

**A PHASE I/II STUDY OF BRENTUXIMAB VEDOTIN IN
COMBINATION WITH MULTI-AGENT CHEMOTHERAPY AS FRONT-
LINE TREATMENT IN PATIENTS WITH CD30 POSITIVE PRIMARY
MEDIASTINAL LARGE B-CELL, DIFFUSE LARGE B-CELL, AND
GREY ZONE LYMPHOMAS**

**Principal Investigator/
Regulatory Sponsor:** Jakub Svoboda, MD
Department of Medicine, Division Hematology-Oncology
Hospital of the University of Pennsylvania
3400 Civic Center Blvd.
Philadelphia, PA 19104
Tel: 215-614-1846

Sub-Investigators: Stephen Schuster, MD (UPenn)
Sunita Nasta, MD (UPenn)
Daniel Landsburg, MD (UPenn)
Joanne Filicko-O'Hara, MD (TJUH)
Stefan K. Barta, MD (FCCC)
Megan S. Lim, MD, PhD (UPenn)
Marco Ruella, MD (UPenn)

Funding Sponsor: Seattle Genetics, Inc.
21823 30th Drive SE
Bothell, WA 98021, USA

Participating Sites: Hospital of the University of Pennsylvania
Thomas Jefferson University
Fox Chase Cancer Center

Study Product: Brentuximab vedotin (Adcetris)

Protocol Number: 818280 / UPCC 17413

IND Number: 118739

Medical Monitor: Naomi Haas, MD

Initial version: 08.13.2013
Amended: 06.02.2014
Amended: 03.09.2015
Amended: 06.22.2015
Amended: 10.25.2017
Amended: 01.12.2018
Amended: 01.31.2018
Amended: 06.21.2018

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

INVESTIGATOR AGREEMENT

Study Title: A Phase I/II Study of Brentuximab Vedotin in Combination with Multi-agent Chemotherapy as Front-Line Treatment in Patients with CD30-Positive Primary Mediastinal Large B-Cell, Diffuse Large B-cell, and Grey Zone Lymphomas (UPCC 17413)

I agree to conduct this clinical trial according to the principles and methods set forth in this protocol and in accordance with GCP, and applicable regulatory requirements.

Investigator's Signature

Investigator's Printed Name

Institution

Date

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Table of Contents

STUDY SUMMARY	1
1 INTRODUCTION	3
1.1 BACKGROUND	3
1.2 INVESTIGATIONAL AGENT.....	5
1.3 PRECLINICAL DATA	5
1.4 CLINICAL DATA TO DATE	6
1.5 STUDY RATIONALE AND RISK/BENEFITS	7
1.5.1 Correlative Study Rationale.....	8
2 STUDY OBJECTIVES	9
3 STUDY DESIGN.....	10
3.1 GENERAL DESIGN	10
3.2 PRIMARY STUDY ENDPOINTS	10
3.3 SECONDARY STUDY ENDPOINTS	11
4 SUBJECT SELECTION AND WITHDRAWAL	11
4.1 INCLUSION CRITERIA FOR PHASE I AND PHASE II	11
4.2 EXCLUSION CRITERIA FOR PHASE I AND PHASE II.....	12
4.3 INCLUSION CRITERIA FOR CORRELATIVE STUDY	13
4.4 EXCLUSION CRITERIA FOR CORRELATIVE STUDY	13
4.5 SUBJECT RECRUITMENT AND SCREENING	13
4.6 EARLY WITHDRAWAL OF SUBJECTS.....	13
4.6.1 When and How to Withdraw Subjects.....	13
4.6.2 Data Collection and Follow-up for Withdrawn Subjects.....	14
5 STUDY DRUG	14
5.1 DESCRIPTION	14
5.2 TREATMENT REGIMEN.....	14
5.2.1 Dose Limiting Toxicities	15
5.2.2 Dose Modifications	17
5.3 PREPARATION AND ADMINISTRATION OF STUDY DRUG.....	19
5.4 SUBJECT COMPLIANCE MONITORING.....	19
5.5 PREMEDICATION AND CONCOMITANT THERAPY	19
5.5.1 Premedication	19
5.5.2 Concomitant Therapy	20
5.6 PACKAGING	21
5.7 RECEIVING, STORAGE, DISPENSING AND RETURN	21
5.7.1 Receipt of Drug Supplies	21
5.7.2 Storage.....	21
5.7.3 Return or Destruction of Study Drug	21

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

6	STUDY PROCEDURES	21
6.1	SCHEDULE OF EVENTS	21
6.2	SCREENING/BASELINE: WITHIN 28 DAYS OF CYCLE 1/DAY 1	22
6.3	TREATMENT PERIOD (CYCLES 1-6)	22
6.4	END OF TREATMENT (30 ± 7 DAYS AFTER LAST DOSE OF BRENTUXIMAB VEDOTIN AND R-CHP)	24
6.5	LONG TERM FOLLOW-UP	24
6.6	STUDY ASSESSMENTS	25
6.7	CORRELATIVE STUDY PROCEDURES	26
7	STATISTICAL PLAN	26
7.1	SAMPLE SIZE DETERMINATION	26
7.2	STATISTICAL METHODS	27
7.3	SUBJECT POPULATION(S) FOR ANALYSIS	28
7.4	STUDY ENDPOINT DEFINITIONS	28
8	SAFETY AND ADVERSE EVENTS	29
8.1	DEFINITIONS	29
8.2	RECORDING OF ADVERSE EVENTS	31
8.3	REPORTING OF SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEMS	31
8.4	STOPPING RULES	36
8.5	MEDICAL MONITORING	36
9	DATA HANDLING AND RECORD KEEPING	36
9.1	CONFIDENTIALITY	36
9.2	SOURCE DOCUMENTS	37
9.3	CASE REPORT FORMS	37
9.4	RECORDS RETENTION	37
10	STUDY MONITORING, AUDITING, AND INSPECTING	37
10.1	STUDY MONITORING PLAN	37
10.2	AUDITING AND INSPECTING	38
11	ETHICAL CONSIDERATIONS	38
12	STUDY FINANCES	39
12.1	FUNDING SOURCE	39
12.2	CONFLICT OF INTEREST	39
12.3	SUBJECT STIPENDS OR PAYMENTS	39
13	PUBLICATION PLAN	39
14	REFERENCES	39
15	APPENDIX A SCHEDULE OF ASSESSMENTS	43

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

List of Abbreviations

ABVD adriamycin-bleomycin-vinblastine-dacarbazine
ACC Abramson Cancer Center
ADC antibody-drug conjugate
AE adverse event
ALCL anaplastic large cell lymphoma
ALT alanine transaminase
ASCT autologous stem cell transplant
AST aspartate transaminase
AVD adriamycin, vinblastine, dacarbazine
CD cluster of differentiation
cHL classical Hodgkin lymphoma
CHP cyclophosphamide-doxorubicin -prednisone
CHOP cyclophosphamide-doxorubicin -vincristine-prednisone
CIITA class II transactivator
CNS central nervous system
CR complete remission
CRF case report form
CT computerized tomography
CTCAE Common Terminology Criteria for Adverse Events
CTMS clinical trials management system
CTSRMC Clinical Trials Scientific Review and Monitoring Committee
DLBCL diffuse large B-cell lymphoma
DLT dose limiting toxicity
DOCM Department of Compliance and Monitoring
DSMC Data Safety Monitoring Committee
EBV Epstein-Barr virus
EFS event free survival
EOT end of treatment
FCCC Fox Chase Cancer Center
FDA Food and Drug Administration
FFPE formalin-fixed, paraffin-embedded
G-CSF granulocyte colony-stimulating factor
GEP gene expression profiling
GFR glomerular filtration rate
GM-CSF granulocyte macrophage colony-stimulating factor
GZL grey zone lymphoma
HB hepatitis B
HBcAb hepatitis B core antibody
HBsAb hepatitis B surface antibody
HBsAg hepatitis B surface antigen
HIPPA Health Insurance Portability and Accountability Act
HIV human immunodeficiency virus
IND investigational new drug
IRB Institutional Review Board
MACOP methotrexate, cytarabine, cyclophosphamide, vincristine, prednisone, bleomycin

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

MMAE monomethyl auristatin E
MTD maximum tolerated dose
NCCN National Comprehensive Cancer Network
NHL non-Hodgkin lymphoma
N/A not applicable
N/D not done
ORR objective response rate
OS overall survival
PCR polymerase chain reaction
PD progressive disease
PD-L programmed death ligand
PET positron emission tomography
PFS progression-free survival
PHI protected health information
PI principal investigator
PMBL primary mediastinal (thymic) large B-cell lymphoma
PML progressive multifocal leukoencephalopathy
PR partial remission
R rituximab
R-CHOP rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone
R-CHP rituximab-cyclophosphamide-doxorubicin-prednisone
RT radiation therapy
SAE serious adverse event
SD stable disease
SMC Safety Monitoring Committee
TJUH Thomas Jefferson University Hospital
ULN upper limit of normal
UPCC University of Pennsylvania Cancer Center
UPENN University of Pennsylvania
WHO World Health Organization

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Study Summary

Title	<i>A phase I/II study of brentuximab vedotin in combination with multi-agent chemotherapy as front-line treatment in patients with CD30 positive primary mediastinal large B-cell, diffuse large B-cell, and grey zone lymphomas</i>
Short Title	<i>Brentuximab plus R-CHP in CD30 positive B-cell lymphomas</i>
Protocol Number	<i>818280 / UPCC 17413</i>
Phase	<i>Phase I/II</i>
Methodology	<i>Open-label, non-randomized</i>
Study Duration	<i>3-5 years</i>
Study Center(s)	<i>Multicenter: Hospital of the University of Pennsylvania, Thomas Jefferson University, Fox Chase Cancer Center</i>
Objectives	<p><u><i>Primary Objective for Phase I component of study:</i></u></p> <ul style="list-style-type: none"> - <i>Safety and maximum tolerated dose of brentuximab vedotin when delivered in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone in untreated CD30-positive primary mediastinal large B-cell, diffuse large B-cell, and grey zone lymphomas</i> <p><u><i>Secondary Objectives for Phase I component of study:</i></u></p> <ul style="list-style-type: none"> - <i>Overall response rate</i> - <i>Complete remission rate</i> - <i>Progression-free survival at year 1 and 2</i> - <i>Overall survival at year 1 and 2</i> - <i>Progression-free and overall survival</i> - <i>Correlation between CD30 expression and clinical outcome</i> - <i>Correlation between B-cell lymphoma subtype and clinical outcome</i> <p><u><i>Primary Objective for Phase II component of study:</i></u></p> <ul style="list-style-type: none"> - <i>Overall response rate of the combination of brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin and prednisone in untreated CD30-positive primary mediastinal large B-cell, diffuse large B-cell, and grey zone lymphomas</i>

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
 Do not disclose or use except as authorized in writing by the study sponsor

	<p><u>Secondary Objectives for Phase II component of study:</u></p> <ul style="list-style-type: none"> - Complete remission rate - Progression-free survival at year 1 and 2 - Overall survival at year 1 and 2 - Progression-free and overall survival - Safety and toxicity of the combination of brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin and prednisone in untreated CD30-positive primary mediastinal large B-cell, diffuse large B-cell and grey zone lymphomas - Correlation between CD30 expression and clinical outcome - Correlation between B-cell lymphoma subtype and clinical outcome <p><u>Correlative objective:</u></p> <ul style="list-style-type: none"> - Conduct multiplexed gene expression profiling of primary tumor samples to characterize differential gene expression patterns in PMBL and DLBCL
Number of Subjects	32
Diagnosis and Main Inclusion Criteria	<i>Patients 18 years and above with histologically confirmed, previously untreated CD30 positive primary mediastinal large B-cell lymphoma, CD30 positive diffuse large B-cell lymphoma or CD30 positive grey zone lymphoma</i>
Study Product, Dose, Route, Regimen	<i>Brentuximab vedotin (1.8 mg/kg or 1.2 mg/kg), intravenous injection as part of combination regimen including rituximab, cyclophosphamide, doxorubicin, and prednisone</i>
Duration of administration	<i>To be administered approximately once every 3 weeks for total of 6 cycles</i>
Statistical Methodology	<i>Phase I study to identify maximum tolerated dose, followed by Phase II study using the Simon optimal two-stage design.</i>

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

1 Introduction

This document is a protocol for a human research study using brentuximab vedotin combined with multi-agent chemotherapy in patients with new diagnosis of primary CD30 positive primary mediastinal (thymic) large B-cell lymphoma (PMBL), diffuse large B-cell lymphoma (DLBCL) or grey zone lymphoma (GZL). This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and institutional research policies and procedures.

