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Version: Amendment 5; 10-August-2015

Protocol Title: A phase 2 study of brentuximab vedotin in combination with standard of care treatment (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [RCHOP]) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) as front-line therapy in patients with diffuse large B-cell lymphoma (DLBCL)

Brief Title: A phase 2 study of brentuximab vedotin given with RCHOP or RCHP for front-line treatment of patients with diffuse large B-cell lymphoma

Investigational Drug: Brentuximab vedotin

Indication: Diffuse large B-cell lymphoma

Phase: 2

IND Number: 71634

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PROTOCOL SYNOPSIS

Protocol Number SGN35-017	Product Name Brentuximab vedotin
Version Amendment 5; 10-August-2015	Sponsor Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Phase 2	

Protocol Title

A phase 2 study of brentuximab vedotin in combination with standard of care treatment (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [RCHOP]) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) as front-line therapy in patients with diffuse large B-cell lymphoma (DLBCL)

Study Objectives

Primary:

- To assess the antitumor activity of brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone, as measured by the complete remission (CR) rate at the end of treatment per investigator assessment in treatment-naïve patients with high-intermediate or high risk systemic DLBCL
- To assess the safety profile of brentuximab vedotin administered at dose levels of 1.2 mg/kg versus 1.8 mg/kg in combination with RCHOP or brentuximab vedotin 1.8 mg/kg in combination with RCHP in treatment-naïve patients with high-intermediate or high risk systemic DLBCL

Secondary:

- To assess the antitumor activity of brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone, as measured by the objective response rate (ORR) at the end of treatment per investigator assessment
- To assess the progression-free survival (PFS) associated with brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone
- To assess survival associated with brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone

Additional:

- To assess CD30 expression on tumor specimens
- To assess the pharmacokinetics (PK) of brentuximab vedotin administered in combination with RCHOP or RCHP

Study Population

The population to be studied includes treatment-naïve patients with systemic de novo or transformed DLBCL or follicular non-Hodgkin lymphoma (NHL) grade 3b. Patients must have high-intermediate or high risk disease based on standard IPI (score ≥ 3 for patients > 60 years of age) or age-adjusted IPI (score 2 or 3 for patients ≤ 60 years of age), and stage IAX (bulk defined as single lymph node mass > 10 cm in diameter), IB–IV disease. Eligible patients must be age ≥ 18 years, have fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET), measurable disease of at least 1.5 cm by computed tomography (CT), an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , and adequate organ function. In addition, patients enrolled in Parts 2 and 3 must have CD30-positive disease; CD30 expression will be determined by visual assessment using immunohistochemistry (IHC).

Patients are not eligible for enrollment if they have a previous history of treated indolent lymphoma; however, newly diagnosed patients with DLBCL who are found to have small cell infiltration of the bone marrow or other diagnostic material (representing a discordant lymphoma) are eligible. Patients are also excluded if they have a history of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years, a history of progressive multifocal leukoencephalopathy (PML), cerebral/meningeal disease related to the underlying malignancy, baseline peripheral neuropathy \geq Grade 2 (per the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 4.03), or the demyelinating form of Charcot-Marie-Tooth syndrome. Patients must not have left ventricular ejection fraction less than 45% or symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), myocardial infarction within the past 6 months, or previous treatment with complete cumulative doses of doxorubicin or other anthracyclines. In addition, patients must not have any active Grade 3 or higher (per the NCI CTCAE, Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study treatment, known urinary outflow obstruction, or known human immunodeficiency virus (HIV) infection, be positive for hepatitis B surface antigen or anti-hepatitis B core antibody, or have known or suspected active hepatitis C infection. Patients must not be receiving current therapy with other systemic anti-neoplastic or investigational agents, have a known hypersensitivity to any excipient contained in any of the drug formulations of study treatments, or be a female who is breastfeeding.

Number of Planned Patients

There are 3 parts to this study. Approximately 50 patients (no less than 25 patients in each cohort) will be randomized in Part 1 of this study. Up to 25 patients will be enrolled (non-randomized) in Part 2 of this study. Approximately 50 patients (no less than approximately 25 patients in each arm) will be randomized in Part 3 of this study.

Study Design

This study has three parts. Part 1 of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin 1.2 and 1.8 mg/kg when administered in combination with standard RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); this regimen is abbreviated as A+RCHOP. Part 2 of the study is a phase 2, non-randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin 1.8 mg/kg when administered in combination with RCHP chemotherapy (rituximab, cyclophosphamide, doxorubicin, and prednisone); this regimen is abbreviated as A+RCHP. Part 3 of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin 1.8 mg/kg when administered in combination with RCHP chemotherapy compared to RCHOP chemotherapy alone.

