. In addition, pharmacokinetics will be studied in a subset of patients to confirm whether alterations in exposure correlate with the AEs.

5.8 Rational for use of PET scans in HIV patients and HIV-HL

The use of FDG-PET scans in HL patients is increasingly being used for prognostic significance in during treatment in the HIV negative setting. Data by Galamini et al. showed a FDG-PET scan done at the completion of cycle 2 was more prognostic than the IPS score for advanced Hodgkin lymphoma [58,59]. A negative PET scan after two cycles of ABVD predicted a 96% 2-year PFS. Similar data reported in abstract form regarding ABVD and rituximab showed a negative PET correlated with a 5-year EFS of 93% vs. 75% for those who remained PET positive (p=0.05)[58-60]. The prognostic significance of PET scanning in the HIV patients with HL is unknown. At issue is FDG-PET scanning in the setting of HIV alone without malignancy is frequently positive. One report suggested FDG activity might correlate with detectable HIV viral loads[61]. Thus, it is important to correlate FDG-PET in combination with CT scans (FDG-

PET/CT scan). Experience with PET scanning in the HIV setting with malignancy requires further study. Therefore, we plan to use baseline, post cycle #2 interim, and post-treatment FDG-PET/CT scans prospectively in this study, to correlate scan positivity with PFS and OS. The Deauville 5 point criteria will be used to record the interim FDG-PET scan [91,92]. The Deauville criteria capture gradations of FDG uptake from no uptake (1 point) to new disease (5 points). For the purposes of this study, we will record the Deauville score and determine whether scores of 3-5 or 4-5 are predictive of relapse. Notably, SUVs can be affected by inflammation related to therapy as in the case of rituximab or HIV related inflammation.

5.9 Brentuximab vedotin relevant preclinical data

Little to no data exists on the dosing of 1.2mg/kg of brentuximab vedotin to be used in this study, and no information exists on its interactions with anti-HIV medications. The data summarized below were obtained using 1.8mg/kg.

Pharmacokinetic parameters for individual patients were determined using concentrations of serum brentuximab vedotin ADC, plasma MMAE, serum TAb, and actual sampling times relative to the start of the infusion. The maximum concentrations for the serum PK of brentuximab vedotin ADC following an IV dose of 1.8 mg/kg were typically observed at the end of infusion. A multi-exponential decline in ADC serum concentrations was observed with a terminal half-life (t1/2) of approximately 4 to 6 days. Exposures were approximately dose proportional. After administration of multiple doses of brentuximab vedotin, steady-state was achieved by 21 days, consistent with the t1/2 estimate. Minimal to no accumulation was observed with multiple doses with the q3wk regimen, and ADC exposure did not decrease with subsequent doses.

The plasma PK profile of MMAE following an IV dose of 1.8 mg/kg brentuximab vedotin appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. Tmax ranged from approximately 1 to 3 days. Exposures were linear and approximately dose proportional with MMAE exposures decreasing after multiple doses with approximately 50% to 80% of the exposure of the first dose observed at subsequent doses. After administration of multiple doses of brentuximab vedotin, MMAE steady-state was achieved by 21 days, similar to ADC. Total antibody exposures were approximately dose proportional and higher than brentuximab vedotin ADC exposures while Tmax was similar.

5.10 Study Design and Rationale

Based on the evidence presented above, specifically the remarkably high response of brentuximab vedotin in the relapse setting, the AMC has proposed a phase 1 clinical trial with a de-escalation design evaluating 3 doses of brentuximab vedotin (1.2 mg/kg, 0.9 mg/kg, and 0.6 mg/kg) given every 2 weeks with AVD in a 28-day cycle followed by a phase 2 clinical trial.

Overall fifty-one patients (20 in France) in the phase II trial will be treated for 6 cycles for a 5-year follow up. The primary end point of the phase II portion will estimate the two-year progression free survival for AVD-brentuximab vedotin. The secondary endpoints of both phases will be to evaluate AVD-brentuximab vedotin with regard to 1) the toxicity of patients taking concurrent HAART, 2) the effects on viral load, CD4, and CD8 counts, and 3) PR, OS, EFS. Other non-treatment related endpoints for both phases will be the predictive value of FDG-PET on 2 year PFS and a characterization of HIV-cHL subtypes in the post HAART era.

We hypothesize that AVD-brentuximab vedotin will 1) improve HIV-cHL OS to be more consistent with the non-HIV population 2) be administered safely with cART regimens lacking ritonavir or AZT. We also anticipate cycle 2 FDG/PET-CT will be prognosticate OS in the HIV population.

We will collect biological samples to be able to participate in correlative studies to monitor the effects brentuximab vedotin will have on the viral replication of HIV. With respect to HIV replication, we will assess viral loads and CD4 counts every 2 cycles during therapy and every 3 months for 1 year post treatment.

6.0 STUDY OBJECTIVES

6.1 Primary Objective

Establish an estimate of the two-year progression free survival for patients with HIV-associated stage III-IV Hodgkin lymphoma when treated using brentuximab vedotin plus the AVD chemotherapy regimen.

6.2 Secondary Objectives

- To evaluate the toxicity of AVD and brentuximab vedotin with HAART.
- To estimate the partial response (PR) rate, complete response (CR) rate, overall survival (OS), and event free survival (EFS) at 2 and 5 years.
- To evaluate the effect of AVD and brentuximab vedotin on CD4 and CD8 counts after cycle 1, 4, at the end of therapy, and every 3 months after treatment completion for one year.
- To investigate the prognostic value of FDG-PET/CT scans at baseline, after cycle 2, and at treatment completion, with respect to 2 year progression free survival.
- To evaluate HAART status at baseline and to correlate this with tumor response to therapy and OS and PFS.
- To characterize the histologic subtypes in HIV-HL in the highly active antiretroviral therapy (HAART) era.
- To assess the neurotoxicity of HAART in combination with AVD and brentuximab vedotin.
- To evaluate effect of AVD and brentuximab vedotin on viral load after cycles 1, 4, at completion of therapy, and every 3 months after treatment completion for one year.

7.0 STUDY DESIGN

This study is a multicenter, phase II trial.

Patients will be recruited over 2 years and followed until 5 years after the completion of therapy.

The anticipated study dates (start / end) are:

- 1st patient included (FPFV): 01/JUN/2015
- Last patient included (LPFV): 01/JUN/2017

It is expected that a total of 20 patients in France among the 51 patients needed in the protocol developed by AMC will be included in the study.

The duration of the treatment period is 6 cycles of 4 weeks of chemotherapy.

End of study is defined by the last visit planned by the protocol of the last patient in follow-up.

8.0 STUDY POPULATION

Previously untreated individuals diagnosed with stage III-IV, HIV-associated, CD30-positive, classic Hodgkin Lymphoma (cHL), as defined by the 2008 WHO classification of hematological malignancies[1].

All protocol participants must meet all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied prior to subject enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

8.1 Inclusion criteria

1. Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of brentuximab vedotin in combination with AVD in patients <18 years of age, children are excluded from this study.
2. HIV-1 positive. Documentation of HIV-1 infection by means of one of the following:
   - Documentation of HIV diagnosis in the medical record by a licensed health care provider;
   - Documentation of receipt of ART by a licensed health care provider;
   - HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstration > 1000 RNA copies/mL;
   - Any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed HIV assay such as a HIV-1 Western blot confirmation or HIV rapid multisport antibody differentiation assay.
3. Histologic diagnosis of CD30-positive classical HL as defined by the 2008 WHO Classification of Hematological diseases. Nodular lymphocyte predominant Hodgkin Lymphoma is not eligible.
4. Stage III or IV disease as defined by the Ann Arbor Staging System.
5. Participants must have previously untreated HIV-cHL, with the exception of up to 14 consecutive days of steroids, emergency radiation, or 1 prior cycle of cyclophosphamide to reduce tumor burden and improve hyperbilirubinemia in the setting of lymphoma related liver involvement.
6. Normal baseline cardiac ejection fraction ≥ 50%.
7. Serum creatinine of ≤ 1.5 mg/dL. If creatinine >1.5 mg/dL (133 micromol/L), creatinine clearance must be ≥ 60 mL/minute according to MDRD/Cockroft-Gault formula.
8. ANC ≥ 1000/μL and platelets ≥ 75,000/μL unless related to bone marrow involvement by HIV-cHL.
9. Total bilirubin must be < 1.5x the upper limit of normal, unless the elevation of bilirubin is thought to be secondary to Gilbert's syndrome or cART.
   - If, however, the elevated bilirubin is felt to be secondary to antiretroviral therapy, the total bilirubin must be ≤ 3.5 mg/dL (60 μmol/L), provided that the direct bilirubin is normal and the AST and ALT ≤ 3 x the upper limit of normal.
   - If the elevation of bilirubin is thought to be secondary to Gilbert's syndrome, the total bilirubin must be ≤ 3x the upper limit of normal or the direct bilirubin must be ≤ 1.5x the upper limit of normal.
   - Also, if the elevated bilirubin is thought to be secondary to cHL the same criteria for hyperbilirubinemia should be applied however 1 prior cycle of cyclophosphamide is permitted in attempt to make the participant eligible (see section 8.1.5). Patients should not be excluded from study participation unless

dosing cannot be safely established per Section 10.6.2.

10. Female subjects must have a negative pregnancy test within 1 week of enrollment and all subjects must agree to use two reliable methods of contraception simultaneously if conception is possible during the study.
    a. Should a woman subject become pregnant or suspect she is pregnant while the subject is participating in this study, she should inform her treating physician immediately. The patient will then be removed from protocol therapy.
    b. Subjects who father a child while participating in the study will be permitted to continue with the protocol. The subject, however, is required to notify the investigator if he fathers a child.
11. Ability to understand and the willingness to sign a written informed consent document.
12. Karnofsky performance status > 30% (given the aggressiveness of this disease and the often severely debilitated nature of the patients at initial presentation). See Appendix 20.5.
13. Measurable or non-measurable (evaluable) tumor parameter(s). Non-measurable tumor parameters will be defined as not having bi-dimensional measurements (i.e., gastric or marrow involvement) but can be followed for response by other diagnostic tests such as gallium, PET imaging and/or bone marrow biopsy.
14. Patients already receiving erythropoietin or GCSF for treatment of HIV-related cytopenia are eligible.
15. CD4 count ≥ 100 cells/µl and serum HIV viral load <50copies/ml
16. Subjects are required to be on antiretroviral regimens that are in accordance with the current International AIDS Society guidelines concurrently with chemotherapy. Use of experimental antiretroviral agents or those containing zidovudine (including Combivir and Trizivir) or ritonavir (includes Norvir® or Kaletra®),, cobicistat or **Didanosine (Videx® or Videx EC®),** or similar potent CYP3 inhibitors are prohibited, as explained in Section 5.7. In order to be eligible, patients taking zidovudine or didanosine or ritonavir, or cobicistat or **Didanosine,** or other CYP3 inhibitors must change to a different regimen 7 days prior to therapy initiation. Subjects must be on HAART for at least 7 days prior to therapy. See section 10.3
17. Patients will be required to obtain a pulmonary function test, despite the exclusion of bleomycin from protocol regimen. The subject's diffusing capacity of the lung for carbon monoxide (DLCO) adjusted for hemoglobin must be greater than 70% predicted to enter the study and to continue with brentuximab vedotin.
18. Negative for Hepatitis B, or if infected with Hepatitis B, receiving anti-Hepatitis B therapy. All subjects will be required to be screened for Hepatitis B. Per IDSA and AASD guidelines, those subjects that show no immunity, defined by the lack of Hepatitis B surface antibody, and show evidence of chronic infection (i.e., HBsAg+, HBcore+, HBsAB-) will be required to be on anti-Hepatitis B therapy during the study in order to be eligible. Patients will be permitted to enroll in the study provided normal liver function tests (see Section 9.3) and no evidence of cirrhosis. The exact Hepatitis B therapy will be at the discretion of the infection disease specialist or investigator. However all patients who present with acute hepatitis B or show normal transaminases and are HBsAg+ and IgM+ for Hepatitis core antigen will not be eligible for trial enrollment.
19. Patients diagnosed with Hepatitis C who are Hepatitis C antibody positive, whether Hepatitis C RNA level is measurable or not, must have no evidence of cirrhosis and have liver function tests that conform to Section 9.3.

20. Brentuximab vedotin is partially metabolized via the CYP3A4 pathway and is cleared from the cells via the P-glycoprotein pump. Therefore, participants must discontinue use of the following agents within 7 days prior to therapy as per Appendix 20.9:

    - Strong CYP 3A4 inhibitors that treat HIV, see 3.1.16.
    - Other strong CYP3A inhibitors.
    - Moderate CYP3A4 inhibitors should be used with Caution but are not excluded. If 2 moderate CYP3A4 inhibitors are used concurrently, one must be discontinued at least 7 days (1 week) prior to the initiation of chemotherapy.
    - P-glycoprotein inhibitors.
    - If patients are taking any of these excluded medications, they must be discontinued at least 7 days (1 week) prior to the initiation of chemotherapy.

    All concomitant medications must be reviewed by the study chair or co-chair prior to enrollment by email.
    Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

8.2 Exclusion criteria

Patients who do not fulfill the criteria as listed in Section 8.1 above, are ineligible. Additionally, the presence of any of the following conditions will exclude a subject from study enrolment:

1. Patients with prior anthracycline therapy will be excluded.
2. Female subjects who are pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum b-human chorionic gonadotropin (b-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
3. Medical illness unrelated to HL, which in the opinion of the study physician will preclude administration of chemotherapy safely. This includes patients with uncontrolled infection (including opportunistic), chronic renal failure, myocardial infarction (MI) within the past 6 months, unstable angina, or cardiac arrhythmias other than chronic atrial fibrillation.
4. Prior malignancy within 5 years of enrollment other than curatively treated cutaneous basal cell or squamous cell carcinoma, carcinoma in situ of the cervix, anal intraepithelial neoplasia, or cutaneous Kaposi's sarcoma (KS).
5. Grade 2 or greater peripheral neuropathy.
6. Evidence of PML identified on the pretreatment MRI.
7. Central nervous system disease.
8. Patients with history of JC Virus identified in the CSF or previous history of PML will be excluded from the study.
9. Cirrhosis secondary to any cause will be excluded.

9.0 STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS

9.1 Study flow chart

See on appendix 20.2.

9.2 Informed consent

To participate in this study and before any baseline or screening evaluation, a written informed consent must be signed by each patient. Written informed consents for biological and genetic studies must be signed before sampling. These consents are signed after investigator gave all information required to the patient.

The patient and the investigator will date and sign the informed consent form.

An original copy of the signed consent will be provided to the patient; the original will be maintained in the investigator's study file.