The study started enrolling patients in January 2013 and as of December 2014, the Phase I portion concluded. Six patients were treated per the Phase I protocol without evidence of DLT. Phase I data established a maximum tolerated dose of 1.8 mg/kg brentuximab vedotin.

1.1 Background

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma worldwide accounting for about 25-30% of all non-Hodgkin lymphomas (NHL). In recent years, it has been increasingly recognized that DLBCL is not just a single entity. It represents a group of aggressive lymphomas that have heterogeneous clinical, immunohistochemical and genetic characteristics.

Cluster of differentiation (CD) 30 is a cell membrane protein of the tumor necrosis factor receptor family and can serve as a tumor marker (Schneider and Hubinger 2002, 1355-1366). It is a positive regulator of apoptosis, and also has been shown to limit the proliferative potential of auto-reactive CD8 effector T cells. CD30 is expressed on malignant cells in classical Hodgkin lymphoma (cHL), anaplastic large cell lymphoma (ALCL), and also on some forms of DLBCL (Campuzano-Zuluaga et al. 2012, 1592; Slack et al. 2012, 1558).

The usage of an anti-CD30 antibody drug conjugate presents an intriguing option for CD30 positive B-cell lymphomas since CD30 expression was shown to be a promising target in other CD30-positive tumors, such as cHL and ALCL. Using standard immunohistochemistry, CD30 is expressed in about 20-25% of DLBCLs, but the number is up to 70-80% in a DLBCL subtype called primary mediastinal large B-cell lymphomas (PMBL). The significance of CD30 expression in B-cell lymphomas is actively being investigated.

The most common form of CD30 positive DLBCL is PMBL. It is considered a unique clinic-pathologic entity by World Health Organization classification of lymphomas (Swerdlow 2008, 439). It arises in the mediastinum, presumably from B-cells of thymic origin and represents less than 5% of DLBCL (A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma. The Non-Hodgkin's Lymphoma Classification Project. 1997, 3909-3918). CD30 positivity in the majority of PMBL cases makes distinction from cHL difficult at times; especially since clinical presentation with bulky mediastinal mass in younger patients is similar for both of these entities. CD30 expression in PMBL is usually heterogeneous when compared to cHL and may range from strong membrane staining of majority of the neoplastic cells to positivity of rare individual cells (Pileri et al. 2003, S21-6; Higgins and Warnke 1999, 241-247). Similarities in genetic and epigenetic signatures between PMBL and cHL have been also reported (Eberle et al. 2011, 558-566; Rosenwald et al. 2003, 851-862). In some cases, pathologists may not be able to distinguish between PMBL and cHL due to overlapping characteristics. In 2008, WHO added an

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

official category of aggressive lymphomas which are described as B-cell lymphomas, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (Swerdlow 2008, 439). These are usually referred to as grey zone lymphomas (GZL) and nearly 100% of these express CD30.

There is limited amount of data on the clinical outcomes of patients with PMBL, CD30 positive DLBCL, and GZL. For PMBL, some of the earlier studies suggested poor results with CHOP chemotherapy alone. Based on non-randomized comparisons, it appeared that more intense multi-agent regimens had better outcomes when compared to standard CHOP (Todeschini et al. 2004, 372-376; Zinzani et al. 2009, 381-385). However, the addition of anti-CD20 monoclonal antibody rituximab to CHOP chemotherapy improved the inferior outcome of PMBL treated with CHOP (Rieger et al. 2011, 664-670; Tai et al. 2011, 604-612). On a subgroup analysis of the phase III Mabthera trial, addition of rituximab to chemotherapy in PMBL revealed improved event-free survival (EFS) compared to chemotherapy alone (78% vs. 52%) (Rieger et al. 2011, 664-670).

While the optimal front-line treatment of PMBL remains controversial, rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone (R-CHOP) is widely used in NCCN institutions (Zelenetz et al. 2010, 288-334). Since residual mass after completing systemic therapy is not uncommon in PMBL patients, some clinicians recommend consolidation with radiation therapy (RT), but this remains controversial.

PET/CT imaging is used by some oncologists to determine the need of additional RT (Savage et al. 2012, 303). The clinical outcome of PMBL patients treated with R-CHOP with or without consolidative radiation remains inferior to those with the biologically related cHL treated with ABVD.

Recently, Dunleavy et al published results of phase II NCI trial using dose adjusted etoposide-prednisone-vincristine-doxorubicin-rituximab (EPOCH-R) regimen in PMBL with excellent result showing EFS of 97% in a group of 51 patients (Dunleavy et al. 2013, 1408-1416). Majority of patients did not require consolidative radiation. However, these results have not been confirmed in a larger cooperative study and there are no randomized trials comparing this regimen to R-CHOP in PMBL. Some concerns such as long term toxicity, need for inpatient administration, and fertility issues with EPOCH-R have been raised.

Outcomes of patients with GZL are not well described in the literature, but anecdotally they appear worse when compared to cHL or to PMBL patients. Patients with CD30-positive DLBCL (excluding PMBL and GZL) as a group may have better prognosis over CD30 negative cases, but that remains controversial (Hu et al. 2013, 2715-2724). The CD30 positive DLBCL cases are more likely to be of non-germinal center origin (Campuzano-Zuluaga et al. 2012, 1592; Slack et al. 2012, 1558). It has been shown that non-germinal center origin subtype of DLBCL is less responsive to chemotherapy, but addition of monoclonal antibody rituximab improved outcomes to some extent (Lenz et al. 2008, 2313-2323).

Patients with DLBCL of the elderly (defined as a histologically malignant polymorphic or monomorphic EBV-positive B-cell lymphoproliferation in patients who are generally older than 50 years without any known immunodeficiency, transplantation, or prior lymphoma) frequently have CD30 expressed on the malignant lymphocytes and have a poor prognosis in small series (Shimoyama et al. 2009, 835-843).

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

There are no clear guidelines for front line treatment for patients with GZL, but most are treated either with R-CHOP or ABVD regimens with or without consolidative RT. Patients with CD30 positive DLBCL (excluding PMBL and GZL) are usually treated with R-CHOP. Some patients with aggressive lymphomas including DLBCL with concerning features on presentation (bone marrow involvement, sinus disease, testicular disease) may be considered for central nervous system (CNS) prophylaxis using intrathecal chemotherapy, but guidelines are not based on randomized trials (Zelenetz et al. 2010, 288-334).

Since the FDA approval of rituximab for NHL 15 years ago, there has been only slow progress in developing new targeted therapies for front-line regimens in B-cell lymphomas. While R-CHOP works well for a significant portion of patients with PMBL and DLBCL, there is a great need to develop less toxic and more effective treatment strategies.

1.2 Investigational Agent

Brentuximab vedotin is an antibody-drug conjugate (ADC) consisting of three components:

- 1) antibody cAC10, specific for human CD30
- 2) highly potent antimicrotubule agent monomethyl auristatin E (MMAE)
- 3) protease-cleavable linker that covalently attaches MMAE to cAC10

Brentuximab vedotin is proposed to have a multistep mechanism of action that is initiated by binding to CD30 on the cell surface and internalization of the ADC. Upon trafficking to lysosomes, MMAE is released from the conjugate through proteolytic degradation of the drug linker (Sutherland et al. 2006). Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis (Francisco et al. 2003).

In August 2011, the FDA granted accelerated approval to this novel agent for the treatment of patients with cHL after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multiple chemotherapy regimens in patients not eligible for ASCT. This marks the first new drug available for cHL in more than 30 years. Currently this agent is under investigation in various clinical settings, including front-line combination therapy with AVD chemotherapy in cHL, as well as in combination with multi-agent chemotherapy for front-line treatment of CD30-positive mature T-cell and NK-cell neoplasms (Fanale et al. 2012, 60; Younes et al. 2011, 955). Brentuximab vedotin was also used in patients with CD30 positive B-cell non-Hodgkin lymphomas as part of a phase II study in patients with refractory or relapsed setting with overall response rate 35% (Jacobsen et al. 2012, 2746). It appears to be well tolerated as a monotherapy or in combination with cytotoxic chemotherapy with the main side effects being peripheral neuropathy, fatigue, pyrexia, nausea and neutropenia.

1.3 Preclinical Data

Preclinical studies of brentuximab vedotin demonstrated antitumor activity in both *in vitro* and *in vivo* models. The toxicity of multiple doses of brentuximab vedotin has been assessed in rats and monkeys. In both species, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed. Histopathologic lesions were also observed in the spleen in monkeys and in the liver and testes in rats.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

In addition, decreases in peripheral blood counts were observed in both species, and elevations in liver enzymes were seen in rats only. The most significant clinical toxicity was neutropenia, observed in monkeys, which resulted in secondary bacterial infections leading to early deaths at the 6 mg/kg dose. Toxicity was dose-dependent, with a no-observable-adverse-effect level of 0.5 mg/kg in rats and 1 mg/kg in monkeys.

1.4 Clinical Data to Date

The clinical safety data observed in the phase I dose-escalation study (SG035-0001) of brentuximab vedotin administered once every 3 weeks support the 1.8 mg/kg dose level as the maximum tolerated dose (MTD) and this dose and schedule has been selected for phase II studies as monotherapy. In this Phase I study, the most frequent adverse events (AEs) were peripheral neuropathy, constitutional (fatigue and pyrexia), gastrointestinal (diarrhea, nausea), and hematologic (neutropenia) (Younes et al. 2010, 1812-1821).

Recently published results of a multinational, open-label, phase II study established the efficacy and safety of brentuximab vedotin in 102 patients with relapsed or refractory cHL after ASCT (Younes et al. 2012, 2183-2189). In the absence of disease progression or prohibitive toxicity, patients received a maximum of 16 cycles. The ORR was 75% with CR in 34% of patients. The median PFS time for all patients was 5.6 months, and the median duration of response for those in CR was 20.5 months. After a median observation time of more than 1.5 years, 31 patients were alive and free of documented progressive disease. The most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea.

The clinical safety and activity of brentuximab vedotin in non-Hodgkin lymphomas (NHL) were further evaluated in a phase II study of patients with relapsed or refractory systemic ALCL (SG035-0004) (Pro et al. 2012, 2190-2196). In this study, interim results showed all patients had previously received at least one prior regimen of multi-agent systemic chemotherapy with curative intent. Relative to the most recent therapy, 50% of patients were refractory. Additionally, approximately 60% of patients had primary refractory disease, defined as failure to achieve a complete remission (CR) with front-line therapy or progression within 3 months of completing front-line therapy, and 24% of patients had never achieved a response with any previous therapy. In this study of highly refractory patients, the objective response (CR + PR) rate was approximately 86%, with 57% of patients achieving a CR. Brentuximab vedotin was generally well tolerated, with manageable side effects.

Interim results of a phase II study using brentuximab vedotin in relapsed and refractory CD30 positive non-Hodgkin lymphomas other than ALCL was recently presented at ASH 2012 (Jacobsen et al. 2012, 2746). Among 53 patients enrolled, 35 patients had B-cell neoplasms including 22 patients with DLBCL. The responses to single agent brentuximab vedotin at 1.8 mg/kg administered every 3 weeks (continued until disease progression or unacceptable toxicity) were encouraging with 47% overall response rate in DLBCL (3 with complete remission, 4 with partial remission) (Jacobsen et al. 2012, 2746).

Brentuximab vedotin has also been used in combination with CHOP like therapy (CHOP minus vincristine=CHP) in a phase I trial as front-line treatment for patients with ALCL (Fanale et al. 2012, 60). Arm 1 of this study used sequential administration of brentuximab vedotin at 1.8 mg/kg x 2 cycles followed by 6 cycles of CHP therapy and then followed by brentuximab vedotin at 1.8 mg/kg x 8 cycles.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

In Arm 2 of this study, the brentuximab vedotin was given concurrently with CHP chemotherapy x 6 cycles followed by brentuximab vedotin at 1.8 mg/kg x 10 cycles. Only 1 of 6 patients in Arm 2 had a dose limiting toxicity (DLT) (Grade 3 rash), but the MTD was not exceeded. Then, Arm 3 was expanded at this dose to 14 more patients who overall tolerated the combination well (serious adverse events related to brentuximab vedotin were rash and febrile neutropenia). At the time of interim analysis, all 26 patients had been assessed for clinical response at the end of 6 cycles of combination therapy or at the latest assessment for 3 patients who had discontinued treatment prior to Cycle 6. All patients (100%) achieved an objective response, with 23 patients (88%) achieving a CR (Fanale et al. 2012, 60). The recommended dose for the front-line therapy for patients with CD30-positive mature T-cell lymphomas was 1.8 mg/kg brentuximab vedotin in combination with CHP.