In Part 1, a total of approximately 50 patients will be randomized 1:1 into 2 dosing cohorts of 1.2 or 1.8 mg/kg brentuximab vedotin administered in combination with RCHOP. Randomization in this part of the study is for the purpose of evaluating the safety of 1.2 and 1.8 mg/kg brentuximab vedotin in combination with RCHOP. Randomization will be stratified by high-intermediate or high risk disease. The safety of the combination of brentuximab vedotin and RCHOP will be assessed by a Safety Monitoring Committee (SMC).

In Part 2, up to 25 patients will be enrolled into a dosing cohort with 1.8 mg/kg brentuximab vedotin administered in combination with RCHP. The safety of the combination of brentuximab vedotin and RCHP will also be assessed by the SMC.

In Part 3, a total of approximately 50 patients will be randomized 1:1 into either 1.8 mg/kg brentuximab vedotin administered in combination with RCHP or RCHOP alone. Randomization in this part of the study is for the purpose of evaluating the safety of 1.8 mg/kg brentuximab vedotin in combination with RCHP versus standard RCHOP chemotherapy. Randomization will be stratified by high-intermediate or high risk disease. The safety of the combination of brentuximab vedotin and RCHP will also be assessed by the SMC.

Each site may only enroll patients into one part of the study at a time. For example, if Part 2 and Part 3 have been approved by the site's IRB and are open at a site, enrollment in Part 2 will close prior to enrolling in Part .

Test Product, Dose, and Mode of Administration

In Part 1, brentuximab vedotin 1.2 or 1.8 mg/kg will be administered every 3 weeks via outpatient intravenous (IV) infusion combined with rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (dose capped at 2 mg total) administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle.

In Part 2, brentuximab vedotin 1.8 mg/kg will be administered every 3 weeks via outpatient IV infusion combined with rituximab 375 mg/m², cyclophosphamide 750 mg/m², and doxorubicin 50 mg/m² administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle.

In Part 3, patients will be randomized to receive either:

- Brentuximab vedotin 1.8 mg/kg administered every 3 weeks combined with rituximab 375 mg/m², cyclophosphamide 750 mg/m², and doxorubicin 50 mg/m² administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle or
- Rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (dose capped at 2 mg total) administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle.

Duration of Treatment

Study treatment consists of a maximum of 6 cycles (approximately 18 weeks).

Efficacy Assessments

Disease response will be assessed by the investigator, based on the Revised Response Criteria for Malignant Lymphoma ([Cheson 2007](#)). Radiographic assessments, including CT scans of chest, neck, abdomen, and pelvis, will be performed at baseline, 5 weeks post last dose of study treatment, every 4 months after the last scan for the first 2 years, and every 6 months thereafter until progression, death, or study closure, whichever comes first.

Pharmacokinetic Assessments

Serum or plasma concentrations of brentuximab vedotin antibody-drug conjugate (ADC) and related analytes will be measured.

Biomarker Assessments

Biomarker assessments include the measurement of soluble CD30 (sCD30) pre-dose prior to each cycle, cell of origin (COO) and molecular characterization of tumor biopsies, and evaluation of minimal residual disease (MRD).

Safety Assessments

Safety assessments will include the surveillance and recording of adverse events (AEs), physical examination findings, and laboratory tests.

Statistical Methods

The CR rate and ORR at the end of treatment will be summarized and exact 95% confidence intervals (CI) will be calculated. PFS and overall survival (OS) will be estimated using Kaplan-Meier methodology. Descriptive summaries of patient disposition, demographics, disease characteristics, safety, and exposure to study drug will be provided. Serum or plasma levels of brentuximab vedotin and related analytes will be summarized with descriptive statistics at each PK sampling time point.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

aaIPI	age-adjusted International Prognostic Index
A+RCHOP	brentuximab vedotin (ADCETRIS [®]), rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine
ABC	activated B-cell
ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AVD	doxorubicin, vinblastine, and dacarbazine
β-hCG	beta human chorionic gonadotrophin
BM	bone marrow
BUN	blood urea nitrogen
CBC	complete blood count
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHP	cyclophosphamide, doxorubicin, and prednisone
CI	confidence interval
C _{max}	maximum concentration
COO	cell of origin
CR	complete remission
CRF	case report form
CT	computed tomography
C _{trough}	trough concentration
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCB	germinal center B-cell
GCP	good clinical practice
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IND	Investigational New Drug
INN	International Nonproprietary Name
IPI	International Prognostic Index
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous

JCV	John Cunningham virus
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
NOS	not otherwise specified
ORR	objective response rate
OS	overall survival
PCP	Pneumocystis jiroveci pneumonia
PCR	polymerase chain reaction
PD	pharmacodynamics
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PR	partial remission
RBC	red blood cell
RCHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCHP	rituximab, cyclophosphamide, doxorubicin, and prednisone
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
sCD30	soluble CD30
SCT	stem cell transplant
SMC	safety monitoring committee
ULN	upper limit of normal
USAN	United States adopted name
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WBC	white blood cell
WHO	World Health Organization

1 INTRODUCTION

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30; 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell. Mechanisms of action in addition to the CD30-targeted hypothesis described above are possible.