9.3 Baseline examination

Unless otherwise specified, the following evaluations must be performed within 6 weeks prior to patient registration:

1. **Medical history**, history of drug allergies, history of current and past anti-retroviral regimens, if available; and history of any prior AIDS-defining conditions. Date of initial lymphoma diagnosis is required, with a copy of the pathology report in the medical record. Presence of systemic "B" symptoms should be noted, as well as other symptoms of cHL. Current concomitant medication list, including all anti-retroviral, anti- viral, antibiotics, and opportunistic prophylaxis should be obtained.
2. **Physical examination**, including performance status (see Appendix 20.5 Performance Status Scale), vital signs (weight, height, body surface area), neurological examination, and if available, two dimensional measurement of all palpable, peripheral lymph nodes and measurement of other sites of disease present on physical exam.
3. A combined FDG-PET/CT or FDG-PET + CT scan with and without IV contrast is required for this study. If a patient has an allergy to IV contrast, a non-IV contrast CT scan will be permitted. To ensure consistency between all centers, FDG-PET/CT scans at diagnosis should be conducted no more than 28 days before enrolment.
   If the CT scan of a PET/CT hybrid is performed with both oral and IV contrast with contrast enhancement in the arterial and/or portal venous phase, with at least a 2-slice CT, and is acquired with at least 80 mAs and CT scans are obtained with contiguous sections (with a maximum of 5 mm slice thickness), then the pre-treatment PET/CT scan alone will suffice for patients enrolled on this trial. If no contrast is used in the FDG- PET/CT, an additional CT scan with contrast is required of the neck, chest, abdomen, and pelvis, see paragraph 9.3.
4. CT scan of the neck (if palpable lymphadenopathy only), chest, abdomen and pelvis with and without IV contrast will be required. If the CT portions of the FDG-PET/CT combination scan is a non-contrast CT scan, then a separate CT scan with and without IV contrast will be required.
5. MRI of the brain with and without IV gadolinium contrast, to look for early evidence of PML.
6. Determination of LVEF by MUGA scan or echocardiogram.
7. **PFTs** with volumes, spirometry, DLCO and room air pulse oximetry. Patients will be required to obtain a pulmonary function test, despite the exclusion of bleomycin. The DLCO adjusted for hemoglobin must be greater than 70% predicted to enter the study and to continue with brentuximab vedotin.

8. **Bone marrow biopsy** for histology and determination of percent bone marrow involvement. If bone marrow involvement by lymphoma has already been documented after bone marrow biopsy performed more than 6 weeks prior to registration, the biopsy does not have to be repeated.
9. **Central pathology review** for confirmation of histology of lymphoma specimen: Biopsy material at diagnosis will be sent to confirm HL and histologic subtype. (See Appendix 20.1 and 20.7 for the acceptable specimens required for central review and for handling instructions).
   All specimens will be reviewed by a panel of pathologists and must be submitted within 30 days of study enrollment. Patients who are found not to have HIV-HL will be withdrawn from the study
10. Laboratory tests, including:
    - CBC with differential and sedimentation rate (within 2 weeks prior to patient registration).
    - Serum chemistries: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, and phosphorus), glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT (within 2 weeks prior to patient registration).
    - CD4 and CD8 cell count.
    - HIV-1 RNA viral load assessed by any approved viral load assay at the local laboratory. This must be performed within 21 days prior to Cycle 1, Day 1. (The HIV viral load assay must detect at minimum viremia >200 copies/mL to be consistent with the DHHS HIV treatment guidelines).
    - Assessment for Hepatitis C antibody, Hepatitis B core antibody, Hepatitis B surface antigen (HBsAg), and Hepatitis B surface antibody.
    - Serum pregnancy test for women of childbearing potential (within 7 days prior to Cycle 1 chemotherapy). (See Section 13.1.1 under pregnancy and breastfeeding for guidelines on the use of pregnancy category D medications, which includes brentuximab vedotin and dacarbazine.)
11. Blood collection for biological analyses (cf. Appendix 20.7) after signature of informed consents for biological and genetic studies.

9.4 Evaluation during treatment

1. Update **medical history** prior to each cycle of chemotherapy. History to include concomitant medication changes and any signs and symptoms. Reportable adverse events must be recorded in AdvantageEDC. To be performed within 48 hours prior to or on first day of each cycle.
2. **Physical examination** prior to each cycle of chemotherapy. Examination to include performance status (Appendix 20.5). All subjects will be evaluated for clinical response by physical examination prior to receiving treatment on each cycle. The exam should occur within 2 days prior to the start of each cycle but may occur on Day 1 of cycle. Disease measurable by physical examination will be recorded in two dimensions if possible. To be performed within 48 hours prior to or on first day of each cycle.
3. **FDG-PET/CT**. Combined FDG-PET/CT or FDG-PET + CT scans with and without IV contrast are required for this study. If a patient has an allergy to IV contrast, a CT scan without contrast will be permitted.
   - Restaging evaluation by a full body FDG-PET/CT within Day 22-28 of Cycle 2 (i.e., 7-13 days after the Cycle 2 Day 15 doses of AVD-BV). If the CT portion of the PET/CT is a non-contrast CT, an additional CT scan with and without contrast must be obtained. Tumor measurements and SUVs must be

documented. A neck CT must be included if palpable neck nodes were present at baseline and a diagnostic CT is being performed.
- As the false positive rate of FDG-PET scans may be higher in the HIV population, a biopsy of an unexpected FDG-PET avid lesion is recommended but remains at the discretion of the investigator.

4. **PFT** with volumes, spirometry, DLCLO, and room air pulse oximetry will be performed after every 2 cycles, on day 1 of cycles 3 and 5, within 7 days of cycle initiation. The DLCO adjusted for hemoglobin must be greater than 70% predicted to continue with therapy.
5. Neuropathy evaluation by completing the **FACT/GOG-neurotoxicity questionnaire** at the beginning of each cycle. To be performed once within 48 hours prior to or on first day of each cycle (Appendix 20.6).
6. **CBC** with differential within 48 hours of day 1 and 15 of each cycle. Results of CBC must be known prior to treatment.
7. **Serum chemistries** within 48 hours of day 1 and 15 of each cycle: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, and phosphorus), glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT. Results do not need to be known prior to treatment unless clinically indicated.
8. **CD4/CD8** count will be performed within 48 hours of cycle 2 and cycle 5 day 1 along with the CBC evaluation.
9. **HIV-1 RNA viral load**, assessed by any approved viral load assay at the local laboratory. This will be performed within 48 hours of cycle 2 and cycle 5 day 1 along with the CBC evaluation. (The HIV viral load assay must detect at minimum viremia >200 copies/mL to be consistent with the DHHS HIV treatment guidelines).
   For patients with undetectable HIV viral at baseline: If the viral load rises above 200 copies per mL, HIV resistance testing will be required. Both viral load and resistance testing information must be shared in real time with the primary HIV provider if different from the protocol investigator. (The HIV viral load assay must detect at minimum viremia >200 copies/mL to be consistent with the DHHS HIV treatment guidelines).
10. **Serum pregnancy test** for women of childbearing potential will be performed per institutional guidelines during the study.

9.5 Follow-up assessments

The studies listed below will be repeated post-therapy within 6-8 weeks of the last treatment dose (6-8 weeks after Cycle 6 Day 15) and then every 3 months (+/- 7 days) thereafter for 2 years; every 6 months (+/- 7 days) for the third through the fifth years unless otherwise specified. All study subjects should be followed for up to 5 years after treatment discontinuation or until death if occurring before 5 years of treatment discontinuation. Patients who discontinue all protocol therapy after a CR or PR are followed for up to 5 years after treatment for recurrence and survival. Patients who discontinue protocol therapy due to disease progression or other reasons are followed for survival for up to 5 years after treatment discontinuation. No additional studies except follow up for survival are required after disease progression. In those instances in which a third party payer denies payment for some or all of these laboratory analyses, absence of these test results will not be considered a protocol violation.

1. **Medical history**.
2. **Physical examination**, including performance status (see Appendix 20.5,

Performance Status Scale), vital signs (weight, height, body surface area), neurological examination, and if possible, two dimensional measurement of all palpable, peripheral lymph nodes and measurement of other sites of disease present on physical exam.

3. At the conclusion of chemotherapy, a full body **FDG-PET/CT scan** will be done between 6-8 weeks post the final treatment dose, Cycle 6 Day 15. This will be the final FDG-PET/CT needed for the study. A combined FDG-PET/CT or FDG-PET + CT scans with and without IV contrast are required for the post- treatment scan. If a patient has an allergy to IV contrast, a CT scan without contrast will be permitted. As the false positive rate of FDG-PET scans may be higher in the HIV population, a biopsy of an unexpected FDG-PET avid lesion is recommended but remains at the discretion of the investigator.
4. **CT scan** with oral/IV contrast every 6 months for 5 years. To begin 6 months from the post treatment FDG- PET/CT scan, obtained 6-8 weeks post the final chemotherapy dose (See Section 9.5).
5. **PFT** with volumes, spirometry, DLCO and pulse oximetry for any patient with a DLCO corrected for hemoglobin ≤ 70% during therapy. To be repeated at all post-treatment evaluations until normalization.
6. **Bone** marrow **biopsy** need only be performed to confirm a CR if positive at baseline (only once, within 8 weeks of the last treatment dose).
7. **CBC** with differential at all post treatment evaluations.
8. **Serum** chemistries: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, and phosphorus), glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT at all post treatment evaluations.
9. **CD4 and CD8 cell** count beginning with the first follow up visit and every 3 months after treatment completion for one year.
10. **HIV-1 RNA viral load**, assessed by any approved viral load assay at the local laboratory beginning with the first follow up visit and every 3 months after treatment completion for one year. (The HIV viral load assay must detect at minimum viremia >200 copies/mL to be consistent with the DHHS HIV treatment guidelines).

9.6 Early Discontinuation of Therapy

Subjects discontinuing therapy early (i.e., PD or stable disease, administrative reasons, subject non- compliance, etc.) will have a medical history update and complete physical examination. The examination will include performance status and blood drawn for the following studies within 1 month after treatment discontinuation, unless otherwise noted. See Section 12 for a list of reasons for study termination. Subjects will be followed for survival only for 5 years after the last date of treatment:

- **CBC** with differential.
- **Serum chemistries**: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, and phosphorus), glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT.
- **CD4 and CD8 cell** count (do not repeat if done within 1 month from removal from treatment).
- **HIV-1 RNA viral load** to be evaluated at the local laboratory, do not repeat if done within 1 month from removal from treatment).

10.0 TREATMENTS

10.1 Treatment schedule and design

AVD dosing, in conjunction with brentuximab vedotin will be as described in Table 2. Drugs will be given on days 1 and 15 on a 28-day cycle for a total of 6 cycles. Brentuximab Vedotin will be administered after AVD (doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2).

If treatment is delayed (<7 days if during cycle 1, or <2 weeks if occurring during subsequent cycles) once treatment is resumed the next dose will be scheduled two weeks after treatment is restarted.

Table 2: Schema for AVD-BV regimen*

Doxorubicin	Vinblastine	Dacarbazine	Brentuximab Vedotin**
Day 1, 15 Of 28-day cycle	**Day 1, 15 Of 28-day cycle**	**Day 1, 15 Of 28-day cycle**	**Day 1, 15 Of 28-day cycle**
25 mg/m^2	6 mg/m^2	375 mg/m^2	1.2 mg/kg**

*GCSF will be administered on Days 2-10 and 16-24 throughout each 28-day cycle using standard doses. Pegfilgrastim may be substituted on days 2 and 16. (See Section 10.10.1)

**For participants with weight exceeding 100kg, the dosage of Brentuximab Vedotin will be calculated based on a weight of 100kg. Maximal dose = 120 mg.

10.2 Radiation Therapy

Involved field radiotherapy should be given at the discretion of the investigator after chemotherapy if there was bulky (>10cm) disease at diagnosis as suggested in the NCCN guidelines. Radiation therapy initiation will be within 2 weeks after protocol therapy. Radiotherapy may be performed during the follow-up period according to institutional standards.

10.3 HAART

HAART is a requirement for the duration of the study. Patients must be on HAART therapy for at least 7 days before therapy. The specific agents are at the discretion of the Investigator. Protease Inhibitors and Integrase Inhibitors boosted with ritonavir or cobistat are contraindicated. Non-nucleosides reverse transcriptase (NNRTIs) are not recommended, however, in the absence of alternative therapy, their use will be discussed in the presence of a pharmacologist in the national “RCP” (réunion de concertation pluridisciplinaire) for patients with HIV associated lymphomas.

The sponsor will not provide the HAART as it is considered as standard care for HIV patients. HAART is to be used according to summary of product characteristics.

10.4 Administration of chemotherapy

The sponsor will not provide the chemotherapy (AVD) as it is considered as standard care for Hodgkin lymphoma. Chemotherapy products are to be used according to summary of product characteristics.

10.4.1 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. Common side effects include myelosuppression, alopecia, and stomatitis, which is dose related

and may be severe. Drug-induced cardiomyopathy which may result in congestive heart failure, is a cumulative dose-dependent effect and risk becomes considerable at total doses exceeding 500 mg/m2. Doxorubicin is given intravenously and is a vesicant causing severe local necrosis at the site of injection if extravasation occurs. Nausea and vomiting are frequent.

10.4.2 Vinblastine

Vinblastine is the salt of an alkaloid derived from Vinca rosea Linn, a common herb known as the periwinkle. Mechanism of Action: Tissue culture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. A number of studies in vitro and in vivo have demonstrated its stathmokinetic effect and various atypical mitotic figures. Other studies indicate an effect on cell energy production required for mitosis and the interference with nucleic acid synthesis. Reversal of antitumor effect by glutamic acid and tryptophan has been observed.

Leukopenia is the usual dose-limiting side effect, with the nadir falling four to seven days post-injection. Thrombocytopenia and anemia may occur. Gastrointestinal toxicities include nausea, vomiting, diarrhea or constipation, abdominal pain, ileus, peptic ulcer, rectal bleeding and anorexia. Fever and phlebitis have also been seen when the drug is given as an infusion. Extravasation may lead to tissue necrosis. Ten percent of the patients will experience peripheral neuropathy. Alopecia can also occur.

10.4.3 Dacarbazine (DTIC)

Three hypotheses have been offered as the mechanism(s) of action of DTIC: inhibition of DNA synthesis by acting as a purine analog, action as an alkylating agent, and/or interaction with SH groups.

Myelosuppression is the dose-limiting toxicity. The predominant side effect observed in humans has been anorexia, nausea and vomiting. This occurs with maximal intensity on the first day of a five-day course, and in many patients, it is less with each subsequent day. Myelosuppression consisting of thrombocytopenia and leukopenia occurs in approximately one-quarter of patients after a five-day course of 250 mg/m2. The time course for this myelosuppression is generally maximal approximately three weeks after administration with the period of recovery variable. Other reported side effects include infrequent flu-like syndrome associated with fever and myalgia, phlebitis, liver necrosis, hepatic toxicity, anaphylaxis, photosensitivity, alopecia, and facial flushing. Rarely, DTIC has caused diarrhea.