1.5 Study Rationale and Risk/Benefits

Targeted, monoclonal antibody based therapies have an increasing role in management of lymphoma patients. Addition of monoclonal anti-CD20 antibody rituximab to cytotoxic chemotherapy has been shown to improve B-cell lymphoma outcomes in several settings, including first line treatment of DLBCL (Coiffier et al. 2002, 235-242). Adding a novel antibody based therapy to chemoimmunotherapy regimen may enhance efficacy and limit toxicity (both acute and long term toxicity). PMBL and GZL in particular affect young adults, who may have 30-50 year life expectancy once cure is achieved. Therefore, avoiding long-term chemotherapy-related toxicities from dose intense regimens such as EPOCH-R or MACOP including secondary myelodysplasia or infertility are pivotal. Also, the convenience of outpatient administration over infusional regimens requiring several days of inpatient hospitalization is of importance to patients. The optimal front-line therapy for PMBL and GZL remains controversial and the management of CD30 positive DLBCL continues to evolve.

We hypothesize that substituting brentuximab vedotin in place of vincristine in R-CHOP as front-line multi-agent chemotherapy for PMBL, CD30 positive DLBCL and GZL may be well tolerated and improve outcomes in these patients. We propose a phase I/II, multi-center, single-arm, non-randomized study in which CD30 positive, previously untreated PMBL, DLBCL and GZL patients will receive a combination of brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin and prednisone for a total of 6 cycles.

The phase I component will evaluate safety and toxicity of the regimen, since the combination of brentuximab vedotin and R-CHP has not previously been studied. The phase II portion will further investigate safety and toxicity. Overall response rate (ORR) at the conclusion of systemic therapy will be the primary end point of the phase II portion of the study, with secondary endpoints of complete remission rate, progression-free survival (PFS) and overall survival (OS). We will also correlate CD30 expression and lymphoma subtype with clinical outcome.

Due to the neurotoxicity profile of vincristine (vinca alkaloid) which is a part of R-CHOP regimen, there is a potential concern for additive neurotoxicity in combination with brentuximab vedotin. Vincristine has only moderate contribution to activity in R-CHOP. Substitution of brentuximab vedotin for vincristine in this multi-agent combination is likely to enhance efficacy of R-CHP while avoiding potential increases in neurotoxicity. This is a safer approach than attempting to administer the two agents concurrently, where doses of one or both agents may be limited by resultant neurotoxicity.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

In the future, lymphoma management will involve combinations of targeted therapies specifically designed for an individual patient as based on various markers including immunohistochemistry. It is also clear that early assessment of response during the course of therapy may become an important tool to tailor treatment strategy (e.g. escalation or de-escalation of therapy). The expression level of CD30 (by immunohistochemistry) on the surface of lymphoma cells did not correlate with the clinical response to brentuximab vedotin in cutaneous T-cell lymphoma/mycosis fungoides (Krathen et al. 2012, 797), but could be an important correlate to investigate in B-cell lymphomas. Interim PET/CT imaging after two cycles of ABVD chemotherapy is an early predictor of outcome in Hodgkin lymphoma patients (Hutchings et al. 2006, 52-59) and is being incorporated into the design of current trials in this disease. PET/CT does not appear to be as strong of a predictor in DLBCL treated with R-CHOP (Pregno et al. 2012, 2066-2073).

The concurrent combination of brentuximab vedotin at 1.8 mg/kg and standard doses of CHP has been studied, reported, and safely administered as part of phase I trial for ALCL (Fanale et al. 2012, 60). However, the combination of brentuximab vedotin with CHP and another monoclonal antibody (rituximab) may result in some unexpected toxicities including higher risk of infections and myelotoxicity. Rituximab administration alone may increase risks of developing progressive multifocal leukoencephalopathy (PML) in some patients, although the absolute risk of developing PML is probably very low (Carson et al. 2009, 4834-4840). PML was also described in a few patients undergoing therapy with brentuximab vedotin.

Therefore, subjects receiving the combination of rituximab and brentuximab vedotin will be closely monitored for signs and symptoms of PML. The one DLT in the 6 ALCL patients treated on the combination of brentuximab vedotin with CHP phase I trial was rash. Rituximab label describes that only 1% of patients experience grade 3 or 4 skin rashes with rituximab therapy and so combining of brentuximab vedotin with R-CHP is unlikely to have severe dermatologic side effects. Other treatment-related adverse events with incidence >30% seen on the combination of brentuximab vedotin with CHP trial included nausea (58%), fatigue (50%), diarrhea (50%), peripheral sensory neuropathy (38%), and alopecia (38%) which are not expected to be greatly enhanced by addition of rituximab.

The Phase I portion of our study has completed and no DLT was found with the combination of standard R-CHP doses and brentuximab at 1.8 mg/kg, but patients continue to be closely monitored for long term side effects or rare effects that might have been missed in the small number of patients in the Phase I portion.

1.5.1 Correlative Study Rationale

DLBCL is increasingly recognized as a very heterogeneous group of diseases in respect to morphologic, immunophenotypic, genetic and clinical features. PMBL is a unique clinic-pathologic large B-cell lymphoma subtype that presents most frequently with large mediastinal mass and affects young adults (with female predominance). There are also some characteristic immunophenotypic features of PMBL such as positivity for CD30, MUM1, and CD23. However, it remains challenging to distinguish between PMBL and DLBCL with mediastinal involvement based on clinical and pathology findings alone.

Interestingly, gene expression profiling (GEP) suggests a relationship between PMBL and classical Hodgkin lymphoma and this is further supported by shared genetic abnormalities.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Translocations involving the MHC class II transactivator (CIITA), as well as gains/amplification of chromosome 9p24.1 including the gene loci of JAK2 and programmed cell death protein 1 ligands (PDL1 and PDL2), have been detected frequently in cases of PMBL. Several groups have described genetic signatures that can distinguish between PMBL vs DLBCL. At this time, testing for these specific signatures is not part of routine pathology testing.

Gene expression profiling of subject tumor samples to distinguish PMBL and non-PMBL subtypes would significantly strengthen pending outcomes and survival analysis of the primary study (UPCC 17413). This data may also further illuminate PMBL biology, including potential new therapeutic targets. We aim to conduct a correlative study using Nanostring PanCancer multiplexed GEP technology to characterize gene expression patterns in the PMBL and DLBCL among our study participants.

For those who participate in this correlative study, there exists a theoretical risk of tissue depletion. This risk is variable for each patient and is dependent primarily upon the size of the archival sample. For those patients with a large archival specimen, the risk of depletion is low, whereas those with a small amount of archived tissue have a higher risk of depletion. It is important to clarify that for the majority of patients in the study, the clinical utility of existing archived tissue is limited. If a participating patient develops recurrent disease, the standard of care would be to obtain tissue from the site of recurrence to guide further treatment decisions (instead of performing additional testing on the existing tissue).

2 Study Objectives

Primary objective for Phase I:

- Safety and MTD of brentuximab vedotin when delivered in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone in untreated CD30-positive PMBL, DLBCL, and GZL

Secondary objective for Phase I:

- ORR rate of the combination of brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone in untreated CD30-positive PMBL, DLBCL, and GZL
- Complete remission rate
- PFS at years 1 and 2
- OS at years 1 and 2
- PFS and OS
- Correlation between CD30 expression and clinical outcome
- Correlation between B-cell lymphoma subtype and clinical outcome

Primary objective for Phase II:

- Overall response rate of the combination of brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone in untreated CD30-positive PMBL, DLBCL, and GZL

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Secondary objective for Phase II:

- Complete remission rate
- PFS at years 1 and 2
- OS at years 1 and 2
- PFS and OS
- Safety and toxicity profile of the combination of brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone in untreated CD30-positive PMBL, DLBCL, and GZL.
- Correlation between CD30 expression and clinical outcome Correlation between B-cell lymphoma subtype and clinical outcome

Correlative objective:

- Conduct multiplexed gene expression profiling of primary tumor samples to characterize differential gene expression patterns in PMBL and DLBCL

3 Study Design

3.1 General Design

This is a Phase I/II, multicenter, single-arm, non-randomized, open label study. All patients will receive combination of brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone approximately every 3 weeks for a total of 6 cycles. The Phase I portion of the study will determine the safety and MTD of brentuximab vedotin when delivered in combination with R-CHP chemotherapy. The Phase II portion of the study will further evaluate the activity of brentuximab vedotin when administered in combination with multi-agent chemotherapy in patients with CD30 positive PMBL, DLBCL, and GZL. Safety assessments will include surveillance and recording of AEs, physical examination findings, and laboratory tests. Disease response will be assessed by the Investigator using the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007, 579-586).

NOTE: As above, Phase I accrual concluded in December 2014; no DLT was observed in Phase I patients and Phase II enrollment concluded in June 2017.

3.2 Primary Study Endpoints

For Phase I:

- Type, incidence, severity, relatedness, and seriousness of AEs
- Type, incidence, and severity of laboratory abnormalities
- Dose-limiting toxicity (DLT)

For Phase II:

- Investigator assessment of ORR as determined by the International Working Group Response Criteria for non-Hodgkin Lymphoma (Cheson et al. 2007, 579-586)

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

3.3 Secondary Study Endpoints

For Phase I:

- Investigator assessment of ORR and CR as determined by the International Working Group Response Criteria for non-Hodgkin Lymphoma (Cheson et al. 2007, 579-586)
- PFS and OS at years 1 and 2
- PFS and OS

For Phase II:

- Type, incidence, severity, relatedness, and seriousness of AEs
- Type, incidence, and severity of laboratory abnormalities
- Investigator assessment of CR as determined by the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007, 579-586)
- PFS and OS at years 1 and 2
- PFS and OS

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria for Phase I and Phase II

- Age 18 and above.
- Histologically confirmed CD30-positive, CD20-positive untreated primary mediastinal B-cell lymphoma, diffuse large B-cell lymphoma, or grey zone lymphoma. Patients with heterogeneous, weak or equivocal CD30 staining will also be included (no specific cut off percentage for CD30 stain is required). Patients with any Ann Arbor stage are eligible.
- Measurable disease, defined by the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007, 579-586).
- Absolute neutrophil count $\geq 1,000/\text{mm}^3$ and platelet count $\geq 75,000/\mu\text{L}$ (unless documented bone marrow involvement with lymphoma).
- Normal left ventricular ejection fraction of $\geq 50\%$ estimated by MUGA scan or echocardiogram.
- Estimated creatinine clearance (using Cockcroft-Gault equation) must be $> 50 \text{ mL/min}$.
- Serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN). Bilirubin $\leq 3 \times$ ULN is permitted in individuals with documented liver involvement by lymphoma or if due to known Gilbert syndrome.
- Aspartate transaminase (AST) or alanine transaminase (ALT) $\leq 3 \times$ ULN.
- Performance status of ECOG 0-2; patients with ECOG of 3 may be allowed to enroll after discussion with the Regulatory-Sponsor/Principal Investigator and medical monitor, and if the performance status is believed to be secondary to lymphoma related symptoms and performance status is expected to improve once chemotherapy commences.
- Capable of understanding the investigational nature, potential risks and benefits of the study, and able to provide valid informed consent. In patients who are not able to consent to the trial due to medical circumstances, the next of kin or power of attorney may consent for the study.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

- Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β -hCG) pregnancy test result within 7 days prior to the first dose of brentuximab vedotin and must agree to use an effective contraception method during the study and for 6 months following the last dose of study drug; females of non-childbearing potential are those who are post-menopausal for more than 1 year or who have had a bilateral tubal ligation or hysterectomy.
- Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last dose of study drug.
- Must be able to comply with the study and follow-up requirements.