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the Investigator's Brochure.

This study has 3 parts. Part 1 of the study is a randomized, open-label, multicenter, phase 2 clinical trial designed to evaluate the efficacy and safety of including brentuximab vedotin in the treatment of patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL). The standard of care in this patient population consists of 6 cycles of RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) delivered in 21-day cycles. Patients will be randomized in a 1:1 manner to receive 6 cycles of RCHOP with brentuximab vedotin 1.2 mg/kg or brentuximab vedotin 1.8 mg/kg. Brentuximab vedotin administered in combination with RCHOP is abbreviated as A+RCHOP.

Part 2 of the study is a non-randomized, open-label, multicenter, phase 2 clinical trial designed to evaluate the efficacy and safety of including brentuximab vedotin in the treatment of patients with newly diagnosed, CD30-positive DLBCL. Patients will receive 6 cycles of RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) with brentuximab vedotin 1.8 mg/kg delivered in 21-day cycles. Brentuximab vedotin administered in combination with RCHP is abbreviated as A+RCHP.

Part 3 of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin 1.8 mg/kg when administered in combination with RCHP chemotherapy compared to RCHOP alone. Patients will be randomized in a 1:1 manner to receive 6 cycles of with brentuximab vedotin 1.8 mg/kg or RCHOP alone delivered in 21-day cycles.

1.1 Diffuse Large B-cell Lymphoma

DLBCL is a subset of non-Hodgkin lymphomas (NHL) that comprises approximately 30% of all newly diagnosed cases of NHL in the United States, representing the most common lymphoid neoplasm in adults ([Swerdlow 2008](#)). According to the 2008 World Health Organization (WHO) classification schema, DLBCL not otherwise specified (NOS) is a heterogeneous grouping of lymphomas comprising neoplasms of large B-lymphoid cells that do not belong to other specific subtypes or disease entities ([Swerdlow 2008](#)). DLBCL NOS

cases can be further subclassified based on morphological, molecular, and immunophenotypical features.

Outcomes for patients with DLBCL have improved over the past decade, with the addition of rituximab to standard anthracycline-based multi-agent chemotherapy. The addition of rituximab to CHOP or CHOP-like multi-agent chemotherapy regimens improved the overall survival (OS) of patients by 10–16% compared to multi-agent chemotherapy alone (Coiffier 2010; Pfreundschuh 2010). Long-term outcomes from the LNH-98.5 trial conducted in older patients have recently been reported, with a 10-year progression-free survival (PFS) and OS rate of 36.5% and 43.5% in the RCHOP arm vs. 20.1% and 27.6% in the CHOP arm, respectively (Coiffier 2010). A total of 204 of 399 patients in the study experienced disease progression and 87% of the progression events occurred during the first 3 years of follow up.

In addition, long-term outcomes from the Mabthera International Trial (MInT) in younger patients have recently been reported, with 6-year PFS and OS rates of 79.9% and 89.8% when rituximab was combined with multi-agent chemotherapy, compared with 63.8% and 80%, respectively, with multi-agent chemotherapy alone (Pfreundschuh 2010). Amidst these excellent results, less favorable patient subgroups were identified with inferior outcomes, namely those patients with an age-adjusted International Prognostic Index (IPI) score of 1 or higher and/or bulky disease.

Taken together, these results highlight the long-term benefit of combining rituximab with multi-agent chemotherapy, while underscoring the need for new agents in subgroups of patients with inferior outcomes. Patients with high-intermediate and high risk disease, as identified by an IPI score of 3 or higher (for patients >60 years of age) or an age-adjusted IPI (aaIPI) of 2 or 3 (for patients who are ≤ 60 years of age) and those with bulky disease, appear to be underserved by the current standard of care and new agents that can be combined with RCHOP are needed.

1.2 Front-line Treatment of Diffuse Large B-cell Lymphoma

The standard of care for newly diagnosed, treatment-naive patients with DLBCL consists of 6 cycles of RCHOP delivered in 21-day cycles (NCCN 2013). In large randomized trials, the benefit of RCHOP has been demonstrated by a 3-year PFS rate of approximately 70% and a 3-year OS rate of approximately 75% (Pfreundschuh 2008; Cunningham 2011). Complete remission (CR) rates of 75%–78% have been reported in analyses that included both high and low risk patients (Coiffier 2002; Pfreundschuh 2008).

Despite the good outcomes achieved with RCHOP in newly diagnosed patients with DLBCL, high risk patient populations still remain. The IPI identifies patients with a score of 3–5 as having inferior outcomes compared to those with a score of 0–2. Higher risk patients with an IPI score of 3–5 have a 3-year PFS rate of approximately 55%. Patients with an IPI score of 3 or higher comprise approximately 40% of the frontline DLBCL population (25% IPI 3, 15% IPI 4–5) (Pfreundschuh 2008). Younger patients (≤ 60 years of age) with aaIPI scores of 2–3 have similarly inferior outcomes as the traditional higher risk patients with IPI scores 3–5 (Shipp 1993; Ziepert 2010).