10.5 Drugs description, storage and handling

10.5.1 Description of investigational product: Brentuximab Vedotin (NSC 749710)

Other Names: AdcetrisTM, SGN-35

Classification: Monoclonal Antibody CAS

Registry Number: 914088-09-8

M.W.: 153 kDa

Mode of Action: A CD-30 directed antibody-drug conjugate (ADC) consisting of 3 components: (1) the chimeric IgG1 antibody cA10, specific for human

CD30, (2) the microtubule disrupting agent monomethyl auristatin E (MMAE), and (3) a protease-cleavable linker that covalently attaches MMAE to cA10. Its cytotoxic activity occurs when ACD binds to the CD-30 expressing cell, forming an ADC-CD30 complex compound and releasing MMAEs via proteolytic cleavage. Subsequently, MMAE binds to tubulin to disrupt the microtubule network within the cells, resulting in cell cycle arrest and apoptosis.

Preparation: Consists of 2 steps: dilution of the stock solution and dilution of the final solution.

- Step 1: To make a 5 mg/mL concentration.
    1. Reconstitute the 50 mg lyophilized powder SGN-35 with 10.5 mL Sterile Water for Injection, USP. Final concentration is 5 mg/mL (Note: total volume is 11 mL).
    2. Swirl the vial gently. Do not shake.
    3. Let the reconstituted vial settle for one minute to eliminate bubbles. The reconstituted solution should be colorless, clear to slightly opalescent and should NOT have visible particulates.
    4. Store the reconstituted vial under refrigeration (2– 8°C), protect from light if not used immediately. Discard after 8 hours.
- Step 2: Further dilute the IV solution. Use vials from the same Lot number for each dose.
    1. Withdraw the calculated amount of drug from the 5 mg/mL reconstituted vial in step 1.
    2. Inject the required amount of drug into a 50 mL to 250 mL of 0.9% NS, Lactated Ringer's Solution, USP, or dextrose 5% in Water (D5W), USP to a final concentration between 0.4 – 1.8 mg/mL.
    3. Brentuximab vedotin solution is compatible in polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, or polyethylene.
    4. Do not shake. Gently invert the bag.
    5. The prepared IV bag is to be stored at 20 – 80 C and must be used within 24 hours of initial product reconstitution. Protect the prepared IV solution from direct sunlight if not used immediately.
    6. Prior to administration, inspect the IV bag for discoloration or floating particulates. Do not use the IV solution if the solution is discolored or/and have particulates.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 8 hours after initial entry.

Route(s) of Administration: Intravenous. Do not administer as an IV Push or bolus.

Method of Administration: Infuse the prepared IV solution over 30 minutes. Do not mix with other medications. Do not use an in-line filter for the IV administration. The IV bag does NOT need light protection during the IV administration.

Patient Care Implications:

- New signs and symptoms of CNS system abnormalities may indicate progressive multifocal leukoencephalopathy (PML).

- Tumor lysis syndrome, particularly in patients with highly proliferative tumors or high tumor burden prior to treatment.
- Infusion-related reactions, including anaphylaxis, may occur. Refer to protocol for the management of infusion- related reactions.
- Signs and symptoms of peripheral neuropathy such as tingling or numbness of the hands, feet, or any muscles weakness.
- Steven-Johnson syndrome
- High fever (≥38°C) or other signs of potential infection.

10.5.2 Packaging and labelling

SGN-35 will be supplied as a single use, preservative free vial containing 50 mg of white to off-white lyophilized powder for Injection. Inactive ingredients are trehalose, sodium citrate, and polysorbate 80. The pH is 6.6 once reconstituted in Sterile Water for Injection.

Study drug labels will contain information to meet the applicable regulation requirements. The investigational product will be labelled as open label material.

10.5.3 Storage conditions and handlings

Storage: Store the intact vials refrigerated at 2-8°C. Protect from direct sunlight.

Stability: The stability testing of the intact vials is ongoing. Reconstituted agent must be diluted and administer within 24 hours.

Refer to investigator brochure for additional information regarding storage and handling.

10.6 Dose adjustments

10.6.1 Brentuximab Vedotin Dose Modifications

10.6.1.1 Intrapatient. Dose Reductions for Starting Dose of 1.2 mg/kg Every 2 Weeks

No further dose reductions will be permitted beyond 0.6 mg/kg of brentuximab vedotin. Patients not tolerating a dose of 0.6mg/kg will continue with standard dose AVD at the discretion of the investigator.

Dose Level:

- 1.2 mg/kg
- 0.9 mg/kg
- 0.6 mg/kg

10.6.1.2 Treatment Modification Guidelines for Brentuximab Vedotin for All Cycles

Event	CTCAE.v4.0 Grade	Action to be Taken
Allergic reactions, or Acute infusional reactions/cytokine release syndrome	Grade 1-2	For first reaction: • Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity) • Treat reactions with diphenhydramine 1 mg/kg (max 50 mg), or follow local institution guidelines. Depending on the reaction severity, dexamethasone 0.2mg/kg (max 10mg) IV should be used or follow local institutions guidelines. • Upon resolution of the symptoms, at the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. paracetamol can also be considered. Brentuximab vedotin may be administered at half of the previously administered rate at the discretion of the investigator. For subsequent doses: • Utilize diphenhydramine with or without paracetamol as pre-treatment for all subsequent infusions. • Dosing will be administered over the shortest infusion period that was well tolerated. If Grade 1-2 infusion reactions recur despite the above measures, either during re- challenge or subsequent treatments: • Take the measures outlined above • With subsequent dosing, add dexamethasone 0.2 mg/kg (max 10mg) IV or equivalent to medications above prior to infusion.
	Grade 3	• Stop infusion immediately • Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2mg/kg (max 10mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated • Once symptoms recover, brentuximab vedotin should not be resumed for that course • Subsequent courses of brentuximab vedotin may be considered at physicians' discretion, after a discussion and approval by one of the French coordinator. • All subsequent infusions will use the following premedications prior to infusion, diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2mg/kg (max 10mg) IV (or equivalent). In addition, the infusion will be administered at 50% of the previous infusion rate
	Grade 4	• Stop infusion immediately • Administer diphenhydramine hydrochloride 1 mg/kg (max 50mg) IV, dexamethasone 0.2 mg/kg (max 10mg) IV (or equivalent), and other anaphylaxis medications as indicated • Adrenaline or bronchodilators at the discretion of the investigator will be administered as indicated. • Hospital admission for observation may be indicated. • Discontinue brentuximab vedotin
Anaphylaxis	Any Grade	• If anaphylaxis occurs, **immediately and permanently discontinue administration of brentuximab vedotin** and administer appropriate medical therapy.

Event	CTCAE.v4.0 Grade	Action to be Taken
Pancreatitis	Grade 2	• Withhold dose until toxicity has returned to baseline, then continue on protocol therapy but resume at one dose reduction. • If Grade 2 pancreatitis recurs after one dose reduction, the patient must be removed from protocol therapy.
	Grades 3-4	• **Permanently discontinue brentuximab vedotin.**
Peripheral Neuropathy	Grade 1	Continue at same dose level.
	Grade 2	• Treatment is to be delayed until neuropathy improves to Grade 1 or baseline • Brentuximab vedotin will be reduced by one dose level for subsequent treatments once peripheral neuropathy returns to baseline or returns to grade 1. • Patients who experience a delay of over 7 days in cycle 1 will be removed from the study. For subsequent cycles, if two sequential doses of brentuximab vedotin are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), participant will discontinue brentuximab vedotin. Participants will have the option to discontinue protocol therapy or continue study with AVD with dose adjustments in vinblastine as clinically necessary based on the level of neuropathy on the day of treatment as per standard label/summary product characteristics.
	Grade 3	• Treatment is to be delayed until neuropathy improves to Grade 1 or baseline. • Brentuximab vedotin will be reduced by one dose level for subsequent treatments once a peripheral neuropathy returns to baseline or returns to grade 1. • Patients who develop grade 3 neuropathy after dose reduction will have to discontinue brentuximab vedotin. Subjects will have the option to be taken off protocol or continue study with AVD with dose adjustments as clinically necessary. • Patients who experience a delay of over 7 days in cycle 1 will be removed from the study. For subsequent cycles, if two sequential doses of brentuximab vedotin are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), the participant will discontinue brentuximab vedotin.. Participants will have the option to discontinue protocol therapy or continue study with AVD with dose adjustments in vinblastine as clinically necessary, based on the level of neuropathy on the day of treatment as per standard label/Summary product characteristics.
	Grade 4	Discontinue brentuximab vedotin.
Neutropenia occurring on the day of treatment	Grade 1-2	Continue at same dose level.

Event	CTCAE.v4.0 Grade	Action to be Taken
	Grade 3-4	• Reinstitute growth factor support (GCSF) for treatment of neutropenia until recovery to ANC ≥1,000/mm3. • If myeloid growth factor support was inadvertently omitted in the previous dose, patients should receive the same full dose of brentuximab vedotin in the next treatment dose, along with myeloid growth factor support • If, as per protocol, the participant was on myeloid growth factor support with the previous dose and presents with treatment day neutropenia, reinstitute myeloid growth factor support (GCSF) until recovery to ANC ≥1,000/mm3 and reduce brentuximab vedotin one dose level for all remaining cycles. • Dose reduction below brentuximab vedotin 0.6 mg/kg is not allowed. Brentuximab vedotin should not be given for any subsequent cycles. • If participants have febrile neutropenia, please see Section 10.6 for dose modifications.
Thrombocytopenia	Grade 1-2	Continue at same dose level.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but at one dose reduction • Patients who experience Grade 3-4 thrombocytopenia after dose reduction must be removed from protocol therapy • Patients who experience a delay of over 7 days in cycle 1 will be removed from the study. For subsequent cycles, if two sequential doses of brentuximab vedotin are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), the patient will be taken off protocol therapy.
Lymphopenia	Grade 1-4	Continue at same dose level.
Non-hematologic[a] events (not including electrolyte abnormalities) or febrile neutropenia) (See Section 10.6.1.5 for treatment modifications for febrile neutropenia)	Grade 1-2	Continue at same dose level.

Event	CTCAE.v4.0 Grade	Action to be Taken
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but resume at one dose reduction of brentuximab vedotin. • If non-hematological Grade 3-4 toxicity recurs after one dose reduction, the patient must be removed from protocol therapy • Patients who experience a delay of over 7 days in cycle 1 will be removed from the study. For subsequent cycles, if two sequential doses of brentuximab vedotin are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), the patients will be taken off protocol therapy, and brentuximab vedotin will be discontinued. Participants will have the option to be taken off protocol or continue study with just AVD without brentuximab vedotin.
Electrolyte Abnormalities	Grade 1-4	• Continue at same dose level, provided electrolyte toxicity is not medically consequential and has been readily corrected • If electrolyte abnormality is medically consequential, refer to guidelines above for non-hematologic events

[a] Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption but should receive appropriate medical therapy at the discretion of the investigator.

[b] GCSF will be administered on Days 2-10 and 16-24 throughout each 28-day cycle using standard doses. Pegfilgrastim may be substituted for GCSF and administered on days 2 and 16.

10.6.1.3 Dose Modifications for Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML.

If PML is suspected, a diagnostic work-up must be performed. The work-up may include, but is not limited to the following:

- Neurologic examinations and neurology consultation, as warranted
- Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically non-enhancing and do not have mass effect.
- PCR analysis. JCV DNA, detectable in CSF or in a brain biopsy, is suggestive of PML.

- **Brentuximab vedotin dosing must be held if PML is suspected. If PML is confirmed, brentuximab vedotin must be permanently discontinued.**

10.6.1.4 Dose Modifications for Pulmonary Toxicity

Pulmonary toxicity will be defined by grade 3 or 4 dyspnea, pneumonitis, and/or hypoxia that persists for at least three days. There must be no evidence of other etiologies, including left atrial hypertension, congestive heart failure, infection, metabolic abnormalities, or cancer related causes (e.g., malignant pericarditis).

Patients who develop pulmonary toxicity associated with brentuximab vedotin may benefit from treatment with corticosteroids. However, there are no published guidelines to suggest the most appropriate dosing or duration of treatment. Administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses has been reported to improve symptoms in adults with pulmonary toxicity secondary to gemcitabine. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. Patients who develop pulmonary toxicity meeting the above definition will be taken off protocol therapy.

See Section 13.1 for a complete listing of potential adverse events and Section 13.1.1 for special precautions and safety issues.

10.6.1.5 Dose Modifications for Febrile Neutropenia

For participants already dosed reduced for reasons other than febrile neutropenia (e.g., neuropathy), dose reduction must start from the level at which the febrile neutropenia occurs.

Treatment Modification Guidelines for AVD-Brentuximab Vedotin for All Cycles.

Episode of Febrile Neutropenia	Action
First Episode of Febrile Neutropenia	Maintain current brentuximab vedotin dose with quinolone prophylaxis, or reduce one dose level (investigator's discretion).
Second Episode of Febrile Neutropenia	Quinolone prophylaxis and reduce one dose level.
Third Episode of Febrile Neutropenia	Quinolone prophylaxis and reduce one dose level.
Fourth Episode of Febrile Neutropenia	Quinolone prophylaxis and reduce one dose level.

Dose Level	Brentuximab Vedotin	AVD
1	1.2 mg/kg	Full dose
-1	0.9 mg/kg	Full dose

-2	0.6 mg/kg	Full dose
-3	0	Full dose
-4	0	0.75

Quinolone prophylaxis: antibacterial therapy is required for all cycles after an initial episode of febrile neutropenia. Suggested regimen can be altered based on availability, allergies, or ANC trends (e.g., levofloxacin 750 mg PO daily, Days 6-13 and Days 20-27).

Participants who are unable to receive at least 4 doses of brentuximab vedotin will not receive further therapy on study.

See Section **Error! Reference source not found.** for a complete listing of potential adverse events and Section **Error! Reference source not found.** for special precautions and safety issues.

10.6.2 AVD-Brentuximab Vedotin Dose Modifications (applies to all cycles)

Hematologic Toxicity	Although it is common practice to attenuate doses or delay treatment due to cytopenias alone, recent studies have shown that in the non-HIV setting for cHL patients receiving delays results in suboptimal treatment outcomes [77,78]. Patients should receive full doses of AVD on schedule on Days 1 and 15 of each 28-day cycle without treatment delays, unless neutropenic fever or documented infections are present.
Febrile Neutropenia	If febrile neutropenia occurs, then prophylaxis with antibacterial therapy is recommended for the subsequent cycle (e.g., levofloxacin 500 mg PO daily, Days 6-13 and Days 20-27 unless neutropenia occurred earlier in the cycle). Continued anti-bacterial antibiotic use thereafter is at the discretion of the treating physician. If a second febrile neutropenia episode occurs, decrease the doses of vinblastine and doxorubicin to 75% of the previous dose received for the next cycle (in addition to above antibiotic and GCSF supportive care measures). Re-escalation is at the discretion of the treating physician. If a third episode of febrile neutropenia occurs, patients should be maintained on therapy with supportive measures unless infection is life threatening.
Transfusions	Erythrocyte and platelet transfusions will be administered as needed at the discretion of the treating physician.
Severe Infection	Severe infection (NCI CTC Version 5.0, Grade 3 or 4) due to chemotherapy- related neutropenia requires a decrease in the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician.