4.2 Exclusion Criteria for Phase I and Phase II

- Previous use of investigational agents, chemotherapy or immunotherapy for lymphoma any time prior to enrollment (i.e. must have untreated disease). Prior allogeneic or autologous transplants are also not allowed.
- Current concomitant chemotherapy, radiation therapy, or immunotherapy other than as specified in the protocol. Consolidative radiation therapy (RT) after completion of planned course and/or concurrent intrathecal chemotherapy for CNS disease prophylaxis is permissible.
- Treatment with systemic steroids for > 4 weeks prior to Cycle 1 Day 1 of study therapy. Prior radiation therapy, with the exception of an abbreviated course (not more than 3 days) if used for SVC syndrome.
- History of serious organ dysfunction or disease involving the heart (left ventricular ejection fraction < 50%; unstable angina, acute myocardial infarction within 6 months prior to randomization, congestive heart failure NYHA III-IV, and arrhythmia unless controlled by therapy, with the exception of extra systoles or minor conduction abnormalities.), the kidney (creatinine clearance \leq 50 mL/min), the liver (chronic hepatitis B as defined below or elevated AST, ALT, or alkaline phosphatase > 3 ULN; serum bilirubin > 1.5 x ULN; bilirubin up to 3 x ULN is permitted in individuals with documented liver involvement by lymphoma or if due to known Gilbert syndrome) or other organ system that may place the patient at undue risk to undergo treatment.
- Uncontrolled systemic fungal, bacterial, viral, or other serious infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment). May be enrolled if controlled on treatment.
- Significant concurrent disease, illness, or psychiatric disorder that would compromise patient safety or compliance, interfere with consent, study participation, follow-up, or interpretation of study results.
- Subjects who have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver involved with lymphoma or stable chronic liver disease per investigator's assessment).
- History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms or sequelae.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

- Other malignancy, unless the patient has been disease-free for at least 3 years following the completion of curative intent therapy, with the following exceptions:
 - Treated non-melanoma skin cancer, any in situ carcinoma, or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed.
 - Organ-confined prostate cancer with no evidence of recurrent or progressive disease based on prostate-specific antigen (PSA) values are also eligible for this study if hormonal therapy has been initiated, or radical prostatectomy or definitive prostate irradiation has been performed.
- Positive test for the Human Immunodeficiency Virus (HIV) unless undetectable viral load within 3 months of enrolment (HIV RNA less than 48 copies/mL) and on HAART therapy.
- Positive serology for hepatitis B (HB) defined as a positive test for hepatitis B surface antigen or hepatitis B core antibody.
- Active involvement of the central nervous system (CNS) by lymphoma. Work-up for CNS involvement at diagnosis will be directed as per the treating physician and will depend on specific clinical circumstances (no brain imaging or lumbar puncture is required by this protocol).
- Pregnant or lactating women.

Exceptions to eligibility may not be accepted.

4.3 Inclusion criteria for correlative study

- Patient participated in Phase I or Phase II of the UPCC 17413 and received at least one cycle of therapy
- Patient consent to participating in this correlative study

4.4 Exclusion criteria for correlative study

- No tissue available for multiplexed gene expression profiling

4.5 Subject Recruitment and Screening

Subjects will be recruited from the clinical oncology practices at participating sites (Hospital of the University of Pennsylvania, Thomas Jefferson University Hospital, and Fox Chase Cancer Center). No advertising or recruitment materials will be utilized. Subjects will not be reimbursed for participation.

4.6 Early Withdrawal of Subjects

4.6.1 When and How to Withdraw Subjects

A patient may be discontinued from treatment regimen using brentuximab vedotin in combination with R-CHP prior the expected completion for disease progression, failure to adhere to protocol requirements, or if the investigator or patient deems it in the patient's best interest to discontinue. The reason justifying study treatment discontinuation should be documented in the case report form (CRF). Patients who discontinue the study regimen prior to completion will remain on study for follow-up, unless they withdraw consent. All patients who receive at least 1 dose of study drug will be followed for toxicity, response and survival.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

A patient may be withdrawn from the study (during treatment or follow-up) for reasons including death, patient withdrawal of consent for further follow-up, if the patient is lost to follow-up, or at study termination by a participating site, study sponsor or by Seattle Genetics (drug manufacturer/funding sponsor).

If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted.

4.6.2 Data Collection and Follow-up for Withdrawn Subjects

The University of Pennsylvania must be notified in writing if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and CRF. The investigators will make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. If a subject withdraws from study treatment, every attempt should be made to follow the patient until death or administrative study closure. If a subject withdraws consent to participate in the study, attempts should be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. Final treatment assessments will be performed before any other therapeutic intervention if possible. Additionally, any planned alternative treatments should be documented on the patient's medical records and CRF. Adequate attempts will be made to reach out to subjects to collect required follow-up. All attempts to reach subjects will be documented appropriately. Subjects will be considered lost to follow-up if phone calls to the subject or to next of kin are not successful.

5 Study Drug

5.1 Description

Brentuximab vedotin is an ADC consisting of the chimeric antibody SGN-30 (cAC10) chemically conjugated to a synthetic analog (monomethyl auristatin E [MMAE]) of the naturally occurring antitubulin agent, dolastatin10. Brentuximab vedotin is proposed to have a multistep mechanism of action that is initiated by binding to CD30 on the cell surface and internalization of the ADC. Upon trafficking to lysosomes, MMAE is released from the conjugate through proteolytic degradation of the drug linker (Sutherland et al. 2006, 10540-10547). Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis (Francisco et al. 2003, 1458-1465).

5.2 Treatment Regimen

The treatment regimen consists of standard R-CHOP chemotherapy, but without vincristine ("R-CHP") and with the addition of brentuximab vedotin. Therapy will be administered in 21-day cycles for a total of 6 cycles, as summarized in Table 1.

During cycle 1, rituximab dosing will be divided between Days 1 and 2 to prevent severe infusion reactions in rituximab naïve patients. This may also allow us to distinguish between infusional reaction from rituximab which occurs usually during the first exposure vs. the less likely infusional reaction from brentuximab. During Cycle 1, the brentuximab vedotin and the cytotoxic chemotherapy will be administered on Day 2. During Cycles 2 through 6, brentuximab vedotin and R-CHP will be administered on Day 1. Prednisone (oral or intravenous steroid equivalent) will be administered on Days 1-5 of each cycle. Patients will receive rituximab first, then cyclophosphamide and doxorubicin, followed by brentuximab. Prednisone (oral or intravenous steroid equivalent) should be taken prior to rituximab infusion.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

TABLE 1: Summary of the combination regimen using brentuximab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP).

Agent	Dose	Route	Cycle 1	Cycle 2-6
Prednisone (or equivalent)	100 mg	PO or IV equivalent	Days 1-5	Day 1-5
Rituximab	375 mg/m ²	IV	Day 1 and 2 (split dose of 100 mg/m ² and 275 mg/m ² , respectively)	Day 1
Cyclophosphamide	750 mg/m ²	IV	Day 2	Day 1
Doxorubicin	50 mg/m ²	IV	Day 2	Day 1
Brentuximab vedotin*	1.8 mg/kg or 1.2 mg/kg	IV	Day 2	Day 1

*1.8 mg/kg brentuximab vedotin has been established as MTD per Phase I enrollment

For R-CHP administration, dosing should be based on the patient's baseline (pre-dose, Cycle 1 Day 1) height and weight, or per institutional standards at the site. Doses will be adjusted for patients who experience a change in weight $\geq 10\%$ from baseline during the study.

For brentuximab vedotin, actual weight at baseline (pre-dose, Cycle 1 Day 1) will be used except for patients weighing greater than 100 kg. For patients > 100 kg, the brentuximab vedotin dose will be calculated based on a weight of 100 kg. Brentuximab vedotin dose should be rounded to the nearest whole number of milligrams. Doses will be adjusted for patients who experience a change in weight $\geq 10\%$ from baseline during the study.

5.2.1 Dose Limiting Toxicities

The initial planned dose of brentuximab vedotin for the Phase I cohort is 1.8 mg/kg. The Phase I 1.8 mg/kg cohort will enroll 6 patients who will be evaluated for DLT in the first cycle of treatment. Dose de-escalation to 1.2 mg/kg will not occur unless ≥ 2 of 6 patients at the 1.8 mg/kg dose level experience a DLT, defined as any grade 3 or 4 new non-hematologic toxicity occurring during Cycle 1 requiring a dose delay of >14 days from the planned Day 1 of Cycle 2 (21 days from Day 1 of Cycle 1).

Hematologic toxicities which are expected from multi-agent chemotherapy will not be considered for DLT unless the hematologic toxicity will not return to baseline or \leq grade 2 by 21 days from the planned Day 1 of Cycle 2. The hematologic toxicities will be managed according to the institutional guidelines. Prophylactic use of G-CSF or GM-CSF and use of transfusions are allowed and should be administered according to institutional guidelines. It is permissible to use G-CSF (filgrastim or pegfilgrastim) or GM-CSF empirically during the first cycle in patients who are felt to be in risk of leukopenia.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

The DLT evaluation period consists of the time between Day 2 of Cycle 1 (following administration of brentuximab vedotin) up through the start of the Cycle 2. Therefore, only delays that occur during this period will be considered for decisions regarding brentuximab vedotin dose de-escalation. Additional safety experiences in Cycles 2-6 of the Phase I cohort will be monitored and closely recorded. These will be considered when declaring MTD for Phase II of the trial.

In Cycles 2-6, the brentuximab vedotin dose may be withheld or modified according to the guidelines in Table 2. Rituximab dose modifications should not occur. Dose modifications to cyclophosphamide, doxorubicin chemotherapy and prednisone due to toxicity are discouraged, but allowed after the DLT evaluation period (after Cycle 2 Day 1) at the discretion of the Investigator. These may include adjustment of prednisone dose due to severe intolerance (e.g. psychiatric issues or severe hyperglycemia). Some elderly patients who develop severe (but expected) toxicities attributed to cytotoxic chemotherapy (e.g. recurrent neutropenic fevers despite G-CSF) may be considered for modification of the chemotherapy dose by the treating physician as per institutional guidelines. Practically, it is not possible to define exact modifications of the standard cytotoxic chemotherapy component of the regimen, but we expect that only a very small minority of patients would need any modifications. Therefore, the impact on the quality of toxicity and efficacy data should be minimal if any.

Initiation of the next cycle (Cycle 3 through 6) may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle. Delays of greater than 3 weeks are prohibited and will result in discontinuation of study participation, unless an exception is granted by the Principal Investigator, Sponsor and the Medical Monitor. Patients who may develop some of the well described (but rare) toxicities of R-CHOP regimen including new onset of cardiomyopathy or hemorrhagic cystitis will also be discontinued from the study and best efforts will be made to attribute the toxicities accurately.

If ≥ 2 of the initial 6 patients in the 1.8 mg/kg cohort experience a DLT, the MTD for brentuximab vedotin in combination with R-CHP will be considered to have been exceeded. Six patients will then be enrolled and treated at 1.2 mg/kg and monitored for DLT during the first cycle of therapy.

If ≤ 1 DLT occurs in the 6 patients in the 1.8 mg/kg cohort during the evaluation period, enrollment in Phase II will commence using 1.8 mg/kg. If the dose was de-escalated to 1.2 mg/kg and ≤ 1 DLT occurs in the 6 patients in the 1.2 mg/kg cohort, then the Phase II will commence using 1.2 mg/kg. If ≥ 2 of 6 patients at the 1.2 mg/kg dose level experience a DLT, then the study will be terminated.

At least 6 patients must be enrolled and complete one cycle of dosing at the determined MTD prior to beginning patient enrollment in Phase II. If any patient enrolled in a cohort does not complete at least 1 Cycle of treatment through Cycle 2 Day 1, that patient will be replaced unless discontinuation is due to a DLT.

NOTE: Six patients were enrolled and treated per Phase I without evidence of DLT. Phase I data established a MTD of 1.8 mg/kg brentuximab vedotin.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

5.2.2 Dose Modifications

The Phase II part of this study will use the determined MTD of brentuximab vedotin. Dose modifications for treatment-associated toxicity with brentuximab vedotin and R-CHP (after the MDT was determined) are summarized in Table 2. As described in detail in Section 7.1, we will raise a red flag if the Bayesian probability that the serious toxicity rate exceeds 20% is greater than 90% in Phase II cohort. If the study raises a red flag, we will review data and consider modification or termination of the trial for lack of safety.