1.3 Clinical Experience with Brentuximab Vedotin

The clinical safety data observed in the phase 1 dose-escalation study (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 was selected for pivotal phase 2 studies. In this phase 1 study, the most frequent adverse events (AEs) were nervous system (peripheral neuropathy), constitutional (fatigue and pyrexia), gastrointestinal (diarrhea, nausea), and hematologic (neutropenia) ([Younes 2010](#)).

The clinical safety and activity of brentuximab vedotin administered sequentially and concurrently with multi-agent chemotherapy were evaluated in a phase 1 study in patients with newly diagnosed CD30-positive mature T- and natural killer (NK)-cell neoplasms, including systemic anaplastic large cell lymphoma (sALCL; Study SGN35-011). This phase 1 study was implemented to determine the safety and activity of sequential and combination frontline treatment approaches of brentuximab vedotin with CHOP or CHP chemotherapy. At an interim analysis of 26 patients in this study ([Fanale 2012](#)), the MTD of brentuximab vedotin in combination with CHP was not exceeded at 1.8 mg/kg, based on 1 dose-limiting toxicity (DLT) (Grade 3 rash) among 6 patients. Treatment-emergent AEs occurring in >30% of patients included nausea, fatigue, diarrhea, peripheral sensory neuropathy, and alopecia. Adverse events with a severity of Grade 3 or higher occurring in >5% of patients included febrile neutropenia, nausea, neutropenia, and pulmonary embolism. The dose of brentuximab vedotin was reduced to 1.2 mg/kg in 4 of 26 patients (15%). At the time of 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 26 patients achieved an objective response, with 23 patients (88%) achieving a CR. All 7 non-sALCL patients achieved a CR with combination therapy. This experience demonstrates the combinability of brentuximab vedotin with CHP chemotherapy and the associated high level of clinical activity.

Brentuximab vedotin has shown activity as a monotherapy treatment in patients with relapsed or refractory DLBCL. In an ongoing Phase 2 study (Study SGN35-012), an objective response rate (ORR) of 44% (11/25) was observed in patients with DLBCL, with 20% of patients achieving a CR. In this study, CD30 expression by immunohistochemistry (IHC) per local pathology assessment was required for enrollment; however, antitumor activity, including CRs, was observed in patients who had no evidence of or very low levels of CD30 expression by central pathology review ([Jacobsen 2012](#)).

1.4 Rationale for Brentuximab Vedotin in Combination with RCHOP

Given the activity observed with brentuximab vedotin in the relapsed DLBCL setting, including activity in patients with low or absent CD30 expression, there is rationale to support the hypothesis that brentuximab vedotin may benefit patients with newly diagnosed DLBCL, irrespective of CD30 expression as assessed by IHC. DLBCL patients with adverse risk factors (IPI score of 3 or higher for patients >60 years of age or an aaIPI score of 2 or 3 for patients who are \leq 60 years of age), have poor outcomes with RCHOP therapy and new agents are needed. It is hypothesized that a treatment approach combining brentuximab

vedotin with RCHOP may yield an improved CR rate, with the potential to prolong PFS and OS.

The current study aims to evaluate the clinical activity of this ADC when combined with RCHOP in newly diagnosed high-risk DLBCL patients and to identify the optimal dose of brentuximab vedotin to safely administer in combination with RCHOP. Peripheral neuropathy (PN) is the most clinically meaningful AE associated with both brentuximab vedotin and vincristine, a microtubule inhibitor that is part of the RCHOP regimen (ADCETRIS® Prescribing Information, Seattle Genetics, Inc., January 2012; Vincristine [Marqibo®] Prescribing Information, Pfizer, October 2012; and ([Coiffier 2002](#); [Pfreundschuh 2008](#)).

Brentuximab vedotin has previously demonstrated combinability with CHP multi-agent chemotherapy in the Phase 1 study SGN35-011 ([Fanale 2012](#)). The rate of PN during the first 6 cycles of combination chemotherapy was 50%; the majority of events were Grade 1 and sensory in nature (Seattle Genetics, data on file). The rate of PN during the first 6 cycles of brentuximab vedotin when given as monotherapy was 39% (62/160 patients) in a combined analysis of patients with relapsed or refractory HL and sALCL. Again, the majority of events were Grade 1 or 2 and sensory in nature; Grade 3 events occurred in 2% of patients (3/160) (Seattle Genetics, data on file).