Impaired Hepatic Function	All patients with direct bilirubin ≤ 2 x the upper limit of normal (ULN) will receive a full initial dose of doxorubicin and vinblastine. If the direct bilirubin rises to > 2 x ULN (but ≤ 5 x ULN), the doxorubicin and vinblastine doses must be reduced by 50% of last dose received to avoid undue hepatic toxicity. Full doses should be given once the direct bilirubin is ≤ 2 x ULN. If the direct bilirubin rises to > 5 x ULN, doxorubicin and vinblastine should be discontinued for that cycle. If the direct bilirubin has not recovered to ≤ 2 x ULN by the time the next cycle is due, then remove patient from protocol treatment. In cases of obstruction of the biliary duct by a tumor mass, a biliary drainage stent should be placed prior to chemotherapy. Values must be within protocol eligibility at treatment initiation. Direct Bilirubin with appropriate Doxorubicin and Vinblastine Dose Adjustments ≤ 2 x ULN = 100% of last dose received > 2 - 5 x ULN = 50% of last dose received > 5 x ULN = discontinue (i.e., do not administer)
Neuropathy	Once brentuximab vedotin has been discontinued, patients experiencing Grade 3 vinblastine-neuropathy (e.g., obstipation, weakness) will have the dose of vinblastine reduced by 50% for all further cycles of AVD. Patients experiencing Grade 4 vinblastine neuropathy will have this drug omitted from all future cycles of AVD.
Pulmonary Toxicity	Every 2 cycles PFT will be performed. The DLCO adjusted for hemoglobin must be greater than 70% to continue with brentuximab vedotin.
Weight	If a subject's weight has changed more than 10% from baseline or the prior dose, the new BSA must be used on the next cycle. For a weight change of 10% or less, doses may be adjusted according to the BSA or remain the same in conjunction with institutional guidelines.

10.7 Drug Dispensation and accountability

10.7.1 Responsibilities

All drug packages are to be inspected upon receipt at the study site prior to being drawn up. If any particulate matter is detected, the packaging is not to be used. Damaged packaging is to be reported to the sponsor and stored until instructions have been given.

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product (SGN-35 / Brentuximab Vedotin) are responsible for ensuring that the Investigational Products used in the clinical trial are securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements. All Investigational Medical Products are stored in accordance with labelling and shall be dispensed in accordance with the Investigator's prescription. The Investigator is in charge of ensuring that an accurate record of Investigational Product issued and returned is maintained. Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pertaining documentation, labelling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure. Under no circumstances will the Investigator supply Investigational Product to a third party, allow the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF),

and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one principal investigator at that institution.

10.7.2 Retrieval or destruction

All partially used or unused treatments will be verified by the Sponsor. A detailed treatment log of the returned Investigational Product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator (or the Pharmacist) and the Sponsor representative. The Investigator (or the pharmacist) will not destroy the unused Investigational Product unless the Sponsor provides written authorization. In case of a potential defect in the quality of Investigational Product, the Sponsor may initiate a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

10.7.3 Accountability and compliance

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational product. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments dispensed and used for each patient, to assess the patient treatment compliance. The sponsor representative will periodically check the supplies of investigational products held by the investigator or pharmacist to verify accountability of all investigational products used. All unused investigational products and all medication containers will be destroyed by the study sites. The Sponsor will verify that a final report of drug accountability at the unit dose level is maintained and archived in the investigator study file. Administration of the study treatment will be supervised by the investigator or sub-investigator.

10.8 Concomitant treatment restrictions

10.8.1 Medications prohibited for enrollment and the duration of the study

Experimental antiretroviral agents or those containing zidovudine (including Combivir and Trizivir) or ritonavir (including Kaletra), Cobicistat or similar potent CYP3 inhibitors are prohibited for enrollment and the duration of the study.

10.8.2 Potential Drug Interactions of Brentuximab Vedotin

In vitro data, one of SGN-35 active metabolites, monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4 but is not a sensitive substrate nor a strong inhibitor/inducer of CYP3A4. However, patients should be monitored for potential drug-interaction when administered drugs known to be a strong CYP 3A4 inhibitor/inducer with SGN-35. In vitro, MMAE is a substrate of P-gp transporter and is not an inhibitor of P-gp.

10.9 Reporting requirements for concomitant medications

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

1. Anti-seizure medications
2. Prophylactic medications
   - Antiviral
   - Antifungal
   - Quinolone/Antibiotic therapy
   - Any other medications used for prophylaxis of opportunistic infections
3. Hepatitis medications
4. Growth colony stimulation factors (GCSF)
5. Erythropoiesis Stimulating Agents (ESA)
6. Anti-retroviral medications. Note: Antiretroviral therapy will be collected in the On Study Form. If the subject remains on the same anti-retroviral medications throughout study participation that have already been reported in the On Study Form, then do not report them in the Concomitant Medications Form. If the subject changes or discontinues anti-retroviral therapy for any reason, then update the Concomitant Medication Form with the start and stop date of the discontinued medication(s) and start date of the new (if applicable) medication(s).
7. Receipt of disallowed medications (CYP3A4 or P-glycoprotein inhibitors) after study enrolment, as per Appendix 20.9.

10.10 Prophylactic measures

10.10.1 Growth Factor

GCSF will be administered on Days 2-10 and 16-24 throughout each 28-day cycle using standard doses. Pegfilgrastim may be substituted for GCSF and administered on days 2 and 16.

10.10.2 Pneumocystis prophylaxis

Trimethoprim sulfamethoxazole (Bactrim) (one double strength tablet twice daily three days per week or one single strength daily) must be given at the onset of therapy for Pneumocystis and Toxoplasmosis prophylaxis. Alternatively, dapsone (50 mg PO twice daily), atovaquone, or aerosolized pentamidine may be substituted for Pneumocystis prophylaxis in subjects allergic to sulfonamides. Pneumocystis prophylaxis will be continued once therapy has been discontinued.

10.10.3 Mycobacterium avium complex (MAC) prophylaxis

Azithromycin 1,200 mg PO once weekly must be initiated for prophylaxis if the CD4 count falls below 50 cells/µL or is expected to drop below 50 cells/µl while on chemotherapy. Prophylaxis may be discontinued once the CD4 count is deemed reliably above 50 cells/µL by the treating investigator.

10.10.4 Pre-infusion prophylaxis

Pre-infusion prophylaxis (e.g., diphenhydramine) may be administered per institutional guidelines.

11.0 STUDY PROCEDURES

11.1 Registration and inclusion procedure

After it has been determined that the subject is eligible and an informed consent has been signed by the subject, the subject must be registered on-line via the AMC AdvantageEDC℠ Internet Data Entry System (AdvantageEDC). Enrollment and data collection will occur via the AMC Internet Data Entry System.

The participating site will ensure a subject meets all eligibility criteria prior to completing the protocol-specific eligibility checklist in AdvantageEDC for enrolment. Subjects will be enrolled on-line via AdvantageEDC 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 email will be sent to the enroller upon successful completion of the subject enrollment. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at amcpm@emmes.com or via phone at 001 301-251-1161) for further instructions.

The investigator should fax **(+33 4 72 66 93 71**) at the same time the following documents: anonym copy of the pathology report (see appendix 20.7). **The LYSARC coordination center (Tel: +33 4.72.66.93.33)** will be the contact for any request.

11.2 Pathological diagnosis

The pathological diagnosis of Hodgkin lymphoma should have been performed locally before the inclusion for each patient.

Histopathology central review process has become in the last years a common and prerequisite procedure for clinical trials in the field of lymphomas. A mandatory pathological review will therefore be organized for all patients included in the trial at diagnosis. The goal of this central review will be to confirm the diagnosis and to precise its classification according to the WHO classification 2008.

The pathological review will be centralized at the LYSA-Pathology (LYSA-P) institute, Hôpital Henri Mondor, Créteil. For each patient, the investigator will be requested to join with the form of inclusion a copy of the anonymised histopathological report where the name and address of the pathologist having diagnosed the lymphoma will be easily identified as well as a copy of the bone marrow report.

All requested tumor paraffin embedded blocks from the formalin fixed sample (that have been used for diagnosis), or 10 unstained slides will be sent to the LYSA-P, according to the process described in Appendix 20.7 “Pathological samples review”. At reception, routinely stained sections will be performed and an appropriate panel of antibodies according to morphological aspects will be applied. A pathological review, performed by at least 2 experts hematopathologists will be organized at the LYSA-P and a consensus diagnosis will be established. A LYSA-P pathological report will then be sent to the clinical coordinator and to the initial pathologist.

Initial tumor block will also be used to make tissue microarray (TMA) and DNA/RNA extraction.

11.3 Biological study/ samples

Blood samples will be collected at inclusion and sent to Bicêtre hospital. The specific informed consents must be signed before any sample procedure. These samples will be integrated in a comprehensive collaborative studies. This may include proteomic, genetic, virological and immunology studies.

The samples processing is described on Appendix 20.7.

The following sample will be collected at baseline, before treatment:

- For proteomic (plasma storage for protein analyses): 10mL (2 tubes) of blood on Heparin Lithium tubes (provided by LYSARC).
- For genetic (cells storage for DNA extraction): 10mL (2 tubes) of blood on EDTA tubes
- For immunology and virological studies (EBV viral load in mononuclear cells and in plasma, analyse of immune response anti-EBV, cytokines analyses): 20mL (4 tubes) of blood on Heparin Lithium tubes (provided by LYSARC).

On the day of blood sampling, the sample will be sent at room temperature by carrier and centralized to the Bicêtre hospital.

12.0 STUDY COMMITTEES

12.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC), including at least three independent members (2 experts in HL including 1 expert in VIH) will be established. The IDMC will meet periodically to review the safety and efficacy data from the trial.
More details about IDMC operation will be provided in the IDMC Chapter.
The first IDMC is planned to occur after the 1st SAE for hematologic or neurologic toxicity after the approval of this current version of protocol or after the completion of 4 cycles according of two first patients according this current version of protocol.

13.0 CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

13.1 Premature withdrawal from trial intervention

After enrollment, subjects will be permanently withdrawn from study treatment for any of the following reasons. In the event of withdrawal from treatment, the reason for study treatment removal and the date the subject was removed must be documented in the Off Protocol Treatment Form in AdvantageEDC^{SM}. See Section 9.6 on evaluations to be performed at early discontinuation of therapy.

1. Participants who experience a delay of over 7 days in cycle 1 will be removed from the study. For subsequent cycles, if two sequential doses of AVD + BV or AVD alone are held due to unresolved toxicity, leading to a treatment delay of an additional 2 weeks (i.e., 4 weeks between doses), the participant will be taken off protocol therapy. The participant will be followed for survival and may resume AVD treatment off study.
2. Severe toxicities as outlined in Section 10.6.1.
3. Progressive lymphoma at any time while on study.
4. Voluntary withdrawal.
5. The investigator has the right to remove subjects from study for clinical reasons which he or she believes to be life threatening or resulting in significant morbidity to the subject.
6. Any subject who develops HBV reactivation or acute Hepatitis B as defined by the reappearance of a previously suppressed hepatitis B surface antigen, a positive IgM hepatitis B core antibody, and a positive viral load. Any patient with Hepatitis B or C who has worsening liver function as defined by Section 10.6.2 will also be removed from study.
7. Any subject who on repeat PFT is found to have a DLCO when corrected for anemia less than 70%.
8. Subjects who become pregnant or breast-feed.
9. Subjects with progressive disease at the end of cycle 2 will be removed from study treatment, while patients with stable disease may be removed from the study treatment at the discretion of the local responsible investigator. Progressive or stable disease defined at cycle 2 will be based by CT criteria only, as FDG-PET has yet to be validated in HIV-associated HL.
10. If found by central pathology review to not have the diagnosis of HL.
11. If the subject has had two cycles of AVD + brentuximab vedotin and develops recurrent Grade 3 peripheral neuropathy despite dose reductions of brentuximab vedotin and vinblastine, the subject may continue the study receiving AVD with dose adjustments in vinblastine as clinically necessary, keeping in mind to maintain the dose and schedule as in standard therapy, or may be removed from protocol treatment. This decision will be at the discretion of the investigator.

13.2 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states his/her wish not to contribute further data to the study, the relevant LYSARC contact should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. However, data up to the time of consent withdrawal will be included in the data reported for the study.

13.3 Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time site investigator must document attempts to contact the patient either by phone or letter.

13.4 Premature discontinuation of the study

The sponsor reserves the right to stop the trial at any time. The investigators will be informed of this decision in writing.

The same applies to any investigator wanting to discontinue his/her participation to the trial. The investigator must immediately inform the sponsor in writing of this decision.

An early stopping rule will be established such that the trial will be terminated if either or both of the following conditions hold:

1. If more than 10% of the subjects experience a grade 3 motor or sensory neurotoxicity lasting for more than 4 weeks, the trial will be terminated. The first 10 patients in the phase II portion of the study at the 1.2 mg/kg dose will be monitored for this outcome. If more than 3 out of the first 10 patients in the phase II study experience grade 3 neurotoxicity, this will be considered sufficient to stop the trial. With an underlying probability of grade 3 neuropathy of no more than 10%, the probability of observing > 3 patients with grade 3 neuropathy is less than 5%.
2. If any PML case is diagnosed when the CD4 count is above 50, the trial will be terminated.

14.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of expected AEs (see section 13.1) and the characteristics of an observed AE (see section 13.2) will determine whether the event requires expedited (via CTEP-AERS) **in addition** to routine reporting (via AdvantageEDC^{SM}).

The CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 5.0 of the CTCAE is identified and located 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 CTEP Version 5.0 of CTCAE.

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.

A conference call, every 2 months, between French and American coordinators will be conducted to discuss all adverse events encountered.

14.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) for SGN-35 (Brentuximab Vedotin, NSC 749710)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 798 patients.* Below is the CAEPR for SGN-35 (brentuximab vedotin).