TABLE 2: Recommended dose modifications for treatment-associated toxicity with brentuximab vedotin and R-CHP (during the period after the MTD was determined) ^a . Toxicities should be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. NOTE: Toxicities reported after March 29, 2018 should be graded using CTCAE version 5.0.					
Toxicity	Therapeutic Agent	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral Neuropathy: Sensory	Brentuximab Vedotin	Continue at same dose level	Continue at same dose level	For patients receiving 1.8 mg/kg, reduce dose to 1.2 mg/kg. For patients on 1.2 mg/kg hold until toxicity resolves to ≤ Grade 1 or has returned to baseline. Treatment may be resumed at the same dose level at the discretion of the Treating Investigator after discussion with the Sponsor-Investigator.	Discontinue treatment with brentuximab vedotin.
Peripheral Neuropathy: Motor	Brentuximab Vedotin	Continue at same dose level	For patients receiving 1.8 mg/kg, reduce dose to 1.2 mg/kg. For patients on 1.2 mg/kg hold until toxicity resolves to ≤ Grade 1 or has returned to baseline. Treatment may be resumed at the same dose level at the discretion of the Treating Investigator after discussion with the Sponsor-Investigator.	Withhold until toxicity resolves to ≤ Grade 1 or has returned to baseline; resume treatment at the discretion of the Treating Investigator after discussion with the Sponsor-Investigator.	Discontinue treatment with brentuximab vedotin.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

TABLE 2: Recommended dose modifications for treatment-associated toxicity with brentuximab vedotin and R-CHP (during the period after the MTD was determined) ^a . Toxicities should be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. NOTE: Toxicities reported after March 29, 2018 should be graded using CTCAE version 5.0.					
Toxicity	Therapeutic Agent	Grade 1	Grade 2	Grade 3	Grade 4
Non-Hematologic	Brentuximab Vedotin	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 2 or baseline, then resume treatment at the same dose level ^b	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline; then for patients receiving 1.8 mg/kg, reduce dose to 1.2 mg/kg. For patients on 1.2 mg/kg, hold until toxicity resolves to < Grade 1 or has returned to baseline. Treatment may be resumed at the same dose level at the discretion of the Treating Investigator after discussion with the Sponsor Investigator. ^b
Hematologic ^c	Brentuximab Vedotin	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 2, or has returned to baseline, then resume treatment at the same dose level. Will be managed as per institutional guidelines ^{c,d}	

a The next cycle may be delayed up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity.

b Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

c The use of colony-stimulating factors and transfusions are permissible during Cycle 1 and subsequent cycles as per institutional preferences.

d Patients who develop Grade 3 or Grade 4 lymphopenia may continue study treatment without interruption.

Patients with any signs and symptoms of PML will have the brentuximab vedotin and rituximab held. They will undergo a diagnostic work-up and if PML confirmed, patients will permanently discontinue brentuximab vedotin and rituximab. Patients will be removed from the study if PML develops.

The decision to use consolidative radiation therapy to any residual mass after completion of systemic treatment will be at the discretion of the treating physician. However, radiation will not be started until after the final response assessment after cycle 6 (days 21-28). The use of prophylactic intrathecal therapy (with intrathecal methotrexate or cytarabine) in patients with high risk for CNS relapse during or after completion of systemic therapy is allowed and will be determined by the treating physician.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Subjects will be followed at routine study visits for 2 years after the last dose of the study drug. Follow-up will be performed every 3 months (+/- 30 days) for the first year and every 3 – 6 months (+/- 30 days) during the second year. Follow-up information about the initiation of alternative therapy and survival status may be obtained from the medical record or via telephone or email correspondence for up to 5 years after the end of treatment.

5.3 Preparation and Administration of Study Drug

Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. Brentuximab vedotin is supplied by Seattle Genetics in single-use, Type 1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab vedotin (SGN-35), trehalose, sodium citrate, and polysorbate 80.

For combination treatment with R-CHP, administration of brentuximab vedotin will begin within approximately one hour (up to 1.5 hours) after the completion of R-CHP infusion on Day 1 (\pm 1 day) of each 21-day cycle for cycles 2-6 and on Day 2 of Cycle 1. Planned dose level is 1.8 mg/kg. Brentuximab vedotin is administered by IV infusion given over approximately 30 minutes. In the absence of infusion toxicities, the infusion rate for all patients should be calculated in order to achieve a 30-minute infusion period. Brentuximab vedotin must not be administered as an IV push or bolus. Brentuximab vedotin may be administered through the same IV line used for R-CHP.

In each case of brentuximab vedotin administration, dosing may be based on the patient's baseline (pre-dose, Cycle 1 Day 1) weight or per institutional standards at the site; doses will be adjusted for patients who experience a $\geq 10\%$ change in weight during the study. Actual weight will be used except for patients weighing greater than 100 kg; then the brentuximab vedotin dose will be calculated based on 100 kg for these individuals. Brentuximab vedotin dose should be rounded to the nearest whole number of milligrams.

The individual components of R-CHP chemotherapy should be prepared and administered per institutional guidelines with standard doses (Table 1).

5.4 Subject Compliance Monitoring

Treatment administration will be performed by site staff and documented in source documents and the CRF. Patient administration of the prednisone component of R-CHP chemotherapy will be documented in the CRF (as self-reported and recorded in a diary) and reviewed to ensure compliance with the treatment regimen.

5.5 Premedication and Concomitant Therapy

5.5.1 Premedication

Routine premedication will be administered prior to rituximab administration for R-CHP regimen on Day 1 of Cycles 2-6 consisting of acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 10–25 mg IV) or as per institutional guidelines. For Cycle 1 (split dose rituximab on Day 1 and Day 2) the same premedication before rituximab will be given on Day 1 and Day 2. Of note, the 100 mg of prednisone (or equivalent) for Day 1 and Day 2 (on Cycle 1) or on Day 1 (Cycles 2-6) should be administered with premedications prior rituximab infusion.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Routine premedication should not be re-administered for the prevention of brentuximab vedotin infusion-related reactions prior to the first dose of brentuximab vedotin (after R-CHP administration is completed). Infusion-related reactions may occur during the infusion of brentuximab vedotin. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis, should it occur. The patient should be observed for 60 minutes following the first infusion of brentuximab vedotin. During this observation period, the IV line should remain open for at least one hour to allow administration of IV drugs, if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institution standards. Medications for infusion related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

Patients who experience a Grade 1 or Grade 2 infusion-related reaction with brentuximab vedotin may receive subsequent brentuximab vedotin infusions with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 10–25 mg IV) or according to institutional standards, administered 30–60 minutes prior to each 30-minute brentuximab vedotin infusion.

Patients who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with brentuximab vedotin at the discretion of the Investigator after discussion with the Sponsor-Investigator. Those patients who will develop anaphylaxis-like reaction to brentuximab vedotin will permanently discontinue the drug, but may continue on the study for the remainder of the treatment.

Patients should be individually evaluated to assess the need for tumor lysis syndrome prophylaxis prior to the first dose of treatment (brentuximab vedotin or any component of R-CHP chemotherapy). Patients should receive prophylaxis (e.g. allopurinol) as appropriate per institution standards.

5.5.2 Concomitant Therapy

The use of blood and platelet transfusions, and/or colony-stimulating factors per institutional practice is permitted during therapy. Empiric use of colony-stimulating factors is allowed as per institutional guidelines. Patients who develop documented neutropenia with an ANC $\leq 500/\mu\text{L}$ during Cycle 1 (CBC will be obtained around day 8 of Cycle 1) will use G-CSF or GM-CSF support at that time and in subsequent cycles. Those who develop any grade 3 or 4 cytopenias or symptomatic cytopenias should be transfused per institutional practice.

Radiotherapy (RT) may be given at the investigator's discretion no sooner than 4 weeks after the last dose of brentuximab vedotin and after completion of final response assessment.

Patients with high risk of developing CNS relapse may be treated with prophylactic intrathecal chemotherapy (methotrexate or cytarabine) at the discretion of the treating physician and as per institutional standards during or after completion of systemic therapy.

Patients may not receive other investigational drugs, immunosuppressive medications, or anti-neoplastic therapy during the study.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

5.6 Packaging

Vial drug product may be labeled as brentuximab vedotin, the United States adopted name (Adcetris), or as SGN-35, the compound code; these names can be used interchangeably. The individual components of R-CHP chemotherapy are commercially available.

5.7 Receiving, Storage, Dispensing and Return

5.7.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.7.2 Storage

Vials containing brentuximab vedotin must be refrigerated at 2–8°C in a controlled location accessible only to the pharmacist, the investigator, or a duly designated person. Brentuximab vedotin (SGN-35) for injection does not contain preservatives; therefore, opened and reconstituted vials of brentuximab vedotin must be used within the same day when stored under refrigeration at 2–8°C. It is recommended that brentuximab vedotin vials and solutions be stored protected from direct sunlight until the time of use.

Reconstituted vials must not be shaken. Drug accountability records will be kept according to the local standards of each institution.

5.7.3 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Schedule of Events

Concomitant medications information will be collected from the time of informed consent until the End of Treatment (EOT) visit or 30 days after the last dose, whichever is later. Adverse events will be collected from the time of first drug administration (Cycle 1/Day 1) until the End of Treatment (EOT) visit or 30 days after the last dose, whichever is later. Other study activities are listed by visit in this section and descriptions of study assessments are presented in Section 6.6. A schedule of events is provided in Appendix A. Note: assessment schedule may be adjusted as needed to account for treatment delays. The calendar may also be adjusted as needed in order to account for additional unscheduled visits (for example, if a subject has an unscheduled visit at 6 weeks following the end of treatment, the calendar may be adjusted to schedule the next assessment at 3 months from the unscheduled visit timepoint).

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

6.2 Screening/Baseline: within 28 days of Cycle 1/Day 1

- Informed consent
- Study eligibility per inclusion/exclusion criteria (see Section 4.1 and 4.2)
- Medical history
- Staging PET/CT or CT scan of neck (if indicated), chest, abdomen and pelvis with contrast, to be performed within 60 days of first dose of study therapy
Note: Use of non-contrast CT imaging is permitted where IV contrast is contraindicated (i.e. documented, reported, or suspected contrast dye allergy). If non-contrast CT scans are used in disease staging, this same modality should be used in subsequent radiographic evaluation
- MUGA scan or ECHO to assess ejection fraction
- Bone marrow aspirate and biopsy is elective and under the discretion of treating physician in patients who underwent PET/CT scan as part of staging
- B symptom assessment
- Physical examination including vital signs and baseline neurological exam (see Section 6.6.3)
- Height/weight
- Serum chemistry panel (see Section 6.6.2)
- Complete blood count (CBC) with differential (see Section 6.6.2)
- Viral (HIV and hepatitis B) studies (see Section 6.6.2)
- Pregnancy test (Day -7 to Day 1) for females of childbearing potential
- ECOG performance status

6.3 Treatment Period (Cycles 1-6)

6.3.1 Cycle 1, Day 1

- Serum chemistry panel (if not previously performed within 7 days of dosing)
- CBC with differential (if not previously performed within 7 days of dosing)
- LDH, uric acid
- Vital signs
- Weight
- Physical examination (if not previously performed within 7 days of C1D1)
- ECOG performance status (if not previously performed within 7 days of C1D1)
- B symptom assessment (if not previously performed within 7 days of C1D1)
- Administration of prednisone (PO or IV steroid equivalent) and premedications
- Administration of rituximab, 100 mg/m²

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

6.3.2 Cycle 1, Day 2

- Administration of prednisone (dosing to continue for days 3-5) and premedications
- Administration of rituximab, 275 mg/m²
- Administration of cyclophosphamide
- Administration of doxorubicin
- Administration of brentuximab vedotin (after completion of rituximab and chemotherapy)
- Observation for one hour after completion of brentuximab vedotin infusion completion

6.3.3 Day 8 (± 3 days) of Cycle 1 only

- Serum chemistry panel
- CBC with differential

6.3.4 Day 1 of Cycle 2-6 (+/- 3 days)

- Administration of brentuximab vedotin in combination with R-CHP
- CBC with differential
- Serum Chemistry
- LDH, Uric Acid
- Physical Exam, including neurological exam (mental status, strength, sensation)
- Vital signs, including weight
- ECOG PS
- Adverse event and concomitant medication assessment
- B Symptom assessment

Responses will be assessed as follows:

- CT scan with contrast after Cycles 2 and 4 and with PET/CT after cycle 6 (3-5 weeks after completion of the last cycle) as well as whenever disease progression is suspected. Non-contrast CT may be used if IV contrast is contraindicated.
- Radiographic imaging should then be performed at least every 8 months (+/- 30 days) for the first two years of follow-up. More frequent imaging may be performed as clinically indicated.
- Bone marrow biopsy should be completed to confirm a complete remission to therapy in patients with bone marrow involvement at baseline

Management of Suspected PML

Patients with any signs and symptoms of PML which may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphagia or agnosia, will have the dose of brentuximab vedotin held and will undertake a diagnostic work-up including (but not limited to):

- Neurologic examination, as warranted
- Brain radiologic features by magnetic resonance imaging (MRI)
- PCR analysis: JC virus DNA detectable in cerebrospinal fluid

If PML is confirmed, patients will permanently discontinue treatment with brentuximab vedotin and rituximab. They will be permanently removed from the study.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

6.4 End of Treatment (30 ± 7 days after last dose of brentuximab vedotin and R-CHP)

Note: EOT evaluations should be obtained prior to initiation of non-protocol therapy, including RT. If the EOT evaluations are completed within 30 days of the last day of treatment, the site will conduct a phone screen 30-37 days following the patient's last treatment to ensure that the adverse event profile has not changed.