The expected incidence of PN with vincristine, delivered as part of RCHOP, is approximately 50%; similar to brentuximab vedotin, the majority of neuropathy events are sensory in nature and low grade (Grade 1 or 2). Grade 3 peripheral sensory neuropathy is observed in approximately 10% of patients; Grade 3 peripheral motor neuropathy events have been infrequently reported in the literature and are typically rare in clinical practice ([Coiffier 2002](#); [Pfreundschuh 2008](#)).

The co-primary objective of this study is to assess the safety and tolerability of combining 2 different doses of brentuximab vedotin with RCHOP. Patients will be randomized to facilitate a comparison of the safety, including peripheral neuropathy, between these 2 dose levels. This study of brentuximab vedotin in combination with RCHOP chemotherapy will provide a better understanding of the efficacy, safety, and tolerability in patients with newly diagnosed DLBCL, who are unselected for CD30 expression.

1.5 Rationale for Brentuximab Vedotin in Combination with RCHP in CD30-Positive DLBCL Patients

After 10 patients in each cohort in Part 1 completed treatment (N=20), a Safety Monitoring Committee (SMC) assessed the safety of the combination of brentuximab vedotin and RCHOP (see Section [9.3.8](#)). In the 1.8 mg/kg brentuximab vedotin cohort, 30% of patients (3/10) had Grade 3 neuropathy; thus, per the stopping rules, no further patients were treated at that dose level and enrollment continued in the 1.2 mg/kg brentuximab vedotin cohort ([Yasenchak 2014](#)).

Vincristine is an anti-tubulin vinca alkaloid and a component of multi-agent RCHOP chemotherapy. Neurotoxicity is the dose-limiting toxicity of vincristine and appears to be cumulative. Neurologic manifestations that have been associated with vincristine include paresthesia, tingling of the hands and feet, numbness, sensory loss, neuropathic pain, pharyngeal and parotid gland pain, loss of deep tendon reflexes, and difficulty in walking (gait disturbances), including slapping gait. Infrequently, hoarseness of voice, ocular palsies, atony of the urinary bladder, and autonomic neuropathy presenting as postural hypotension have occurred (Oncovin®) ([Tangun 1977](#); [Legha 1986](#); [Tobias 1991](#)). As a result of toxic neuropathy, vincristine is often dose-reduced or eliminated after several cycles of RCHOP. The rationale to administer brentuximab vedotin as a substitution in place of vincristine in RCHOP as front-line multi-agent chemotherapy is due to the potential concern for additive neurotoxicity in combination with brentuximab vedotin.

In a previous study (SGN35-011), brentuximab vedotin and CHP exhibited manageable toxicity with substantial and durable antitumor activity observed in both sALCL and non-ALCL patients (ORR 100%, CR rate 88%) with CD30-positive disease ([Fanale 2014](#)). The estimated 2-year PFS and OS rates were 54% and 80%, respectively. Therefore, it is reasonable to expect the safety profile would be acceptable and manageable.

This amendment also restricts the patient population to CD30-positive DLBCL patients. Preliminary data from the current study suggest that the CR rate in CD30-positive patients was higher (>90%, 10/11) than in CD30-negative patients ([Yasenchak 2014](#)). Interim results from another study (SGN35-012) appeared to show higher response in DLBCL patients who are confirmed CD30-positive ([Bartlett 2014](#)). In addition, brentuximab vedotin is recommended as treatment for CD30-positive relapsed/refractory DLBCL patients ([NCCN 2015](#)). Based on the known brentuximab vedotin mechanism of action and recent recommendations from the NCCN guidelines, it is reasonable to assume CD30-positive patients will benefit more from treatment than CD30-negative patients.

2 OBJECTIVES

2.1 Primary Objectives

- To assess the antitumor activity of brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone, as measured by the CR rate at the end of treatment per investigator assessment in treatment-naïve patients with high-intermediate or high risk systemic DLBCL
- To assess the safety profile of brentuximab vedotin administered at dose levels of 1.2 mg/kg versus 1.8 mg/kg in combination with RCHOP or brentuximab vedotin 1.8 mg/kg in combination with RCHP in treatment-naïve patients with high-intermediate or high risk systemic DLBCL

2.2 Secondary Objectives

- To assess the antitumor activity of brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone, as

measured by the objective response rate (ORR) at the end of treatment per investigator assessment

- To assess the progression-free survival (PFS) associated with brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone
- To assess survival associated with brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone

2.3 Additional Objectives

- To assess CD30 expression on tumor specimens
- To assess the pharmacokinetics (PK) of brentuximab vedotin administered in combination with RCHOP or RCHP

2.4 Endpoints

2.4.1 Primary Endpoints

- Complete remission (CR) rate per investigator assessment following the completion of study treatment
- Type, incidence, severity, seriousness, and relatedness of adverse events and laboratory abnormalities

2.4.2 Secondary Endpoints

- Objective response rate (ORR) per investigator
- Progression-free survival (PFS) per investigator
- Overall Survival (OS)

2.4.3 Additional Endpoints

- CD30 expression on tumor specimens
- Estimates of selected PK parameters

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This study has 3 parts. Part 1 of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin when administered in combination with standard RCHOP chemotherapy (A+RCHOP) in newly diagnosed DLBCL patients with high-intermediate or high risk disease (IPI score of 3 or higher for patients ≥ 60 years of age or aaIPI score of 2 or 3 for patients ≤ 60 years of age).