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

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
		Colitis[2]	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
		Enterocolitis	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal obstruction[4]	
		Gastrointestinal perforation[5]	
		Gastrointestinal ulcer[6]	
		Ileus	
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Pain		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatotoxicity)[7]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Lung infection		
	Upper respiratory infection		***Upper respiratory infection (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		
	Weight loss		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Muscle cramp		
	Myalgia		***Myalgia (Gr 2)***

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
	Paresthesia		
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 2)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr 2)***
PSYCHIATRIC DISORDERS			
	Anxiety		
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Oropharyngeal pain		
		Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity)[8]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
[2]Colitis may also include the term neutropenic colitis.
[3]Fatal and/or serious gastrointestinal hemorrhages have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.
[4]Fatal and/or serious gastrointestinal obstructions have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[5]Fatal and/or serious gastrointestinal perforations have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. Lymphoma with preexisting GI involvement may increase the risk of perforation.
[6]Fatal and/or serious gastrointestinal ulcers have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer,

Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.
[7]Hepatotoxicity may manifest as increased ALT/AST, bilirubin, alkaline phosphatase, and/or GGT.
[8]Pulmonary toxicity, which may manifest as pneumonitis, interstitial lung disease, or adult respiratory distress syndrome (ARDS), has been observed in patients treated in brentuximab vedotin monotherapy trials as well as in combination with bleomycin.

Adverse events reported on SGN-35 (brentuximab vedotin) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that SGN-35 (brentuximab vedotin) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy)
CARDIAC DISORDERS - Myocardial infarction; Pericardial effusion; Sinus tachycardia
GASTROINTESTINAL DISORDERS - Dyspepsia; Esophagitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Meningitis; Pharyngitis; Sepsis; Shingles; Sinusitis; Skin infection; Soft tissue infection; Thrush; Urinary tract infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; Carbon monoxide diffusing capacity decreased; Creatinine increased; Lipase increased; Lymphocyte count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Myositis; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome
NERVOUS SYSTEM DISORDERS - Dysesthesia; Encephalopathy; Nervous system disorders - Other (demyelinating polyneuropathy); Seizure; Syncope
PSYCHIATRIC DISORDERS - Depression
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (pyelonephritis)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (groin pain)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome[8]; Pleural effusion[8]; Pneumothorax[8]; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (bronchitis)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: SGN-35 (brentuximab vedotin) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

14.1.1 Special Precautions/Safety Issues

Infusion-Related Reactions

Some patients experienced an infusion-related reaction during or soon after SGN-35 treatment. Symptoms of infusion-related reactions included chills, nausea, cough, itching, and shortness of breath. Two patients experienced a serious allergic reaction (wheezing/difficulty breathing, hives, itching, swelling) that required immediate medical attention and treatment discontinuation.

Peripheral Neuropathy

Some patients who received SGN-35 developed peripheral neuropathy. Symptoms reported by these patients included burning sensation, pain, weakness, numbness and tingling of hands and/or feet, and severe abnormal nerve function that caused difficulty walking.

Neutropenia

Some patients experienced neutropenia that was related to treatment with

SGN-35. This could result in an increased risk of infection.

Infection Risk

SGN-35 may cause patients to be less resistant to infections, including severe infections.

Other Important Side Effects

The following important or potentially life-threatening side effects have been reported infrequently in patients treated with SGN-35:

- Serious allergic reaction (wheezing/difficulty breathing, hives, itching, swelling) during or soon after SGN- 35 treatment, which requires immediate medical attention and treatment discontinuation
- Severe leukopenia, fever, and possible infection that resulted in death
- Stevens-Johnson syndrome (unexplained widespread skin pain, blisters on skin and mucous membranes, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of skin)
- Tumor lysis syndrome (TLS) is a potentially life-threatening complication. TLS usually occurs within a few days of the start of cancer treatment and may result in metabolic complications. Potential complications may include nausea, vomiting, edema (swelling), shortness of breath, heart rhythm disturbances, and acute renal failure.
- Progressive Multifocal Leukoencephalopathy (PML) is a rare, serious brain infection caused by a certain virus. People with a weakened immune system can experience PML. PML can result in death or severe disability. Care providers should be mindful of confusion or problems thinking, loss of balance or problems walking, difficulty speaking, decreased strength or weakness on one side of your body, blurred vision or loss of vision.

Pregnancy and Breastfeeding

Brentuximab vedotin is pregnancy category D; therefore patients should not receive SGN-35 if they are pregnant because of the risk to the fetus. SGN-35 affects the testes in animals; therefore, men should not get their partner pregnant while being treated with SGN-35.

- Female study volunteers of reproductive potential (defined as girls who have reached menarche and pre- menopausal women who have not had a sterilization procedure such hysterectomy, bilateral oophorectomy or salpingectomy) **must** have a negative serum or urine pregnancy test performed within 48 hours before initiating the protocol-specified medication(s). Women are considered menopausal if they have not had a menses for at least 12 months and have a FSH of greater than 40 IU/L or, if FSH testing is not available, they have had amenorrhea for 24 consecutive months.
- All study volunteers, male and female, must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, sperm donation, or in vitro fertilization)
- If participating in sexual activity that could lead to pregnancy, **all** study volunteers must agree to use **two reliable methods of contraception simultaneously** while receiving protocol-specified medication(s) and for 6 months after stopping the medication(s).
- If the female volunteer is not of reproductive potential (defined above) or the

man has documented azoospermia, contraception is not required.

Patients who could become pregnant or who have partners who could become pregnant must use birth control during the study and for 6 months after stopping treatment. If a patient or a patient's partner becomes pregnant while taking part in this study or within 30 days after stopping treatment, the patient should inform the study doctor right away. Seattle Genetics will follow the pregnancy to term. In addition, the resultant progeny will be followed for potential side effects for some period of time after birth.

It is not known whether SGN-35 or its breakdown products end up in breast milk. If it does end up in breast milk, it could cause harm to a nursing baby. Therefore, breast feeding is prohibited while on study drug and for 6 months after the last dose of study drug.

Possible Risks in Combination with Other Therapies

Concomitant use of SGN-35 and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial that studied SGN-35 with bleomycin as part of a combination regimen (ABVD), the rate of noninfectious pulmonary toxicity was higher than the historical incidence reported with ABVD. Monotherapy with SGN-35 has not been associated with a clinically meaningful risk of pulmonary toxicity.

An ongoing phase 1 study is investigating the combination of SGN-35 with ABVD or AVD as front-line therapy for HL. Noninfectious pulmonary toxicity was observed in some patients treated with SGN-35 in combination with ABVD. The incidence of pulmonary toxicity in the ABVD + SGN-35 arm of the trial was approximately 40% (10 of 25 patients), compared to an incidence of 10% to 25% most commonly reported in the literature with bleomycin-based regimens [79-81]. Patients presented with cough and dyspnea. Interstitial infiltration and/or inflammation were observed on X-ray and computed tomography of the chest. Five patients had a maximum severity ≥ Grade 3 (3 with Grade 3 and 2 with Grade 4). Most patients responded favorably to corticosteroid therapy.

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

14.2.1 Adverse Event

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

14.2.2 Life-threatening Adverse Event

Any AE that places the subject or subject, in view of the Investigator, at immediate risk of death from the reaction.

14.2.3 Serious Adverse Event (SAE)

Any AE occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other

situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

14.2.4 Hospitalization

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

14.2.5 Toxicity

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

14.2.6 Unexpected Adverse Event

Any AE that is not listed in available sources including the package insert, the Investigator's Brochure, or the protocol.

14.2.7 CTEP Adverse Event Reporting System (CTEP-AERS)

An electronic system for expedited submission of AE reports.

14.2.8 Attribution

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

Definite – The AE is clearly related to the investigational agent.

Probable – The AE is likely related to the investigational agent.

Possible – The AE may be related to the investigational agent.

Unlikely – The AE is doubtfully related to the investigational agent.

Unrelated – The AE is clearly NOT related to the investigational agent.

14.3 Expedited Adverse Event Reporting

14.3.1 Expedited AE reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System) accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 13.3).

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

CTEP-AERS by the original submitter at the site.

14.3.2 CTEP-AERS

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Protocol Chair, Principal Investigator at the local AMC treating institution and AMC Operations and Data Management Center. CTEP-AERS provides a copy feature for other e-mail recipients.

14.3.3 Phase 1 and Early Phase 2 Studies:

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

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

Death due to progressive disease should be reported as Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)" under the system organ class (SOC) of the same name. 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.

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

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

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

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

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

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.

1Serious 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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 1 and grade 2 AEs resulting in hospitalization or prolongation of hospitalization

2 For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "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.
- 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 adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the nine-digit AMC subject ID assigned during trial registration on all reports.

14.3.4 Clinical Laboratory Results

Clinical laboratory results that are outside of the institution's reference ranges must be reported as adverse events if they are deemed clinically significant by the investigator(s).

- A clinical laboratory abnormality should be deemed clinically significant if any one of the following conditions is met:
- The laboratory abnormality is not otherwise proved false by a repeat confirmation test.
- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug(s), close observation, more

frequent follow-up assessments, or further diagnostic investigation.

- In this protocol the following clinical laboratory abnormalities are expected and will not be considered AEs:
  - HIV viral load
  - T Cell subsets
  - LDH

14.4 Routine Adverse Event Reporting

All AEs that require expedited reporting via CTEP-AERS must also be reported in routine study data submissions (Adverse Event Form CRF). Routine reporting of all AEs attributed to therapy (possible, probable or definitely), regardless of grade, should be reported on the Adverse Event Form CRF. Similarly, if patients require radiotherapy, post-treatment AEs related to radiation therapy do not require routine reporting. All Grade 5 events, regardless of attribution to therapy, must be reported in the Adverse Event and Death Forms in AdvantageEDC℠.

14.5 Secondary Malignancy

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

Acute myeloid leukemia (AML)/Myelodysplastic syndrome (MDS) events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) MDS, or 3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS report should include the following: tumor pathology; history of prior tumors; prior treatment/current treatment including duration; any associated risk factors or evidence regarding how long the tumor may have been present; when and how the tumor was detected; molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor; and tumor treatment and outcome, if available. These events should be reported for the duration of the study treatment and during the protocol-specified follow-up period.

15.0 EFFICACY AND SAFETY MEASUREMENTS

15.1 Efficacy Measurements

All subjects will be evaluated for clinical response by physical examination prior to receiving treatment on each cycle. The exam should occur within 3 days prior to the start of each cycle, but may occur on Day 1 of cycle.

All subjects will be evaluated for clinical response by imaging studies after by FDG-PET/CT at the completion of cycle 2 and at the completion of therapy (See Section 10.6.1).

15.2 Response Assessment

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

15.2.1 Definition of Response

The response definitions used for this study are the 2007 Cheson criteria. A major distinction in the 2007 criteria is that PET/Gallium studies are used to facilitate the distinction between persistent tumor and scar/fibrosis.

15.2.2 Complete Response (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: In patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: In patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry.

15.2.3 Partial Response (PR) requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least two perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include

mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for a patient with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: if a pretreatment PET scan was negative, CT criteria should be used.

15.2.4 Stable Disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]) below.
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

15.2.5 Relapsed Disease (after CR)/Progressive Disease (after PR, SD):

1. Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes 1.0 x 1.0 cm will not be considered as abnormal for relapse or progressive disease.
2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis. At

least a 50% increase in the long est. diameter of any single previously identified node more than 1 cm in its short axis. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

15.2.6 Recurrent Disease

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

15.2.7. Time to Response

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

15.2.8. Time to Progression

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

15.2.9 Response Duration

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

15.3 Safety Measures

All AE will be monitored by ongoing review of reported adverse events by the protocol chair and the AMC Operations and Data Management Center, and will be discussed during the monthly investigators' Lymphoma Working Group conference calls (see Section 12.4 for rules for early study termination).

16.0 STATISTICAL CONSIDERATIONS

Statistical analysis will be performed by AMC Statistical Center on pooled data obtained by French participants and US participants.

16.1 Study Design/Endpoints

This multicenter, Phase II open label study will determine the safety and tolerability of patients with stage III/IV HIV- associated Hodgkin Lymphoma and evaluate the treatment effect of AVD in addition to brentuximab vedotin (SGN- 35). The primary objective of the Phase II portion of the study is to establish an estimate of the two-year progression-free survival for patients using brentuximab vedotin plus AVD regimen with HIV-associated advanced stage Hodgkin lymphoma.

The primary endpoint will estimate the two-year progression-free survival for AVD-brentuximab vedotin which will be done using a one sample nonparametric survival analysis.

Secondary objectives include:

1. To evaluate toxicity of AVD and brentuximab vedotin with HAART.
2. To estimate the partial response (PR) rate, complete response (CR) rate, overall survival (OS), event free survival at 2 and 5 years.
3. To evaluate effect of AVD and brentuximab vedotin on CD4 and CD8 counts after cycle 1, 4, at the end of therapy, and every 3 months after treatment completion for one year.
4. To investigate the prognostic value of FDG-PET/CT scans at baseline, after cycle 2, and at treatment completion, with respect to 2 year progression free survival.
5. To evaluate HAART status at baseline and to correlate this with tumor response to therapy and OS and PFS.
6. To characterize the histologic subtypes in HIV-HL in the highly active antiretroviral therapy (HAART) era.
7. To assess the neurotoxicity of HAART in combination with AVD and brentuximab vedotin.
8. To evaluate effect of AVD and brentuximab vedotin on viral load after cycles 1, 4, at completion of therapy, and every 3 months after treatment completion for one year.
9. To perform pharmacokinetic and immunogenicity studies to determine drug levels during therapy (not applicable for French participants).
10. To perform miRNA profile analysis on the HIV-HL tumor specimens and to correlate miRNA expression with OS, PFS, tumor response to therapy, histologic subtype of HIV-HL, and HIV disease characteristics not applicable for French participants).
11. To perform tissue microarray analysis on HIV-HL tumor specimens and to correlate the markers studied with OS, PFS, and tumor response to therapy (not applicable for French participants).
12. To identify EBV associated tumor derived DNA in the plasma of study patients, and to correlate these levels during therapy with disease response and OS (not applicable for French participants).
13. To identify cytokines in the plasma of patients during therapy, that can be used as tumor and prognostic markers. (Not applicable for French participants).
14. To assess latent and expressed HIV reservoirs before, during, and post chemotherapy. To understand how cytotoxic chemotherapeutic agents effect HIV expression (not applicable for French participants).

16.2 Sample Size/Accrual Rate

In the Phase II portion of the study, 51 patients will be enrolled worldwide to estimate the 2-year progression free survival. Sample size calculation is based on providing an estimate of the PFS with a 95% confidence interval ±10% under the hypothesis that 2-year PFS is 85%.

The primary endpoint of the phase II portion will be to estimate the two-year progression-free survival for AVD- brentuximab vedotin which will be done using Kaplan-Meier estimates and corresponding 95% confidence intervals based on standard errors using Greenwood's formula.

16.3 Stratification Factors

No stratification is planned for this study.

16.4 Analysis of Secondary Endpoints

Descriptive summaries and exploratory analyses for secondary objectives will be conducted. Significance for comparisons will be at the $p<0.05$ level.