- Serum chemistry panel
- CBC with differential
- Pregnancy test
- Weight/Vital signs
- Physical exam
- ECOG performance status
- Response assessment with imaging to be done prior any RT
- B symptoms assessment
- Bone marrow aspirate and biopsy (only if positive prior starting therapy; if bone marrow aspirate and biopsy were done prior during the treatment and found to be negative for lymphoma involvement – then this does not have to be performed again)

6.5 Long Term Follow-up

Patients who discontinue study treatment for any reason other than disease progression or initiation of a non-protocol therapy for treatment of lymphoma (other than RT or CNS prophylaxis with intrathecal chemotherapy) will remain on study for follow-up visits until 2 years from EOT or until disease progression or relapse or until they withdraw from the study (see Section 4.6). Follow-up information about the initiation of alternative therapy and survival status may be obtained from the medical record or via telephone or email correspondence for up to 5 years after the end of treatment.

All patients who receive at least 1 dose of study drug will be followed for survival and disease status according to the following schedule:

- Year 1 following EOT: Physical exam and blood work (CBC, platelet, differential) every 3 months (± 30 days)
- Year 2 following EOT: Physical exam and blood work (CBC, platelet, differential) every 3 - 6 months (± 30 days)
- Years 1 and 2 following EOT: imaging (by dedicated CT scan or PET/CT) will be performed at least every 8 months (± 30 days). Of note, patients undergoing consolidative RT may delay imaging for response assessment until after 2 months of completing RT
- After 2 years from EOT, routine care evaluations should be performed per the practice of the treating physician. The frequency of imaging will be at discretion of the treating physician.
- The initiation of an alternative form of treatment for lymphoma will also be collected for up to 5 years from the EOT.
- Patients who are no longer seen at the participating institution may be queried by phone or email to obtain survivorship data and initiation of alternative therapy for up to 5 years from the EOT.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

6.6 Study Assessments

Only patients who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled onto this study.

6.6.1 Response Assessments

Treatment response will be assessed by imaging with PET/CT and/or standard CT scans with IV contrast (chest, abdomen, pelvis and if clinically indicated the neck) at protocol-specified time points. Non-contrast CT imaging may be used if IV contrast is contraindicated – a single modality should be used throughout the study. The determination of antitumor efficacy will be based on objective response assessments made according to the International Working Group Response Criteria for non-Hodgkin Lymphoma (Cheson et al. 2007, 579-586) and treatment decisions by the investigator will be based on these assessments. Clinical response of progressive disease (PD), stable disease (SD), partial remission (PR), or complete remission (CR) will be determined at each assessment. Up to 6 of the largest dominant nodes or nodal masses will be followed for response assessment. They should be clearly measurable in at least 2 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. If the bone marrow was positive at baseline, a follow-up bone marrow aspirate and biopsy is required and must be negative for assessment of a CR. If the follow-up morphology is indeterminate, the biopsy tissue must be negative by immunohistochemistry or the patient will be assessed as a PR.

Tumor imaging will be performed at screening, after Cycles 2, 4, and three to five weeks after Cycle 6, as well as whenever disease progression is suspected. The post-therapy imaging (3-5 weeks after completion of Cycle 6) will be performed prior initiation of RT in patients who are planned to undergo consolidative RT.

After the patient is withdrawn from study treatment for any reason, an additional response assessment will be performed if an assessment has not been performed within the prior 6 weeks. Patients may continue on study treatment for a total of 6 cycles in the absence of disease progression, unacceptable toxicity or withdrawal of consent. All patients' clinical data and tumor images must be available for CRF source verification. Copies of all imaging studies must be made available for review by the Sponsor (or its designee).

6.6.2 Clinical Laboratory Evaluations

The following laboratory assessments will be performed to evaluate safety at scheduled time points (see Appendix A) during the course of the study:

- Chemistry panel, including sodium, chloride, potassium, blood urea nitrogen (BUN), serum creatinine, calcium, total protein, albumin, glucose, total bilirubin, alkaline phosphatase, ALT, AST
- The hematology panel includes the following tests: white blood cell count, hemoglobin/hematocrit, and platelets and the differential includes: neutrophils, lymphocytes, monocytes, eosinophils, and basophils
- Initial blood work will also include testing for HIV and Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis B surface antigen

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

6.6.3 Other Study Assessments

Other study assessments include the following:

- Biopsies for CD30 expression: results of CD30 expression (quantitative estimate) from the diagnostic biopsy of PMBL, DLBCL or GZL will be obtained from pathology reports or from review of the biopsy specimen
- Patient medical history, including a thorough review of:
 - The patient's current and previous conditions
 - Concomitant medications and prior therapies
- Physical examination, including evaluation of skin, HEENT (head, eyes, ears, nose, and throat), nodes, spleen, heart, lungs, abdomen, back, and extremities. Neurological exam will include gross assessment of mental status, strength, and sensation. Any new neurological symptoms concerning for PML will be worked up immediately.
- ECOG performance status
- B symptom assessment (unexplained fevers greater than 38°C, drenching night sweats and/or weight loss greater than 10% of body weight)

6.7 Correlative Study Procedures

Patients will be consented in person or by telephone or email correspondence depending on study follow-up requirements. Those consented by telephone will be sent a description of the correlative study to patients via the United States Postal Service. A member of the study team will then call patients to describe the study and risks and to provide an opportunity to ask any questions. The study staff will then obtain verbal consent for participation in the correlative study. If the study team is unable to reach patients by telephone, an email will be sent to the address previously provided by the patient, requesting the patient to reply via email to indicate willingness to participate. A phone number will be included in order to provide an opportunity to answer any questions and to further discuss the correlative study.

After consent has been obtained, archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue will be retrieved and 8-10 rolls (or slices) of fixed tissue will be collected from each specimen as available. RNA will be isolated from each specimen and, in collaboration with the Centre for Lymphoid Cancer, gene expression profiling will be performed using a customized Nanostring PanCancer Immune Profiling Panel. This panel has been designed to help distinguish between PMBL and CD30+ DLBCL. Statistical analysis will be conducted by Dr. Marco Ruella and Dr. Megan Lim at the University of Pennsylvania in conjunction with statistical support from NanoString Technologies, Inc.

7 Statistical Plan

7.1 Sample Size Determination

The number of patients enrolled and evaluable in the Phase I cohort is defined as at least 6 patients. The operating characteristics of the dose de-escalation scheme are presented here. If the true proportion of patients that would experience a DLT is 10%, then the probability of de-escalating to the lower dose cohort when 2 or more patients experiences a DLT is 9%. If the true proportion of patients that would experience a DLT is 50%, then the probability of dose de-escalation is 83%.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

With this type of study design, the exact number of patients that will be enrolled in Phase I is unknown because it depends upon the number of patients required to reach MTD and the number of patients enrolled in each cohort. A maximum of 12 safety-evaluable patients will participate in Phase I.

Since the Phase I subjects will be recruited, treated and followed in the same way as the Phase II subjects, the 6 Phase I subjects accrued at the MTD will be considered as accrued to the Phase II study as well. The total number of subjects recruited to Phase II will be affected by the CR rate.

We design this trial with the potential for early termination in the case of a poor overall response rate (ORR). We will use the optimal two-stage design of Simon. Choice of design is guided by a desire to stop the trial early if the actual ORR is 50% or less. If the ORR is 70% or greater, we would like to have a low probability of failing to conclude the combination is effective. We select the type I error rate (probability of accepting the drug if the ORR = 50%) to be 10% and the type II error rate (probability of rejecting the drug if the ORR = 70%) to be 20%. The table below gives the optimal (smallest expected sample size under the null) two-stage design exhibiting these properties.

Patients treated	Stop/Reject if number of successes < than
12	7
32	20

Under the null hypothesis of a 50% ORR, this design has an expected sample size of 19.7 and a probability of early termination of 0.61.

With n=32 patients, we will have 90% power to detect any unforeseen toxicity that occurs in 6.9% or more of patients. The standard error of any proportion will be no larger than 8.8%.

We will monitor continuously for toxicity in the phase II portion of the trial. We will raise a red flag if the Bayesian probability that the serious toxicity rate exceeds 20% is greater than 90%. Assuming a beta (2,6) prior (equivalent to 1 toxicity in 6 prior patients), we will raise a red flag if the first 2 subjects experience serious toxicities, if there are 3 serious toxicities occurring by the 6th patient, 4 by the 9th, 5 by the 13th, 6 by the 17th, 7 by the 21st, 8 by the 25th, 9 by the 29th, and 10 by the 32nd. If the study raises a red flag, we will review data and consider modification or termination of the trial for lack of safety.

7.2 Statistical Methods

The ORR and CR rate and its two-sided 95% exact confidence interval will be calculated using the Clopper-Pearson method. PFS and OS at year 1 and 2 will be estimated using the Kaplan-Meier method. The median PFS and 95% confidence interval will be calculated where possible. We will calculate ORR, CR, PFS, and OS for all the subjects as a group and also separately for each subtype (PMBL, DLBCL, GZL).

We will assess correlation of baseline CD30 expression level with clinical response by a two-sample *t* test comparing mean CD30 level among complete responders to the level among those who do not have complete responses. We will assess correlation of baseline CD30 level with survival outcomes (PFS, OS) by the Cox proportional hazards regression model, taking baseline CD30 level as a continuous predictor.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

For the correlative study with multiplexed gene expression profiling of primary tumor samples, the statistics are descriptive. The data will be analyzed by calculating a single linear predictor score for each biopsy sample. Based on the distributions of linear predictor scores in each cancer group, Bayes rule can be used to estimate the probability that a sample belongs to cancer group A (ie PMBL) vs cancer group B (DLBCL, non-PMBL). An arbitrary probability cutoff of $\geq 90\%$ will be used to classify a sample into a subgroup and correlation with outcome will be conducted.

7.3 Subject Population(s) for Analysis

All patients who are enrolled in the study and receive any clinical trial material will be included in the intent-to-treat analysis. All safety analyses will be performed on the intent-to-treat population. The efficacy analysis will include any patient who has received at least one dose of the investigational drug brentuximab vedotin and were evaluable for response. We will allow up to 4 additional patients to be enrolled in the Phase II part of the study to substitute for the missing data. All estimates of rates (e.g., response and toxicity) will be presented with corresponding confidence intervals.

7.4 Study Endpoint Definitions

7.4.1 Objective Response Rate

Objective response rate is defined as the proportion of patients with CR or PR according to the International Working Group Response Criteria for non-Hodgkin Lymphoma (Cheson et al. 2007, 579-586) as of the designated time point for the treatment period under consideration. Patients whose disease response cannot be assessed, including those patients who do not have CT scans performed, will be scored as non-responders for calculating the ORR.

7.4.2 Complete Remission Rate

Complete remission rate is defined as the proportion of patients with CR according to the International Working Group Response Criteria for non-Hodgkin Lymphoma (Cheson et al. 2007, 579-586) as of the designated time point for the treatment period under consideration.

7.4.3 Progression-Free Survival

Progression-free survival is defined as the time from start of study treatment (brentuximab vedotin with R-CHP chemotherapy) to first documentation of objective tumor progression or to death due to any cause, whichever comes first. Progression-free survival data will be censored on the day following the date of the last lymphoma assessment documenting absence of progressive disease for patients who do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment or stem cell transplant, or are removed from study prior to documentation of objective tumor progression. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at day one.

7.4.4 Overall Survival

Overall survival (OS) is defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond the day of first dose will have their survival time censored at day one.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm)

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of the first study treatment (Cycle 1/Day 1) to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). Adverse events will be graded according to the CTCAE v4.0. NOTE: Adverse events reported after March 29, 2018 should be graded according to the CTCAE v5.0. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately. Of note, disease progression is not considered an AE or SAE.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation
- unexpected, and
- serious or involve risks to subjects or others (see definitions, Section 8.1).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are NOT to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

For both serious and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. If the relationship to the study drug cannot be determined at the time of the initial SAE report, the event should be considered possibly related until additional information is available to fully evaluate the event.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.0. NOTE: Adverse events reported after March 29, 2018 should be graded using the CTCAE version 5.0.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

University of Pennsylvania Institutional Review Board:

Serious adverse events which in the opinion of the principal investigator are **both unexpected and** related to research procedures should be reported to the IRB within 10 working days of investigator notification. An event is considered “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, applicable package insert information, and/or the current IRB-approved informed consent document. An event is considered “related to the research procedures” if the event is deemed probably or definitely related.

Deaths occurring for patients on-study and within 30 days of study drug administration that are considered unforeseen and indicates participants or others are at increased risk of harm (i.e. unexpected and probably/definitely related), must be reported to the IRB within 24 hours of notification.