Part 1 of this study will evaluate brentuximab vedotin 1.2 or 1.8 mg/kg administered intravenously (IV) every 21 days in combination with standard RCHOP chemotherapy (rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² [dose capped at 2 mg total] administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle) for 6 cycles. A total of approximately 50 patients will be randomized 1:1 into 2 dosing cohorts of 1.2 or 1.8 mg/kg brentuximab vedotin administered in combination with RCHOP. The safety of the combination of brentuximab vedotin and RCHOP will be assessed by a Safety Monitoring Committee (SMC) as detailed in Section 9.3.8. The SMC will review accumulating safety data after 10 patients in each cohort (N=20) have completed treatment and after all patients in both dose cohorts have completed treatment (N=50). If Grade 3 neuropathy (sensory or motor) is observed in >20% of patients in either dosing cohort, that dose level will have exceeded the stopping criteria. If the 1.8 mg/kg brentuximab vedotin cohort exceeds the stopping criteria, but acceptable safety is observed at 1.2 mg/kg during the first SMC review, patients receiving treatment at 1.8 mg/kg will be dose reduced to 1.2 mg/kg, randomization will cease, and all remaining patients will be enrolled and treated at 1.2 mg/kg brentuximab vedotin. If the SMC determines that the risks outweigh the benefits of study treatment at both dose levels, no further patients will be enrolled.

Part 2 of the study is designed as an open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin when administered in combination with RCHP chemotherapy (A+RCHP) in CD30-positive, newly diagnosed DLBCL patients with high-intermediate or high risk disease (IPI score of 3 or higher for patients >60 years of age or aaIPI score of 2 or 3 for patients ≤60 years of age).

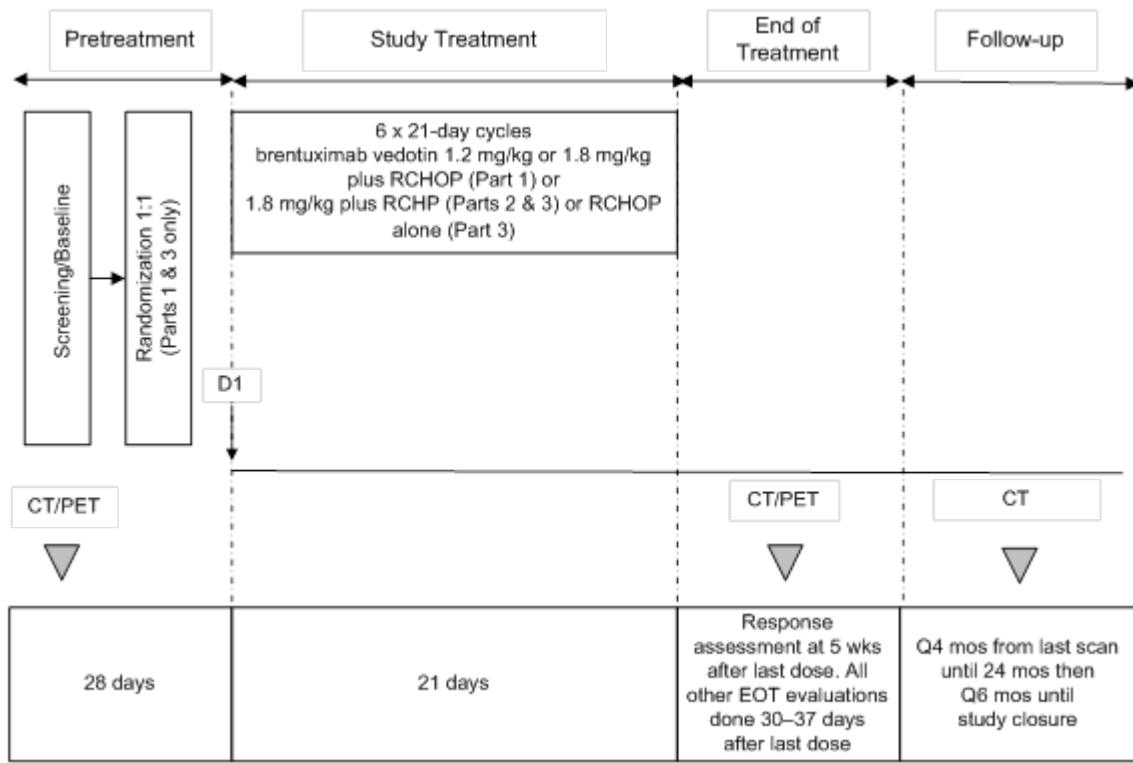
Part 2 of this study will evaluate brentuximab vedotin 1.8 mg/kg administered IV every 21 days in combination with RCHP chemotherapy (rituximab 375 mg/m², cyclophosphamide 750 mg/m², and doxorubicin 50 mg/m² administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle) for 6 cycles. A total of approximately 25 patients will be enrolled into Part 2 of the study. An SMC will also assess the safety of the combination of brentuximab vedotin and RCHP as detailed in Section 9.3.8. The SMC will review accumulating safety data after 10 patients have completed treatment and after all patients have completed treatment.