Secondary objectives include:

1. To evaluate toxicity of AVD and brentuximab vedotin with HAART.
2. To estimate the partial response rate, complete response rate, overall survival (OS), event free survival at 2 and 5 years.
3. To evaluate effect of AVD and brentuximab vedotin on CD4 and CD8 counts after 2 cycles, 6 cycles, and every 3 months after treatment completion for one year.
4. To evaluate effect of AVD and brentuximab vedotin on viral load after 2 cycles, 6 cycles, and every 3 months after treatment completion for one year.
5. To investigate the prognostic value of FDG-PET scans at baseline and after 2 cycles in patient with HIV and HL with respect to 2 year progression free survival.
6. To evaluate HAART status at baseline for difference in outcome.
7. The characterization of histologic subtypes in HIV-HL in the HAART era.
8. To assess additional neurotoxicity in combination with HAART and AVD and brentuximab vedotin.

The frequency of AEs and their severity will be tabulated to evaluate tolerance of AVD and brentuximab vedotin with HAART. Further, binomial probabilities and their 95% confidence intervals will be used to estimate the response rates (i.e., partial response rate, complete response rate, overall response rate) and event free survival at 2 and 5 years of AVD and brentuximab vedotin for a treatment of patients with stage III/IV HIV-associated Hodgkin Lymphoma.

Repeated measures analysis of variance (ANOVA) models will be used to evaluate the effect of AVD and brentuximab vedotin on CD4 counts, CD8 counts and viral load after 1, 4, and 6 cycles, and every 3 months after treatment completion for one year.

Log-rank analysis will be used to investigate the prognostic value of FDG-PET scans at baseline, after 2 cycles and post-therapy in patients with HIV and HL with respect to progression free survival.

After cycle 2 and post-therapy, progression-free survival will be estimated for patients whose FDG-PET findings were negative and those whose findings were positive using Kaplan-Meier estimates and corresponding 95% confidence intervals based on standard errors using Greenwood's formula. Positive predictive value after 2 cycles and post-therapy will be estimated as the proportion of PET-positive patients who progress or

die before two years; negative predictive value after 2 cycles and post-therapy will be estimated as the proportion of PET-negative patients who are progression-free and alive at two years. Sensitivity of FDG-PET at cycle 2 and post-therapy will be estimated as the proportion of patients who progressed or died prior to year 2 whose FDG-PET was positive. Specificity of FDG-PET at cycle 2 and post-therapy will be estimated as the proportion of patients who are alive and progress-free at 2 years whose FDG-PET was positive. Exact two-sided 95% confidence intervals will be used for all estimates.

Log-rank analysis will be used to evaluate HAART status at baseline for difference in outcome in terms of overall survival and progression free survival. The frequency and proportion of different histologic subtypes will be calculated.

The frequency of neurotoxicity in patients taking AVD and brentuximab vedotin in combination with/without HAART will be tabulated. A binomial test of proportions will be used to test the difference in additional toxicity between those patients taking AVD and brentuximab vedotin on HAART vs. those patients not on HAART.

17.0 STUDY MONITORING

17.1 Responsibilities of investigators

The investigator(s) undertake(s) to perform the study in accordance with Good Clinical Practice and specifically either European 2001/20/CE and 2005/28/CE directives, ICH E6 or US regulations 21 CFR - Part 312 subpart D and guidelines for the monitoring of clinical investigations.

The investigators ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the study. The investigators agree to provide all information requested in the case report form in an accurate and legible manner according to instructions provided.

As may be required by the local legislation, the investigators will check that the patients are directly or indirectly affiliated to the national health insurance or coverage system if there is any.

17.2 Responsibilities of the sponsor

The sponsor (LYSARC) of this study in France has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, study adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the sponsor project leader and of the Sponsor clinical research support team (LYSARC) is to help the investigator maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, by a representative of the project team (LYSARC) to review study progress, investigator and subject adherence to study requirements and any emergent problems.

During monitoring visits, the following points will be assessed with the investigator or a designee for each patient selected and included: subject informed consent signature, patient eligibility (inclusion and exclusion criteria), subject recruitment and follow-up, subject compliance to the study treatment, study treatment accountability (if applicable), concomitant therapy use, evaluations of response, serious/non serious adverse event documentation and reporting, and quality of data. Sections of Case Report Forms may be collected/entered (in case of e-CRF) on a visit per visit basis. A monitoring plan will be written describing monitoring process.

17.3 Source document requirements

According to the guidelines on Good Clinical Practice, the sponsor representative will check the case report form entries against the source documents. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

17.4 Use and completion of electronic case report form (eCRF)

An electronic Case Report Form (eCRF) will be completed for each study subject. It is the investigator's responsibility to ensure the accuracy, completeness, legibility and timeliness of the data reported in the subject's eCRF.

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

Source documentation supporting the eCRF data should indicate the subject's participation in

the study and should document the dates and details of study procedures, adverse events and subject status.

The investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

All data entry and corrections are recorded in the audit trail (date of data entry/correction, name of person, type of action).

18.0 ETHICAL AND REGULATORY STANDARDS

18.1 Ethical Principles

This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and subsequent amendments and will be conducted according to ICH/GCP guidelines.

18.2 Laws and Regulations

This study is performed also in accordance with applicable laws and regulations of each country involved in the trial, as well as any applicable guidelines.

All data of the patients collected by the sponsor will be anonymized.

18.3 Informed Consent

It is the responsibility of the investigator to obtain informed consent in compliance with national requirements from each subject prior to entering the trial or, where relevant, prior to evaluating the patient's suitability for the study.

The informed consent document used by the investigator for obtaining subject's informed consent must be reviewed and approved by LYSARC prior to Ethics Review Committee submission.

The investigator must explain to potential patient the aims, methods, reasonable anticipated benefits and potential hazards of the trial and any discomfort it may entail. Patients will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.

The consent form will include a statement by which the patients allow the sponsor's duly authorized personnel (trial monitoring team) to have direct access to source data which supports data on the case report forms (e.g., patient's medical file, appointment books, original laboratory records, etc.).

The patient should receive a signed and dated copy of the informed consent form and patient information leaflet. The randomization/inclusion process will be documented in each patient’s medical records.

For biological studies, a specific informed consent form will be signed and dated by patients

18.4 Ethics Review Committee and Competent Authorities Submission

The sponsor must submit this study to country central ethics review committee, and to competent authorities and it is required to forward a copy of written approvals/advices signed to the investigators.

19.0 ADMINISTRATIVE PROCEDURES

19.1 Curriculum Vitae

An updated copy of the *curriculum vitae* of each investigator and sub-investigator will be provided to LYSARC prior to the beginning of the study.

19.2 Registration with CTEP

The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

19.3 Confidentiality Agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this study, the patient case report forms are the exclusive property of LYSARC.

They may not be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of LYSARC.

It is specified that the submission of this study and other necessary documentation to the Ethics Review Committee or a like body is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

19.4 Record Retention in Investigating Center(s)

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.

However national regulations should be taken into account, the longest time having to be considered.

For trials performed in the European Community, the investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

Any center will notify the sponsor before destroying any data or records.

19.5 Ownership of Data and Use of the Study Results

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor or any third Party either appointed by the Sponsor or having concluded a specific agreement with the Sponsor, reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

The Investigator is committed to give his support to any requests for a patent or any property title based on, or illustrated with the results of the present Study for any country.

19.6 Publication

The results of the trial will be published after complete data collection and evaluation. Partial or preliminary results can be published beforehand. Publication is to be initiated by the two

coordinating investigators in charge of the study with approval of partner if applicable.

Any publication in the form of a lecture, poster or article must be basically approved by the Scientific Committee of LYSA.

The authors will be proposed (according to the updated LYSA publication rules) by the coordinating investigators in charge of the study, and finally decided by the Steering Committee of LYSA.

All study data and publications are the property of LYSA/LYSARC.

19.7 Insurance Compensation

The sponsor certifies having taken out appropriate liability insurance policy which covers the Sponsor, the investigator and his co-workers and which is in accordance with the local laws and requirements. Specific statements will be contained in appendix where needed.

A certificate of insurance will be provided to the investigator in countries in which this document is required.

The Investigator(s) will remain responsible towards the Sponsor of any fault or misconduct regarding the performance of the Study.

19.8 Company Audits and Inspections by Regulatory Agencies

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines it may be necessary to conduct a site audit or an inspection.

By signing this study, the investigator agrees to allow LYSARC and its representative, drug regulatory agencies (ANSM) and auditor(s) from Seattle Genetics, AMC or the NCI and regulatory authorities (FDA) to have direct access to his study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in CRF, review of documentation required to be maintained, and checks on drug accountability.

LYSARC will in all cases help the investigator prepare for an inspection by any regulatory agency.

19.9 Clinical study Report

The sponsor will inform of the end of the trial the Competent Authorities and Ethics Committees during the 3 months following the end of the study. A publication, as a study report will be prepared under the responsibility of the sponsor, less than one year after the end of the study and forwarded to the Competent Authorities and Ethics Committees.

19.10 Protocol Amendments

It is specified that the appendices attached to this study and referred to in the main text of this study, form an integral part of the study.

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the investigator and the LYSARC.

Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be appended to this study.

Approval/advice of amendments by Ethics Review Committee and Competent Authorities are required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.

In some instances, an amendment may require a change to a consent form. The investigator must receive approval/ advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

Prior to initiating the changes, study amendment must be submitted to regulatory agencies, where applicable, except under emergency conditions.

20.0 REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed. 4th). Lyon, France: IARC Press; 2008.
2. Hodgkin T (1832). "On some morbid experiences of the absorbent glands and spleen". Med Chir Trans 17: 69–97.
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008: 57;43-66.
4. Kuppers R, Rajewsky K, Zhao M et al. Hodgkin disease: Hodgkin and Reed-Sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from B cells at various stages of development. Proc Natl Acad Sci USA 1994; 91:10962.
5. Hummel M, Ziemann K, Lammert H et al. Hodgkin's disease with monoclonal and polyclonal populations of Reed-Sternberg cells. N Engl J Med 1995; 333:901.
6. Kanzler H, Küppers R, Hansmann M-L et al. Hodgkin and Reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. J Exp Med 1996; 184:1495
7. Marafioti T, Hummel M, Anagnostopoulos I et al. Origen of nodular lymphocyte-predominant Hodgkin's disease from a clonal expansion of highly mutated germinal- center B cells. N Engl J Med 1997; 337:459.
8. Carbone A, Gloghini A, Gaidano G et al. Expression status of BCL-6 and syndecan-1 identifies distinct histogenetic subtypes of Hodgkin's disease. Blood 1998; 92:2220.
9. Shiels MS, Pfeiffer RM, Gail MH et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011;103(9):753-62.
10. Patel, P., D. L. Hanson, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med 2008;148: 728-36.
11. Levine A. HIV-associated Hodgkin's disease. Hematol Oncol Clin North Am 1996; 10; 1135-48.
12. Skinnider BF, Mak TW. The role of cytokines in classical Hodgkin lymphoma. Blood. 2002;99:4283-4297.
13. Levine AM. Hodgkin lymphoma: to the HAART of the matter. Blood 2006; 108; 3630.
14. Biggar RJ, Jaffe ES, Goedert JJ et al. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood 2006;108: 3786-91.
15. Spina M, Carbone A, Gloghini A, Serraino D, Berretta M, Tirelli U. Hodgkin's Disease in Patients with HIV Infection. Adv Hematol. 2011;!doi:10.1155/2011/402682.
16. Hasenclever D. and Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;19:1506-14.
17. Ambinder RF. Epstein-Barr virus and Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2007:204-9.
18. Keegan TH, Glaser SL, and Clarke CA et al. Epstein-Barr virus as a marker of survival after Hodgkin's lymphoma: a population-based study. J Clin Oncol. 2005; 23: 7604-1.
19. Carbone A, Gloghini A, Larocca LM et al. Human immunodeficiency virus-associated Hodgkin's disease derives from post-germinal center B cells. Blood. 1999; 93: 2319-26.
20. Powles T and Bower M. HIV-associated Hodgkin's Disease. Int J STD AIDS 2000; 11, 492-4.
21. Gerard L, Galicier L, Boulanger E, et.al Improved survival in HIV-related Hodgkin's lymphoma since the introduction of highly active antiretroviral therapy. AIDS. 2003 Jan 3;17(1):81-7.
22. Hentrich M, Maretta L, Chow KU et al. Highly active antiretroviral therapy (HAART) improves

survival in HIV-associated Hodgkin's disease: results of a multicenter study. Ann Oncol. 2006; 17: 914-9.

23. Spina M, Gabarre J, Rossi G et al. Stanford V regimen and concomitant HAART in 59 patients with Hodgkin disease and HIV infection. Blood. 2002;100:1984-8.
24. Xicoy B, Ribera JM et al. Results of treatment with doxorubicin, bleomycin, vinblastine and dacarbazine and highly active antiretroviral therapy in advanced stage, human immunodeficiency virus- related Hodgkin's Lymphoma. Haematologica 2007; 92: 191-198.
25. Spina M, Rossi G, Antinori A et al. VEBEP regimen and highly active antiretroviral therapy (HAART) in patients with HD and HIV Infection (HD-HIV). Blood 2005; 106:100a.
26. Hartmann P, Rehwald U, Salzberger B et al. BEACOPP therapeutic regimen for patients with Hodgkin's disease and HIV infection. Ann Oncol. 2003;14 :1562-9.
27. Levine A M, Li P, et al.. "Chemotherapy consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine with granulocyte-colony-stimulating factor in HIV-infected patients with newly diagnosed Hodgkin's disease: a prospective, multi-institutional AIDS clinical trials group study (ACTG 149)." J Acquir Immune Defic Syndr. 2000;24(5): 444-50.
28. Errante D, Gabarre J, Ridolfo AL et al. Hodgkin's disease in 35 patients with HIV infection: an experience with epirubicin, bleomycin, vinblastine and prednisone chemotherapy in combination with antiretroviral therapy and primary use of G-CSF. Ann Oncol. 1999;10:189-95.
29. Errante D, Tirelli U, Gastaldi R et al. Combined antineoplastic and antiretroviral therapy for patients with Hodgkin's disease and human immunodeficiency virus infection: a prospective study of 17 patients. Cancer 1994;73: 437-444.
30. Gastaldi R, Martino P, Gentile G et al. Hodgkin's disease in HIV-infected patients: report of eight cases usefully treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) plus granulocyte colony- stimulating factor. Ann. of Oncol 2002; 13: 1158-1160.
31. Tirelli U. Errante D, Vaccher E et al. Hodgkin's disease in 92 patients with HIV infection: The Italian experience. Ann Oncol 1992; 3: S69-72.
32. Andrieu JM, Roithmann S, Tourani JM et al. Hodgkin's disease during HIV-I infection: The French registry experience. Ann Oncol 1993; 4: 635-41.
33. Berenguer J, Miralles P et al. Characteristics and outcome of AIDS-related Hodgkin lymphoma before and after the introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2008; 47: 422-8.
34. Francisco JA, Cerveny CG, Meyer DL, et al. cAC10-vcMMAE, an anti-CD30–monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood 2003; 102: 1458-1465.
35. Wahl AF, Klussman K, Thompson JD, Chen JH, Francisco LV, Risdon G, Chace DF, Siegall CB and Francisco JA (2002). The anti-CD30 monoclonal antibody SGN-30 promotes growth arrest and DNA fragmentation in vitro and affects antitumor activity in models of Hodgkin's disease. Cancer Res 62: 3736- 42.
36. Younes A, Forero-Torres A, Bartlett NL, et al. Multiple complete responses in a phase 1 dose-escalation study of the antibody-drug conjugate SGN-35 in patients with relapsed or refractory CD30-positive lymphomas. Blood (ASH Annual Meeting Abstracts) 2008. 112:1006.
37. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010; 363: 1812-21
38. Chen, Gopal A, Smith SE, Ansell SM, Rosenblatt JD, Klasa R, Connors JM, Engert A, Larsen EK, Kennedy D, Sievers E and Younes A. Results of a Pivotal Phase 2 Study of brentuximab

Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract 283.