In addition, if other information becomes available that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency, this should be reported within 3 days. Examples of this include:

- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Any adverse event that represents a serious, unexpected problem that is rare in absence of drug exposure.
- Withdrawal from marketing for safety of a drug, device, or biologic used in a research protocol.
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Violation, meaning an accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk, or has potential to occur again.
- Breach of confidentiality.

The IRB will accept other reports when the investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold for an unanticipated event presenting risk to the participant.

Office of Regulatory Affairs, Institutional Review Board
3800 Spruce Street
Old Vet Quad Building
First Floor Room 151
Philadelphia, PA 19104
Phone: 215-573-2540
Fax: 215-573-9438

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Abramson Cancer Center Data Safety Monitoring Committee (DSMC):

Grade 3 or higher AEs, determined to be related to the study drug regardless of expectedness, or that affect subject safety, must be submitted to the Abramson Cancer Center's DSMC within 10 days of notification. Other events should be submitted if clinically significant or if a relationship to the study drug cannot be ruled out. AEs that are related to the subjects' disease and/or other co-morbidity, or routine therapy, are not reportable to the ACC DSMC. All unexpected deaths or deaths related to the study drug should be reported within 24 hours of notification. All other deaths should be reported within 30 days. All AEs occurring within 30 days of the last dose of the study drug must be record/reported appropriately.

AEs will be submitted to the DSMC through the Velos Clinical Trial Management System.

Data and Safety Monitoring Committee
3400 Spruce Street, 2017 Penn Tower
Philadelphia, PA 19104-4283
Website: https://pennctms.pmacs.upenn.edu/velos/jsp/ereslogin_new.jsp

Reportable Events:

A one-time accidental or unintentional deviation from the approved protocol, identified retrospectively, that in the opinion of the investigator or as defined by the protocol, placed one or more participants at increased risk, compromises the rights or welfare of subjects, and/or disrupts the study design, is considered a reportable event and must be reported to the Study Principal Investigator, Study Medical Monitor, IRB, and ACC DSMC within 10 working days of notification. Principal Investigator and Medical Monitor approval/ acknowledgement must be received first and included in with the IRB/DSMC submission.

Deviations to protect subjects from immediate harm/danger should be reported immediately following the event to the entities outlined above.

Exceptions:

An exception is defined as a one-time, unintentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. AND this action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects (i.e. requests to enroll and/or treat subjects outside of the current protocol criteria). Exceptions that meet this criteria will not be allowed unless reviewed and approved first by the Study Medical Monitor and the Study Principal Investigator/Sponsor-Investigator, and then subsequently by the ACC DSMC, and UPenn IRB prior to this subject being enrolled/treated. PI/Sponsor-Investigator and Medical Monitor approval must be received first and included in with the IRB/DSMC submission. All entities should be given sufficient time to evaluate this request.

Examples of Exceptions/Deviations that require submission include:

- Dose adjustments/stopping rules that were not completed per protocol
- Other dosing errors

Exceptions to eligibility may not be granted.

Events not deemed reportable as outlined above will require a PI assessment regarding study and/or safety impact. This assessment should be documented appropriately.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Seattle Genetics SAE Reporting:

All serious adverse events that occur during the onstudy period must be reported to the drug manufacturer within 24 hours of awareness of the event. Events occurring more than 30 days after discontinuation of the study product that are assessed by the Investigator to be related to the study product should also be reported.

A MedWatch 3500A form should be used to report all SAEs. This report must include an assessment of the causality of this event to the study product. The investigator will keep a copy of this SAE form and fax/email confirmation on file at the study site. Report serious adverse events by email or fax to:

Seattle Genetics Drug Safety:

Email: drug.safety@seagen.com

Fax: 425-527-4308

Phone: 866-333-6627

Follow-up information on this event should be reported when received.

AE Reporting Requirements - Participating Institutions:

The Participating Institution should report all on-site SAEs to their local IRB per their guidelines. In addition, all on-site SAEs occurring at the Participating Site must be reported to the University of Pennsylvania Sponsor-Investigator and Study Team within 24 hours of notification. This initial notification to the Sponsor-Investigator and Study Team can take place via email to meet the 24 hour deadline, but must be followed by submission of a formal report. SAEs should be reported using an FDA MedWatch Form 3500A and should include a full written summary, detailing relevant aspects of the adverse event in question. Once received, the University of Pennsylvania Study Team/PI will provide a copy of this SAE report to UPenn Medical Monitor, and report this event to the FDA (as applicable) and the UPenn IRB (as applicable).

All Grade 3 or higher AEs, determined to be related to the study drug regardless of expectedness, or that affect subject safety, must be submitted to the Abramson Cancer Center's DSMC through the Velos CTMS within 10 days of notification. Other events should be submitted if clinically significant or if a relationship to the study drug cannot be ruled out. AEs that are related to the subjects' disease and/or other co-morbidity, or routine therapy, are not reportable to the ACC DSMC. All unexpected deaths or deaths related to the study drug should be reported within 24 hours of notification. All other deaths should be reported within 30 days. All AEs occurring within 30 days of the last dose of the study drug must be record/reported appropriately.

U.S. Food and Drug Administration:

In accordance with 21 CFR 312.32, sponsor-investigators of studies conducted under an IND must notify the FDA of the following:

- Any adverse experience associated with the use of the drug that is both serious and unexpected; or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor-investigator's initial receipt of the information. Each written notification may be submitted on the FDA Form 3500A which should clearly identify its contents and the Study IND Number.

Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division that has responsibility for review of the IND (Division of Medical Imaging and Hematology Products). If FDA determines that additional data are needed, the agency may require further data to be submitted.

Telephone and facsimile transmission safety reports: The sponsor-investigator shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor-investigator's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division that has responsibility for review of the IND.

Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

The following describes the overall safety reporting requirements by timeline for reporting and associated type of event:

- **Within 7 calendar days**

- Any study event that is:

- associated with the use of the study drug
 - unexpected
 - fatal or life-threatening

- **Within 15 calendar days**

- Any study event that is:

- associated with the use of the study drug
 - unexpected
 - serious, but not fatal or life-threatening

-or-

- a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable)

- Any finding from tests in laboratory animals that:

- suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

8.3.1 Sponsor reporting: Notifying Participating Investigators

It is the responsibility of the study sponsor to notify all participating investigators, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

These reports will be issued to the participating investigators via email by the University of Pennsylvania study team upon receipt, for local review and processing.

8.4 Stopping Rules

See Section 7.1 for a safety monitoring plan. We will also stop enrollment if 2 or more patients are unable to complete 6 cycles of treatment with the combination therapy.

8.5 Medical Monitoring

The medical monitor for this study will be Dr. Naomi Haas from the University of Pennsylvania. Dr. Haas is an Associated Professor in the Department of Hematology-Oncology at University of Pennsylvania, with extensive oncology and research experience. Dr. Haas is not directly involved in the trial and is not collaborating with the Sponsor-Investigator on any other trials.

In the role, Dr. Haas will review all AEs including grading, toxicity assignments, all other safety data and activity data observed in the ongoing clinical trial. This will include a real-time review of safety data in the event of any unexpected and related SAE regardless of grade, and any on-study deaths. The Medical Monitor will also be consulted in the case of exception requests or the evaluation of deviations that may compromise subject safety or disrupt the design of the study. This information will be communicated to the Medical Monitor via email and filed in the Regulatory Binder/Subject Chart appropriately. As applicable, copies of this correspondence will be included in the corresponding IRB/ACC DSMC submission of these events.

The Medical Monitor will also be asked to review study data and comprehensive adverse event data at least bi-annually (every 6 months). This meeting will take place in person, and all study/safety information will be presented appropriately. This meeting will be clearly documented on a Medical Monitor Review Sheet, signed off on by the Medical Monitor. At any point during the course of the study, the Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

Velos electronic case report forms (eCRFs) are the primary data collection instrument for this study. All data requested on the CRF must be recorded according to the guidelines set forth in the Multi-Site Manual of Procedures. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. This monitoring will include a regular assessment of the number and type of serious adverse events.

It is the responsibility of the Sponsor-Investigator to oversee the safety and conduct of this study at all participating sites. Please refer to the Penn MultiSite Manual of Procedures for an overview of the Sponsor-Investigator's role, the expectations for Participating Sites, sponsor monitoring requirements, and guidelines for overseeing this research at participating institutions.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

This investigator-initiated protocol is considered high risk as per the ACC DSMC. As such, high risk protocols are audited approximately six months from their first subject accrual and approximately every six months thereafter for the duration of the study by the ACC Department of Compliance and Monitoring (DOCM). However, this schedule may be changed at the discretion of the DSMC. High or quick enrolling studies may be audited more frequently as necessary.

The investigator will be notified in advance of the selection of their protocol for review and cases are randomly selected. Three randomly selected subjects or 10% of the total accrual (up to 10 subjects), whichever is higher, are audited. A formal report is written to the PI within about 5 business days of the audit. The committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies.

Upon review of inspection findings, the Committee designates the audit outcome as Minor, Moderate, or Major deficiencies. The deficiency assigned by the Committee initiates specific follow-up actions.

If an audit is unacceptable due to major deficiencies, representatives from the Department of Monitoring and Compliance (DOCM) meet with the PI to discuss the findings of the audit and review necessary corrective actions mandated by the DSMC. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DSMC Administrative Director will meet to discuss necessary actions concerning study status.

An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response. At this time, if the DSMC Chair and the Administrative Director do not find the response satisfactory, the IRB will be alerted of the actions taken by the ACC. The DSMC Director will update the IRB of the corrective actions being taken and progress being made.

Team meetings may also be held throughout the course of this study in order to discuss the protocol, ongoing patients, toxicity data, and applicable recruitment issues.

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the Sponsor-Investigator before commencement of this study.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study will be supported by funds from Seattle Genetics.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the applicable University conflict of interest policies.

12.3 Subject Stipends or Payments

There are no plans to provide payments or stipends to subjects.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma. the Non-Hodgkin's Lymphoma Classification Project." 1997. *Blood* 89 (11): 3909-3918.

Campuzano-Zuluaga, German, Maureen Cioffi-Lavina, Izidore S. Lossos, and Jennifer R. Chapman-Fredricks. 2012. "CD30 Expression in Diffuse Large B-Cell Lymphoma and its Relation to Important Clinical and Biological Disease Features." *ASH Annual Meeting Abstracts* 120 (21): 1592.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Carson, Kenneth R., Andrew M. Evens, Elizabeth A. Richey, Thomas M. Habermann, Daniele Focosi, John F. Seymour, Jacob Laubach, et al. 2009. "Progressive Multifocal Leukoencephalopathy After Rituximab Therapy in HIV-Negative Patients: A Report of 57 Cases from the Research on Adverse Drug Events and Reports Project." *Blood* 113 (20): 4834-4840.

Cheson, B. D., S. J. Horning, B. Coiffier, M. A. Shipp, R. I. Fisher, J. M. Connors, T. A. Lister, et al. 1999. "Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. NCI Sponsored International Working Group." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 17 (4): 1244.

Cheson, B. D., B. Pfistner, M. E. Juweid, R. D. Gascoyne, L. Specht, S. J. Horning, B. Coiffier, et al. 2007. "Revised Response Criteria for Malignant Lymphoma." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 25 (5): 579-586.

Coiffier, B., E. Lepage, J. Briere, R. Herbrecht, H. Tilly, R. Bouabdallah, P. Morel, et al. 2002. "CHOP Chemotherapy Plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma." *The New England Journal of Medicine* 346 (4): 235-242.

Dunleavy, K., S. Pittaluga, L. S. Maeda, R. Advani, C. C. Chen, J. Hessler, S. M. Steinberg, et al. 2013. "Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma." *The New England Journal of Medicine* 368 (15): 1408-1416.

Eberle, F. C., J. Rodriguez-Canales, L. Wei, J. C. Hanson, J. K. Killian, H. W. Sun, L. G. Adams, et al. 2011. "Methylation Profiling of Mediastinal Gray Zone Lymphoma Reveals a Distinctive Signature with Elements Shared by Classical Hodgkin's Lymphoma and Primary Mediastinal Large B-Cell Lymphoma." *Haematologica* 96 (4): 558-566.

Fanale, Michelle A., Andrei R. Shustov, Andres Forero-Torres, Nancy L. Bartlett, Ranjana H. Advani, Barbara Pro, Robert W. Chen, et al. 2012. "Brentuximab Vedotin Administered Concurrently with Multi-Agent Chemotherapy as Frontline Treatment of ALCL and Other CD30-Positive Mature T-Cell and NK-Cell Lymphomas." *ASH Annual Meeting Abstracts* 120 (21): 60.