Part 3 of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin 1.8 mg/kg when administered in combination with RCHP chemotherapy compared to RCHOP alone.

Part 3 of the study will evaluate brentuximab vedotin 1.8 mg/kg administered IV every 21 days in combination with RCHP chemotherapy compared to standard RCHOP chemotherapy for 6 cycles. A total of approximately 50 patients will be randomized 1:1 into either 1.8 mg/kg brentuximab vedotin administered in combination with RCHP or RCHOP alone. The safety of the combination of brentuximab vedotin and RCHP will also be assessed by the SMC.

A study schema is provided in [Figure 1](#). See [Appendix A](#) for a schedule of evaluations.

Figure 1: Study design



3.2 Discussion and Rationale for Study Design

The activity observed with brentuximab vedotin in the relapsed DLBCL setting, including activity in patients with low or absent CD30 expression ([Jacobsen 2012](#)) suggests that brentuximab vedotin may benefit patients with newly diagnosed DLBCL, irrespective of CD30 expression as assessed by IHC. Additionally, the activity observed with brentuximab vedotin in patients with CD30-positive mature T-cell and NK-cell neoplasms (including systemic ALCL) suggests that CD30-positive patients, regardless of disease diagnosis, may benefit from combination therapy with brentuximab vedotin 1.8 mg/kg plus RCHP ([Bartlett 2014](#)). Patients with DLBCL who are >60 years of age and have an IPI score of 3 or higher or patients who are ≤ 60 years of age with an aaIPI score of 2 or 3 have poor outcomes with RCHOP therapy. Combining brentuximab vedotin with components of RCHOP may improve response rates with the potential to prolong PFS and OS. Additionally, further development in this indication would be supported by understanding response rates to each regimen (A+RCHP versus RCHOP alone) in a randomized part of the study.

The endpoints of this study are appropriate for evaluating efficacy and safety in this patient population. The frequency of blood draws for evaluation of pharmacokinetics is appropriate based on prior experience with brentuximab vedotin.

3.2.1 Method of Assigning Patients to Treatment Groups

Following informed consent and screening assessments, patients in Part 1 will be randomly assigned to 1 of 2 dosing cohorts in a 1:1 ratio. Randomization in this part of the study is for the purpose of evaluating the safety of 1.2 and 1.8 mg/kg brentuximab vedotin in combination with RCHOP. Randomization will be centrally performed using a system that will assign a unique patient randomization number and specify the actual treatment assignment. Randomization procedures are detailed in the Study Manual. Randomization will be stratified by high-intermediate versus high risk disease based on standard IPI for patients >60 years of age or aaIPI for patients ≤60 years of age (i.e., standard IPI score ≥3 and aaIPI score of 2 versus IPI score of 4 or 5 and aaIPI score of 3).

Following informed consent and screening assessments, patients in Part 2 who meet eligibility criteria and have detectable CD30 expression by visual assessment using IHC will receive combination treatment with A+RCHP.

Following informed consent and screening assessments, patients in Part 3 will be randomly assigned to 1 of 2 arms in a 1:1 ratio. Randomization in this part of the study is for the purpose of evaluating the safety of 1.8 mg/kg brentuximab vedotin in combination with RCHP versus RCHOP alone. Randomization will be centrally performed using a system that will assign a unique patient randomization number and specify the actual treatment assignment. Randomization will be stratified by high-intermediate versus high risk disease based on standard IPI for patients >60 years of age or aaIPI for patients ≤60 years of age (i.e., standard IPI score ≥3 and aaIPI score of 2 versus IPI score of 4 or 5 and aaIPI score of 3).

Each site may only enroll patients into one part of the study at a time. For example, if Part 2 and Part 3 have been approved by the site's IRB and are open at a site, enrollment in Part 2 will close prior to enrolling in Part 3.

3.2.2 Rationale for Selection of Doses

In a phase 1 dose-escalation study of brentuximab vedotin (SG035-0001), the MTD was defined as 1.8 mg/kg via IV infusion administered every 3 weeks. This dose and schedule was further evaluated in 2 pivotal phase 2 studies (SG035-0003 and SG035-0004) in patients with CD30-positive hematologic malignancies. When brentuximab vedotin is administered as a single agent, the recommended dose modification in the setting of Grade 2 or higher peripheral neuropathy is a reduction to 1.2 mg/kg IV every 3 weeks.