39. Advani RH, Shustov AR, Brice P, et al. Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma: A Phase 2 Study Update. American Society of Hematology 2011. Abstract 443.
40. Forero-Torres A, Berryman RB, Advani RH et al. Prolonged Treatment with brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL). American Society of Hematology 2011. Abstract 3711.
41. Younes A, Connors J, Park S, et al. Frontline Therapy with brentuximab Vedotin Combined with ABVD or AVD in Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma. American Society of Hematology 2011. Abstract 955.
42. Hoskin PJ, Lowry L, Horwich A, et al. Randomized Comparison of the Stanford V Regimen and ABVD in the Treatment of Advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2011 Nov 10;29(32):4227-33.
43. Ngeow J, Tan IB, Kanesvaran R, Tan HC, Tao M, Quek R, Lim ST. Prognostic impact of bleomycin- induced pneumonitis on the outcome of Hodgkin's lymphoma. Ann Hematol. 2011 Jan;90(1):67-72.
44. Pizzolo G, Vinante F, Morosato L, Nadali G, Chilosi M, Gandini, G, Sinicco A, Raiteri R, Semenzato G, Stein H, and Perona G. High serum level of the soluble form of CD30 molecule in the early phase of HIV-1 infection as an independent predictor of progression to AIDS. AIDS 1994. 8: 741–745.
45. Rizzardi GP, Barcellini W, Tambussi G, Lillo F, Malnati M, Perrin L, and Lazzarin A. Plasma levels of soluble CD30, tumour necrosis factor (TNF)- § and TNF receptors during primary HIV-1 infection: correlation with HIV-1 RNA and the clinical outcome. AIDS 1996. 10:45-50.
46. Pizzolo, G., Vinante, F., Nadali, G., Krampera, M., Morosato, L., Chilosi, M., Raiteri, R. and Sinicco, A., High serum level of soluble CD30 in acute primary HIV-1 infection. Clin. Exp. Immunol. 1997. 108: 251– 253.
47. Maggi E, Annunziato F, Biagiotti R, Giudizi MG, Ravina A, Almerigogna F, Boiani N, Alderson M, Romagnani S. Activation of HIV expression by CD30 triggering in CD4 + T cells from HIV infected individuals. Immunity 1995; 3:251–255.
48. Brew BJ, Davies NW, Cinque P, Clifford DB and Nath A. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. Nat Rev Neurol 2010; 6: 667-79.
49. Koralnik IJ, Schellingerhout D, Frosch MP. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 14-2004. A 66-year-old man with progressive neurologic deficits. N Engl J Med. 2004;350(18):1882.
50. Cinque P, Koralnik IJ, Gerevini S, Miro JM, and Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. Lancet Infect Dis. 2009 Oct;9(10):625-36.
51. Engsig FN, Hansen AB, Omland LH et al. Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIV-infected patients during the highly active antiretroviral therapy era: a nationwide cohort study. J Infect Dis. 2009;199(1):77.
52. Khanna N, Elzi L, Mueller NJ et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. Clin Infect Dis. 2009 May 15;48(10):1459-66.
53. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory

therapies. Annu Rev Med. 2010;61:35-47.

54. FDA Drug Safety Communication, New Boxed Warning and Contraindication for Adcetris (brentuximab vedotin) 1/13/2012. http://www.fda.gov/Drugs/DrugSafety/ucm287668.htm.
55. Antoniou T and Tseng AL. Interactions Between Antiretrovirals and Antineoplastic Drugs. Clin Pharmacokinet 2005; 44: 111-145.
56. Rubinstein PG, Braik T, Jain S et al. Ritonavir Based Highly Active Antiretroviral Therapy (HAART) Correlates with Early Neurotoxicity When Combined with ABVD Treated HIV Associated Hodgkin Lymphoma but Not Non-Hodgkin Lymphoma. A Retrospective Study. American Society of Hematology 2010. Abstract # 2807.
57. Sandu S, Gupta S, Itokazu G et al. Suspension of Ritonavir and Zidovudine Prevents Adverse Events During the Treatment of HIV Associated Hodgkin Lymphoma. ASCO 2012, abstract #8085.
58. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J. Clin. Oncol. 25:3746-52, 2007.
59. Hutchings M, Loft A, Hansen M, et. al FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma Blood, 1 January 2006, Vol. 107, No. 1, pp. 52-59.
60. Wedgwood A.R, Fanale A, Fayad L.E, et al. Rituximab + ABVD Improves Event-Free Survival (EFS) in Patients with Classical Hodgkin Lymphoma in All International Prognostic Score (IPS) Groups and in Patients Who Have PET Positive Disease after 2–3 Cycles of Therapy. Blood (ASH Annual Meeting Abstracts) 2007 110: Abstract 215.
61. Brust D, Polis M, Davey R, et al. Fluorodeoxyglucose imaging in healthy subjects with HIV infection: impact of disease stage and therapy on pattern of nodal activation. AIDS 2006, Vol 20 No 7.
62. Kelley T, Pohlman B, Elson P, et al. The ratio of FOXP3+ regulatory T cells to granzyme B+ cytotoxic T/NK cells predicts prognosis in classical Hodgkin lymphoma and is independent of bcl-2 and MAL expression. Am J Clin Pathol 128:958-65, 2007.
63. Epeldegui M, Lee JY, Martinez AC, Widney DP, Magpantay L, Regidor D, Mitsuyasu R, Sparano JA, Ambinder RF and Martínez-Maza O. Serum levels of several molecules associated with B cell activation and inflammation are elevated in AIDS-NHL and predict response to treatment. In preparation.
64. Epeldegui, M. D. P. Widney, A. C. Martínez, D. Regidor, L. Magpantay, R. Mitsuyasu, J. A. Sparano, J. Y. Lee, R. F. Ambinder, O. Martínez-Maza. 2011. Serum levels of several molecules that are associated with B cell activation and inflammation are elevated in AIDS-associated non-Hodgkin's lymphoma (AIDS-NHL) and predict response to treatment. International Conference on Malignancies in AIDS and Opportunistic Infections (ICAMOI). Abstract. Bethesda, MD.
65. Levin, L., E. C. Breen, B. Birmann, J. J. Kasperzyk, L. Magpantay, R. F. Ambinder, N. Mueller and O. Martínez-Maza. Elevated serum levels of soluble CD30, IL-6 and IL-10 precede the diagnosis of Hodgkin lymphoma. In preparation.
66. Levin, L., E. C. Breen, C. Kitchen, D. Widney, B. Kim B, A. Marrogi, R. Krampf, L. Magpantay, and O. Martínez-Maza. 2010. Elevated Serum Levels of CXCL13 Precede the Diagnosis of B Cell Non Hodgkin Lymphoma (NHL). AACR Special Conference on The Future of Molecular Epidemiology: New Tools, Biomarkers, and Opportunities. Abstract. Miami, FL.
67. Yeung ML, Bennasser Y, LE SY, Jeang KT. siRNA, miRNA and HIV: promises and challenges.

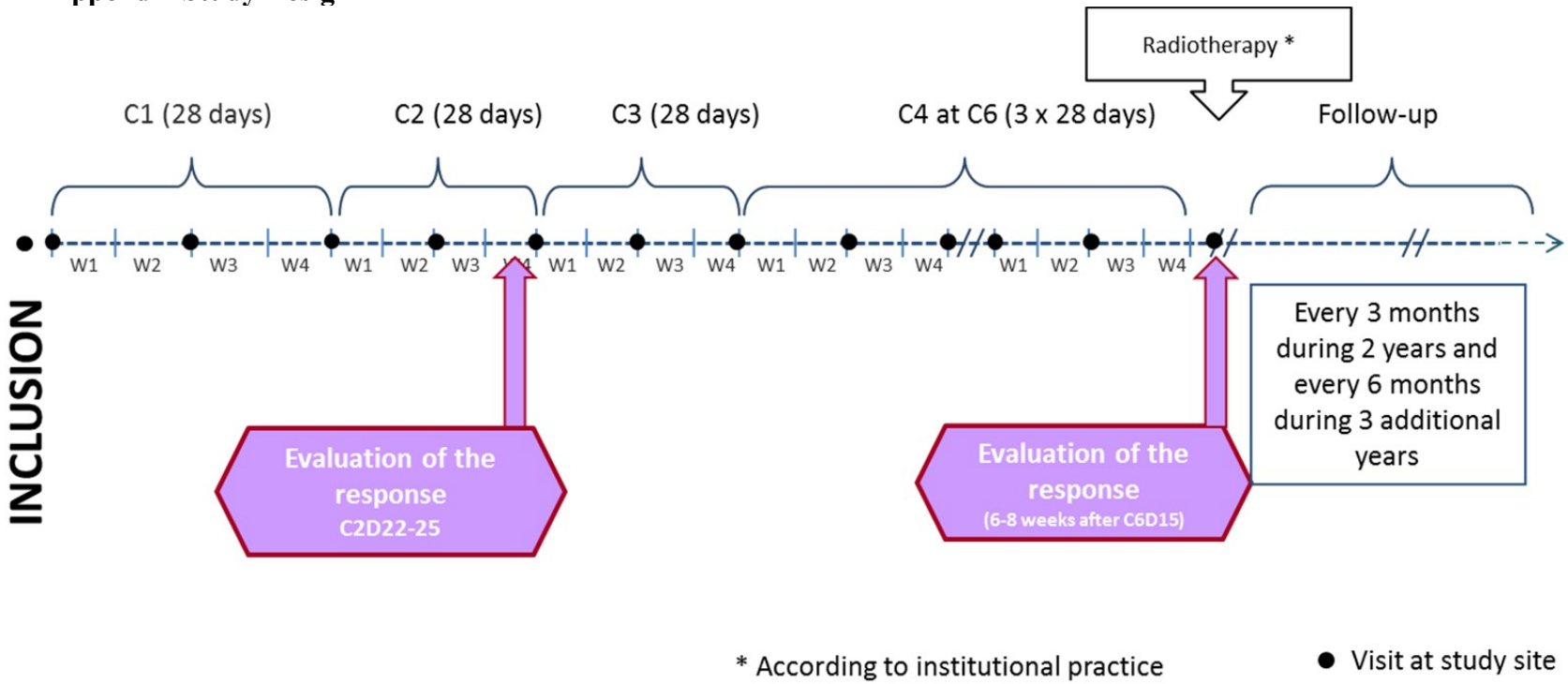
Cell Res. 2005 ;15(11-12):935-46.

68. Qi P, Han JX, Lu YQ, Wang C, Bu FF. Virus-encoded microRNAs: future therapeutic targets? Cell Mol Immunol. 2006;3(6):411-9.
69. Visone R, Croce CM. MiRNAs and Cancer. Am J Pathol. 2009;174(4):1131-8.
70. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009; 136 (2): 215–33.
71. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004; 116 (2): 281–97.
72. Bentwich I, Avniel A, Karov Y et al. Identification of hundreds of conserved and nonconserved human microRNAs. Nat. Genet. 2005; 37 (7): 766–70.
73. Homo sapiens miRNAs in the miRBase at Manchester University.
74. Lu J, Getz G, Miska EA, et al. MicroRNA expression profiles classify human cancers. Nature 2005;435:834-838.
75. Navarro A, Gaya A, and Martinez A et. al. MicroRNA expression profiling in classic Hodgkin lymphoma. Blood 2008; 111: 2825-2832
76. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009 Sep;50(3):1-36.
77. Boleti E and Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. Ann Oncol 18:376-80, 2007.
78. Evens A, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. Br J Haematol 137:545-52, 2007.
79. Duggan DB, Petroni GR, Johnson JL, Glick JH, Fisher RI, Connors JM, Canellos GP and Peterson BA. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease. report of an intergroup trial. J Clin Oncol; 2003 21: 607-14.
80. Martin WG, Ristow KM, Habermann TM, Colgan JP, Witzig TE and Ansell SM. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol; 2005 23: 7614-20.
81. Hoskin PJ, Lowry L, Horwich A, Jack A, Mead B, Hancock BW, Smith P, Qian W, Patrick P, Popova B, Pettiti A, Cunningham D, Pettengell R, Sweetenham J, Linch D and Johnson PW. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol 2009; 27: 5390-6.
82. Glaser, S.L., et al., Population-based patterns of human immunodeficiency virus-related Hodgkin lymphoma in the Greater San Francisco Bay Area, 1988-1998. Cancer, 2003. 98(2): p. 300-9.
83. Keegan, T.H., et al., Epstein-Barr virus as a marker of survival after Hodgkin's lymphoma: a population- based study. J Clin Oncol, 2005. 23(30): p. 7604-13.
84. Hohaus, S., et al., The viral load of Epstein-Barr virus (EBV) DNA in peripheral blood predicts for biological and clinical characteristics in Hodgkin lymphoma. Clinical Cancer Research: an official journal of the American Association for Cancer Research, 2011. 17(9): p. 2885-92.
85. Gandhi, M.K., et al., Plasma Epstein-Barr virus (EBV) DNA is a biomarker for EBV-positive Hodgkin's lymphoma. Clinical cancer research : an official journal of the American Association for Cancer Research, 2006. 12(2): p. 460-4.
86. Kanakry, J.A., Plasma viral DNA as a marker of tumor response in EBV(+) Hodgkin lymphoma in a phase III study (E2496). Journal of clinical oncology, 2012. 30.