Francisco, J. A., C. G. Cervený, D. L. Meyer, B. J. Mixan, K. Klussman, D. F. Chace, S. X. Rejniak, et al. 2003. "cAC10-vcMMAE, an Anti-CD30-Monomethyl Auristatin E Conjugate with Potent and Selective Antitumor Activity." *Blood* 102 (4): 1458-1465.

Higgins, J. P. and R. A. Warnke. 1999. "CD30 Expression is Common in Mediastinal Large B-Cell Lymphoma." *American Journal of Clinical Pathology* 112 (2): 241-247.

Hu, S., Z. Y. Xu-Monette, A. Balasubramanyam, G. C. Manyam, C. Visco, A. Tzankov, W. M. Liu, et al. 2013. "CD30 Expression Defines a Novel Subgroup of Diffuse Large B-Cell Lymphoma with Favorable Prognosis and Distinct Gene Expression Signature: A Report from the International DLBCL Rituximab-CHOP Consortium Program Study." *Blood* 121 (14): 2715-2724.

Hutchings, Martin, Annika Loft, Mads Hansen, Lars Møller Pedersen, Thora Buhl, Jesper Jurlander, Simon Buus, et al. 2006. "FDG-PET After Two Cycles of Chemotherapy Predicts Treatment Failure and Progression-Free Survival in Hodgkin Lymphoma." *Blood* 107 (1): 52-59.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Jacobsen, Eric D., Ranjana H. Advani, Yasuhiro Oki, Jeff Sharman, Steven M. Horwitz, Andres Forero-Torres, Owen A. O'Connor, et al. 2012. "A Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed Or Refractory CD30-Positive Non-Hodgkin Lymphomas: Interim Results." *ASH Annual Meeting Abstracts* 120 (21): 2746.

Krathen, Michael, Uma Sundram, Sameer Bashey, Katherine Sutherland, Katrin Salva, Gary S. Wood, Ranjana H. Advani, et al. 2012. "Brentuximab Vedotin Demonstrates Significant Clinical Activity in Relapsed Or Refractory Mycosis Fungoides with Variable CD30 Expression." *ASH Annual Meeting Abstracts* 120 (21): 797.

Lenz, G., G. Wright, S. S. Dave, W. Xiao, J. Powell, H. Zhao, W. Xu, et al. 2008. "Stromal Gene Signatures in Large-B-Cell Lymphomas." *The New England Journal of Medicine* 359 (22): 2313-2323.

Moskowitz, C. H., H. Schoder, J. Teruya-Feldstein, C. Sima, A. Iasonos, C. S. Portlock, D. Straus, et al. 2010. "Risk-Adapted Dose-Dense Immunotherapy Determined by Interim FDG-PET in Advanced-Stage Diffuse Large B-Cell Lymphoma." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 28 (11): 1896-1903.

Pileri, S. A., P. L. Zinzani, G. Gaidano, B. Falini, P. Gaulard, E. Zucca, E. Sabattini, et al. 2003. "Pathobiology of Primary Mediastinal B-Cell Lymphoma." *Leukemia & Lymphoma* 44 Suppl 3: S21-6.

Pregno, Patrizia, Annalisa Chiappella, Marilena Bellò, Barbara Botto, Simone Ferrero, Silvia Franceschetti, Francesca Giunta, et al. 2012. "Interim 18-FDG-PET/CT Failed to Predict the Outcome in Diffuse Large B-Cell Lymphoma Patients Treated at the Diagnosis with Rituximab-CHOP." *Blood* 119 (9): 2066-2073.

Pro, B., R. Advani, P. Brice, N. L. Bartlett, J. D. Rosenblatt, T. Illidge, J. Matous, et al. 2012. "Brentuximab Vedotin (SGN-35) in Patients with Relapsed Or Refractory Systemic Anaplastic Large-Cell Lymphoma: Results of a Phase II Study." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 30 (18): 2190-2196.

Rieger, M., A. Osterborg, R. Pettengell, D. White, D. Gill, J. Walewski, E. Kuhnt, et al. 2011. "Primary Mediastinal B-Cell Lymphoma Treated with CHOP-Like Chemotherapy with Or without Rituximab: Results of the Mabthera International Trial Group Study." *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO* 22 (3): 664-670.

Rosenwald, A., G. Wright, K. Leroy, X. Yu, P. Gaulard, R. D. Gascoyne, W. C. Chan, et al. 2003. "Molecular Diagnosis of Primary Mediastinal B Cell Lymphoma Identifies a Clinically Favorable Subgroup of Diffuse Large B Cell Lymphoma Related to Hodgkin Lymphoma." *The Journal of Experimental Medicine* 198 (6): 851-862.

Savage, Kerry J., Paul R. Yenson, Tamara Shenkier, Richard Klasa, Diego Villa, Ozge Goktepe, Christian Steidl, et al. 2012. "The Outcome of Primary Mediastinal Large B-Cell Lymphoma (PMBCL) in the R-CHOP Treatment Era." *ASH Annual Meeting Abstracts* 120 (21): 303.

Schneider, C. and G. Hubinger. 2002. "Pleiotropic Signal Transduction Mediated by Human CD30: A Member of the Tumor Necrosis Factor Receptor (TNFR) Family." *Leukemia & Lymphoma* 43 (7): 1355-1366.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

Shimoyama, Y., N. Asano, M. Kojima, S. Morishima, K. Yamamoto, T. Oyama, T. Kinoshita, and S. Nakamura. 2009. "Age-Related EBV-Associated B-Cell Lymphoproliferative Disorders: Diagnostic Approach to a Newly Recognized Clinicopathological Entity." *Pathology International* 59 (12): 835-843.

Slack, Graham W., Christian Steidl, Laurie H. Sehn, and Randy D. Gascoyne. 2012. "CD30 Expression in Diffuse Large B-Cell Lymphoma." *ASH Annual Meeting Abstracts* 120 (21): 1558.

Sutherland, M. S., R. J. Sanderson, K. A. Gordon, J. Andreyka, C. G. Cervený, C. Yu, T. S. Lewis, et al. 2006. "Lysosomal Trafficking and Cysteine Protease Metabolism Confer Target-Specific Cytotoxicity by Peptide-Linked Anti-CD30-Auristatin Conjugates." *The Journal of Biological Chemistry* 281 (15): 10540-10547.

Swerdlow, S. H., ed. 2008. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition*.

Tai, W. M., D. Quah, S. P. Yap, S. H. Tan, T. Tang, K. W. Tay, Y. X. Koo, M. Tao, R. Quek, and S. T. Lim. 2011. "Primary Mediastinal Large B-Cell Lymphoma: Optimal Therapy and Prognostic Factors in 41 Consecutive Asian Patients." *Leukemia & Lymphoma* 52 (4): 604-612.

Todeschini, G., S. Secchi, E. Morra, U. Vitolo, E. Orlandi, F. Pasini, E. Gallo, et al. 2004. "Primary Mediastinal Large B-Cell Lymphoma (PMLBCL): Long-Term Results from a Retrospective Multicentre Italian Experience in 138 Patients Treated with CHOP Or MACOP-B/VACOP-B." *British Journal of Cancer* 90 (2): 372-376.

Younes, A., N. L. Bartlett, J. P. Leonard, D. A. Kennedy, C. M. Lynch, E. L. Sievers, and A. Forero-Torres. 2010. "Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas." *The New England Journal of Medicine* 363 (19): 1812-1821.

Younes, A., A. K. Gopal, S. E. Smith, S. M. Ansell, J. D. Rosenblatt, K. J. Savage, R. Ramchandren, et al. 2012. "Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients with Relapsed Or Refractory Hodgkin's Lymphoma." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 30 (18): 2183-2189.

Younes, Anas, Joseph M. Connors, Steven I. Park, Naomi N. H. Hunder, and Stephen M. Ansell. 2011. "Frontline Therapy with Brentuximab Vedotin Combined with ABVD Or AVD in Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma." *ASH Annual Meeting Abstracts* 118 (21): 955.

Zelenetz, A. D., J. S. Abramson, R. H. Advani, C. B. Andreadis, J. C. Byrd, M. S. Czuczman, L. Fayad, et al. 2010. "NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas." *Journal of the National Comprehensive Cancer Network : JNCCN* 8 (3): 288-334.

Zinzani, P. L., V. Stefoni, E. Finolezzi, E. Brusamolino, M. G. Cabras, A. Chiappella, F. Salvi, A. Rossi, A. Broccoli, and M. Martelli. 2009. "Rituximab Combined with MACOP-B Or VACOP-B and Radiation Therapy in Primary Mediastinal Large B-Cell Lymphoma: A Retrospective Study." *Clinical Lymphoma & Myeloma* 9 (5): 381-385.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor

15 Appendix A

Schedule of Assessments¹⁴

	Screening ¹	C1D1 ²	C1D2 ³	C1D8 ³	C2D1 ³	C3D1 ³	C4D1 ³	C5D1 ³	C6D1 ³	EOT visit 30 days post-therapy completion ⁴	Q3 month FU visit year 1 ¹³	Q3-6 month FU visits year 2 ¹³
Sign Informed Consent	X											
Physical Exam	X	X			X	X	X	X	X	X	X	X
Vital Signs ⁵	X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X	X			X	X	X	X	X	X	X	X
Pathology Review	X											
Medical History	X											
Concomitant Medications	X	X	X		X	X	X	X	X	X		
Adverse Events		X	X	X	X	X	X	X	X	X		
Echocardiogram/MUGA	X											
Hematology Panel ⁶	X	X		X	X	X	X	X	X	X	X	X
Chemistry Panel ⁷	X	X		X	X	X	X	X	X	X	X	X
LDH/Uric Acid	X	X			X	X	X	X	X	X	X	X
Serum Pregnancy Test ⁸	X									X		
HIV/Hepatitis B sAg, cAb, sAb	X											
Bone Marrow Biopsy/Aspirate ⁹	X									X		
Radiographic Disease Evaluation ¹⁰	X					X		X		X	X	X
IV Brentuximab Vedotin			X		X	X	X	X	X			
IV Rituximab ¹¹		X	X		X	X	X	X	X			
IV Cyclophosphamide			X		X	X	X	X	X			
IV Doxorubicin			X		X	X	X	X	X			
IV or PO Prednisone ¹²		X	X		X	X	X	X	X			

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor
page 43

1. All screening procedures should be performed within 28 days of C1D1, with the exception of baseline imaging, which should be obtained within 2 months (60 days) of C1D1.
2. Assessments performed within 7 days of starting therapy do not need to be repeated on C1D1.
3. +/- 3 days
4. +/- 7 days
5. Vital signs to include blood pressure, heart rate, oral temperature, and body weight. Vital signs during infusions should be performed per institutional standards of care.
6. Hematology panels should include a complete blood count, platelet count and differential.
7. Chemistry panel to include sodium, potassium, chloride, calcium, glucose, BUN, serum creatinine, total protein, albumin, total bilirubin, AST and ALT.
8. Negative serum pregnancy test within 7 days of starting therapy is required for women of childbearing potential.
9. Bone marrow biopsy at screening is elective and at discretion of the treating physician. EOT bone marrow should be done in those patients who had positive screening bone marrow biopsy in order to document complete response.
10. PET/CT and/or dedicated CT with contrast of chest, abdomen, pelvis (+/- neck) are the recommended modality of radiographic imaging during staging and final response assessment after cycle 6. (unless contrast is contraindicated). Imaging studies should be performed within 60 days of C1D1 of treatment and three to five weeks after the completion of Cycle 6 (prior to radiation therapy). Interim imaging (using CT scans) will be done after cycle 2 and 4. Surveillance imaging using PET/CT or dedicated CT C/A/P at least every 8 months (+/- 30 days) thereafter for the first 2 years of follow-up. Imaging can be performed more frequently as clinically indicated.
11. The first dose of rituximab will be administered as a split dose: 100 mg/ m² will be administered on Cycle 1, Day 1, and 275 mg/ m² will be administered on Cycle 1, Day 2. The full dose of rituximab (375 mg/m²) will be administered on Day 1 of subsequent cycles.
12. Prednisone should be administered on Days 1-5 of each cycle, at a dose of 100 mg po, or the IV equivalent steroid dose.
13. Evaluations to be performed +/- 30 days
14. Follow-up information about the initiation of alternative therapy and survival status may be obtained from the medical record or via telephone or email correspondence for up to 5 years after the end of treatment.

CONFIDENTIAL

This material is the property of the University of Pennsylvania.
Do not disclose or use except as authorized in writing by the study sponsor
page 44