87. Chan, K.C., et al., Molecular characterization of circulating EBV DNA in the plasma of nasopharyngeal carcinoma and lymphoma patients. Cancer research, 2003. 63(9): p. 2028-32.
88. Lin, L., et al., Effects of chemotherapy in AIDS-associated non-Hodgkin's lymphoma on Kaposi's sarcoma herpesvirus DNA in blood. J Clin Oncol, 2009. 27(15): p. 2496-502.
89. Shamay, M., et al., CpG methylation as a tool to characterize cell-free Kaposi sarcoma herpesvirus DNA. J Infect Dis, 2012. 205(7): p. 1095-9.
90. Kasamon, Y.L., et al., Multicenter phase II study of rituximab-ABVD in classic Hodgkin lymphoma (cHL). ASCO Meeting Abstracts, 2011. 29(15_suppl): p. 8039.
91. Meignan M, Barrington S, Itti E, Gallamini A, Haioun C, Polliack A. Report on the 4th International Workshop on Positron Emission Tomography in Lymphoma held in Menton, France, 3-5 October 2012. Leuk Lymphoma. 2013 Jun 14. [Epub ahead of print]
92. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma. 2009 Aug;50(8):1257-60.

21.0 APPENDIXES

21.1 Appendix Study Design



21.2 Appendix Schedule of Evaluations (study flow-chart)

	Treatment (W-2) Must be completed within 2 weeks prior to patient registration (D-7) To be performed within 7 days prior to first day of cycle (D-21) To be performed within 21 days prior to Cycle 1, Day 1 (D-28) To be performed no more than 28 days before enrollment. (H-48) To be performed within 48 hours of day 1 and 15 of every cycle.																**Follow-up**	
Date (weeks or months)	Eligibility (Baseline) 6 weeks before C1D1	C1D1	C1D15	C2D1	C2D15	C2D22 -28	C3D1	C3D15	C4D1	C4D15	C5D1	C5D1 5	C6D1	C6D15	End of treatment 6 -8 w after C6D15	Early Treatment Discontinuation 1 m after discontinuation	Every 3 m 2 y (+/-7d)	Every 6 m 3 y (+/-7d)
Informed consent	X																	
Medical history and physical examination	X	X (h-48)		X (h-48)			X (h-48)		X (h-48)		X (h-48)		X (h-48)		X	X	X	X
FDG-PET/CT or FDG-PET + CT	X (D-28)					X									X			
CT scan with oral/IV contrast (d) To be done if the CT portion of the PET/CT is without contrast.	X (d)														X		Every 6 m	X
PFTs with volumes, spirometry, DLCO and pulse oximetry (b) To be performed only for patients with DLCO (corrected for hemoglobin) <70% during treatment until normalization.	X						X (d-7)				X (D-7)				X (b)			
MRI of brain with and without IV gadolinium contrast	X																	
MUGA or echocardiogram	X																	

	Treatment (W-2) Must be completed within 2 weeks prior to patient registration (D-7) To be performed within 7 days prior to first day of cycle (D-21) To be performed within 21 days prior to Cycle 1, Day 1 (D-28) To be performed no more than 28 days before enrollment. (H-48) To be performed within 48 hours of day 1 and 15 of every cycle.																**Follow-up**	
Date (weeks or months)	Eligibility (Baseline) 6 weeks before C1D1	C1D1	C1D15	C2D1	C2D15	C2D22 -28	C3D1	C3D15	C4D1	C4D15	C5D1	C5D1 5	C6D1	C6D15	End of treatment 6 -8 w after C6D15	Early Treatment Discontinuation 1 m after discontinuation	Every 3 m 2 y (+/-7d)	Every 6 m 3 y (+/-7d)
FACT-GOG-neurotoxicity questionnaire	X	X (h-48)		X (h-48)			X (h-48)		X (h-48)		X (h-48)		X (h-48)					
Bone marrow biopsy (a) Does not have to be repeated if bone marrow involvement by lymphoma already documented after bone marrow biopsy more than 6 weeks prior to registration (if+) Only need to perform to confirm CR is positive at baseline (only once, within 8 weeks of last treatment dose)	X(a)														X (if +)			
Central pathology review	X																	
Blood sampling for biological studies	X																	
CBC with diff Results must be known prior to treatment **Sedimentation rate (only at baseline)**	X (W-2)	X (h-48)	X (h-48)	X (h-48)	X (h-48)		X (h-48)	X (h-48)	X (h-48)	X (h-48)	X (h-48)	X (h-48)	X (h-48)	X (h-48)	X	X	X	X

	Treatment (W-2) Must be completed within 2 weeks prior to patient registration (D-7) To be performed within 7 days prior to first day of cycle (D-21) To be performed within 21 days prior to Cycle 1, Day 1 (D-28) To be performed no more than 28 days before enrollment. (H-48) To be performed within 48 hours of day 1 and 15 of every cycle.															**Follow-up**	
Date (weeks or months)	Eligibility (Baseline) 6 weeks before C1D1	C1D1	C1D15	C2D1	C2D15	C2D22-28	C3D1	C3D15	C4D1	C4D15	C5D1	C5D15	C6D1	C6D15	End of treatment 6-8 w after C6D15	Early Treatment Discontinuation 1 m after discontinuation	Every 3 m 2 y (+/-7d)	Every 6 m 3 y (+/-7d)
Serum chemistries: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, phosphorus), glucose, BUN, creatinine, total bilirubin, alkaline phosphatase (ALP), LDH, total protein, albumin, AST and ALT	X (W-2)	X (h-48)	X (h-48)	X (h-48)	X (h-48)		X (h-48)	X (h-48)	X (h-48)	X (h-48)	X (h-48)	X (h-48)	X (h-48)	X (h-48)	X	X	X	X
CD4/CD8 cell count (e) to be performed at study completion and every **3 months for one year** (f) Do not repeat if done within 1 month from removal from treatment.	X			X (h-48)							X (h-48)				X(e)	X(f)		
HIV-1 RNA viral load (g) to be performed at study completion and every **3 months for one year** (h) Do not repeat if done within 1 month from removal from treatment.	X (D-21)			X (h-48)							X (h-48)				X (g)	X(h)		
Hepatitis C antibody, Hepatitis B core antibody, Hepatitis B surface antigen (HBsAg), and Hepatitis B surface antibody	X																	

	Treatment (W-2) Must be completed within 2 weeks prior to patient registration (D-7) To be performed within 7 days prior to first day of cycle (D-21) To be performed within 21 days prior to Cycle 1, Day 1 (D-28) To be performed no more than 28 days before enrollment. (H-48) To be performed within 48 hours of day 1 and 15 of every cycle.																**Follow-up**	
Date (weeks or months)	Eligibility (Baseline) 6 weeks before C1D1	C1D1	C1D15	C2D1	C2D15	C2D22 -28	C3D1	C3D15	C4D1	C4D15	C5D1	C5D1 5	C6D1	C6D15	End of treatment 6 -8 w after C6D15	Early Treatment Discontinuation 1 m after discontinuation		Every 3 m 2 y (+/-7d)	Every 6 m 3 y (+/-7d)
Serum pregnancy test	X (D-7)																		
Administration of treatment		X	X	X	X		X	X	X	X	X	X	X	X					
Adverse event	Continuous report																		

21.3 Appendix Ann Arbor Staging

- **Stage I:**
  - I: Involvement of a single lymph node region.
  - IE: Localized involvement of a single extralymphatic organ or site.
- **Stage II:**
  - II: Involvement of 2 or more lymph node regions on the same side of the diaphragm.
  - IIE: Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm.
- **Stage III:**
  - III: Involvement of lymph node regions on both sides of the diaphragm.
  - IIIE: Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site.
  - IIIS: Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen.
  - IIIS+E: Both IIIS+IIIE.
- **Stage IV:**
  - IV: Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non regional) nodal involvement.
  - IVE: Extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

Source: American Joint Committee on Cancer. Non Hodgkin's lymphoma. In: AJCC Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven;1997:289-294.

21.4 Appendix Body Surface Area Calculation

The algorithm to be used in this study is Mosteller formula (1987):

BSA = √ [(Height (cm) x Weight (kg))/3600]

21.5 Appendix Performance Status Criteria

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

21.6 Appendix FACT-GOG-Neurotoxicity Questionnaire v4.0

Veuillez indiquer votre réponse en entourant un seul chiffre par ligne et en tenant compte des 7 derniers jours.

AUTRES SUJETS D'INQUIÉTUDE

		Pas du tout	**Un peu**	**Moyen-nement**	**Beau-coup**	**Énormé-ment**
NTX 1	J'ai les mains qui s'engourdissent ou qui picotent	0	1	2	3	4
NTX 2	J'ai les pieds qui s'engourdissent ou qui picotent	0	1	2	3	4
NTX 3	J'ai une gêne dans les mains	0	1	2	3	4
NTX 4	Je sens une gêne dans mes pieds	0	1	2	3	4
NTX 5	J'ai des douleurs aux articulations et/ou des cramps aux muscles	0	1	2	3	4
HI 12	Je ressens une faiblesse générale	0	1	2	3	4
NTX 6	J'ai du mal à entendre	0	1	2	3	4
NTX 7	J'ai les oreilles qui tintent ou qui bourdonnent	0	1	2	3	4
NTX 8	J'ai du mal à boutonner les vêtements	0	1	2	3	4
NTX 9	J'ai du mal à palper la forme de petits objects quand ils sont dans ma main	0	1	2	3	4
An 6	J'ai du mal à marcher	0	1	2	3	4

21.7 Appendix Pathological Samples Review

General principles and organization of the pathological review:

The AMC-85 study requires a histological review of all cases included in the trial at diagnosis. The aims of the centralized histopathological review will be to **confirm the diagnosis of Hodgkin lymphoma**, according to the criteria of the updated WHO classification 2008 (S. Swerdlow et al.) for each patient in the AMC-085 study. Histological criteria of inclusion and exclusion have been detailed in the current protocol.

The review process will be organized by the LYSA-Pathology institute, Hopital Henri Mondor, Créteil (LYSA-P). Therefore for each included patient, tumor tissue blocks - or only when not possible - unstained slides will have to be sent for analysis and confirmation of diagnosis to LYSA-P.

Practical aspects of the LYSA review:

1. Information on patient inclusion

   At patient randomization/inclusion, the investigator will be requested to fax to LYSARC registration center with the inclusion form a copy of the histopathological report on which the name and address of the pathologist having diagnosed the Hodgkin lymphoma will be easily identified as well as the bone marrow report when possible.

   The LYSARC registration center will transmit these documents to the LYSA-P.

2. Sample request

   At reception of the pathological report and inclusion form, the LYSA-P will sent to the initial pathologist a letter requesting:

   - The paraffin block from the formalin fixed sample that was used to set the diagnosis and/ or 10 unstained Superfrost+ slides
   - A copy of the bone marrow pathological report if not sent previously
   - To notify the LYSA-P of the presence of frozen tissue

3. Sample centralisation at LYSA-P

   All these requirements will be sent in prepaid envelope and centralized by the LYSA-P at the following address:

   LYSA-P, LYSA – AMC-085 study,
   Hôpital Henri Mondor
   51, avenue de Lattre de Tassigny, 94010
   Créteil France

4. Sample review

   At sample reception, routinely stained sections will be performed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a pathological review will be organized at the LYSA-P with the designated panel of pathologists for this study. All the cases will be reviewed by at least 2 experts hematopathologists and a consensus diagnosis will be set and registered in the LYSA-P data base. This consensus diagnosis will then be sent to the clinical investigator and to the initial pathologist. For the need of the ancillary study, blocks will be kept temporarily to avoid a second request. Meanwhile, the block will be at the entire disposition of the initial anatomopathology laboratory under request if they need it.

21.8 Appendix Biological samples for further ancillary studies

A) RATIONALE

The AMC-085 study represents a unique opportunity to collect biological samples from patients with Hodgkin lymphoma and HIV at diagnosis that can be used to improve comprehension of the disease, better define the prognostic criteria in Hodgkin lymphoma and identify new factors that influence treatments results and outcome. These scientific studies will be performed as ancillary studies based on the AMC-085 protocol.

B) TUMOR BIOPSY

A tissue microarray as well as DNA and RNA extraction will be performed on each paraffin embedded tissue block received.

C) BLOOD SAMPLE

Specific informed consents must be signed before any sample procedure.

Every collected samples will be part of a comprehensive collaborative studies. This may include genetic, proteomic, virological and immunology studies.

The following sample will be collected at baseline, before treatment:

- 30mL of blood on heparin lithium tubes
- 10mL of blood on EDTA tubes

LYSARC provides consumables for realisation of biological studies: tubes heparin lithium, labels, traceability form.

LYSARC supports the transporting of biological sample until hospital Bicêtre:

> The day before blood sampling, contact the carrier to schedule the removing of samples. The day of blood sampling, complete the traceability form, and send the tubes and the form to Bicêtre hospital, at room temperature, by carrier.
>
> Address: CHU Bicetre,
> Laboratoire d'immnunologie,
> 4ème étage pavillon Broca
> 78 rue du Gal Leclerc,
> 94275 LE KREMLIN BICETRE FRANCE

D) CONTROL AND IDENTIFICATION OF THE BIOLOGICAL SAMPLES FROM THE BLOOD

In order to organize the tracking of biological samples, the LYSARC asks the centres to complete a document “AMC- 085– traceability form (in investigator file). This document must be completed on site, shipped with the blood sample.

The complete procedure will remain anonymous all along the biological analysis. Observations will be linked with the LYSA clinical database (registered to the CNIL) only after the end of the study. This database contains the main information about patients participating to the study including demographic data, baseline clinical evaluation, treatment, response to treatment and follow-up (relapse, death).

21.9 Appendix: Prohibited and use with caution medications that are p-glycoprotein and cyp3a4 inhibitors

Strong CYP3A inhibitors and P-glycoprotein inhibitors must be discontinued 7 days prior to therapy. Moderate CYP3A4 inhibitors should be used with Caution but are not excluded. If 2 moderate CYP3A4 inhibitors are used concurrently, one must be discontinued at least 7 days prior to chemotherapy.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

P-Glycoprotein Inhibitors	Strong CYP 3A4 Inhibitors	Moderate CYP 3A4 Inhibitors
Antiretrovirals	**Antiretrovirals**	**Antiretrovirals**
Lopinavir and ritonavir	Cobicistat	Atazanavir
	Indinavir	
Other Agents	Nelfinavir	**Other Agents**
Amiodarone	Ritonavir	Aprepitant
Azithromycin	Saquinavir	Amprenavir
Captopril		Amiodarone
Carvedilol	**Other Agents**	Ciprofloxacin
Clarithromycin	Boceprevir	Dronedarone
Conivaptan	Clarithromycin	Erythromycin
Cyclosporine	Itraconazole	Diltiazem
Diltiazem	Ketoconazole	Fluconazole
Dronedarone	Mibefradil	Fosamprenavir
Erythromycin	Nefazodone	Grapefruit juice
Felodipine	Posaconazole	Seville orange juice
Itraconazole	Suboxone	Verapamil
Ketoconazole	Telithromycin	Voriconazole
Quercetin	Telaprevir	
Quinidine	Troleandomycin	
Ranolazine		
Tacrolimus		
Verapamil		