In a previous Phase 1 experience (Study SGN35-009), when brentuximab vedotin was combined with another anti-microtubule agent with the potential for additive peripheral neuropathy (vinblastine, as part of ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine]/AVD), an equivalent dose of 1.8 mg/kg every 3 weeks was achieved with manageable toxicity. In addition, the combinability of 1.8 mg/kg brentuximab vedotin with CHP chemotherapy was previously demonstrated in a Phase 1 study in CD30-positive lymphomas (Study SGN35-011). In the current study, there will be a randomized comparison of the safety and tolerability of 2 dose levels of brentuximab vedotin when combined with RCHOP: 1.8 mg/kg IV every 21 days, which is the FDA-approved dose of

brentuximab vedotin monotherapy and 1.2 mg/kg IV every 21 days, which is the reduced dose in the setting of neuropathy. There will be a non-randomized dose cohort of 1.8 mg/kg brentuximab vedotin combined with RCHP chemotherapy to assess the safety and tolerability in a regimen that omits vincristine. There will also be a randomized part to assess the safety and tolerability of 1.8 mg/kg brentuximab vedotin combined with RCHP chemotherapy compared to standard RCHOP chemotherapy.

3.2.3 Blinding

This study will not be blinded.

4 STUDY POPULATION

The population to be studied includes treatment-naive patients with high-intermediate or high risk systemic DLBCL.

Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of Good Clinical Practice (GCP) or health regulatory authority inspection.

4.1 Inclusion Criteria

1. Treatment-naive patients with systemic de novo or transformed DLBCL, or follicular NHL grade 3b; patients must have high-intermediate or high risk disease based on standard IPI (score ≥ 3 for patients >60 years of age) or aaIPI (score 2 or 3 for patients ≤ 60 years of age), and stage IAX (bulk defined as single lymph node mass >10 cm in diameter), IB–IV disease
2. Fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and measurable disease of at least 1.5 cm by computed tomography (CT), as assessed by the site radiologist
3. An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
4. Age 18 years or older
5. Patients must have the following baseline laboratory data:
 - bilirubin ≤ 1.5 X upper limit of normal (ULN) or ≤ 3 X ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma
 - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 X ULN or ≤ 5 X ULN for patients with documented hepatic involvement with lymphoma
 - serum creatinine ≤ 2 X ULN
 - absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$ (unless documented bone marrow involvement with lymphoma)
 - platelet count $\geq 50,000/\mu\text{L}$ (unless documented bone marrow involvement with lymphoma)

6. 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. 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.
7. Females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraception methods during the study and for 12 months following the last dose of study drug
8. Patients or their legally authorized representative must provide written informed consent
9. Patients in Parts 2 and 3 must have histologically confirmed diagnosis of CD30-positive DLBCL (see Section 7.1.1)

4.2 Exclusion Criteria

1. Previous history of treated indolent lymphoma. Newly diagnosed patients with DLBCL who are found to have small cell infiltration of the bone marrow or other diagnostic material (representing a discordant lymphoma) are eligible.
2. History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years
3. History of progressive multifocal leukoencephalopathy (PML)
4. Cerebral/meningeal disease related to the underlying malignancy
5. Baseline peripheral neuropathy \geq Grade 2 (per the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 4.03) or patients with the demyelinating form of Charcot-Marie-Tooth syndrome
6. Left ventricular ejection fraction less than 45% or symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), or myocardial infarction within the past 6 months or previous treatment with complete cumulative doses of doxorubicin or other anthracyclines
7. Any active Grade 3 or higher (per the NCI CTCAE, Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study treatment
8. Current therapy with other systemic anti-neoplastic or investigational agents
9. Females who are breastfeeding
10. Known hypersensitivity to any excipient contained in any of the drug formulations of study treatments
11. Patients with known urinary outflow obstruction

12. Known human immunodeficiency virus (HIV) infection or known or suspected active hepatitis C infection. Patients with a positive hepatitis B polymerase chain reaction (PCR) assay who have also tested positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody; patients with a negative PCR assay are permitted with effective anti-viral prophylaxis.

4.3 Removal of Patients From Therapy or Assessment

Seattle Genetics or their designee must be notified 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 case report form (CRF).

4.3.1 Discontinuation of Study Drug

A patient's treatment with study drug may be discontinued for any of the following reasons:

- Completed treatment
- Progressive disease
- Adverse event (AE)
- Investigator decision
- Patient decision, non-AE
- Study termination by sponsor
- Other, non-AE

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

4.3.2 Patient Withdrawal From Study

Any patient may be discontinued from the study for any of the following reasons:

- Patient withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

Brentuximab vedotin, the investigational agent under study in this protocol, is an ADC consisting of the antibody cAC10, specific for human CD30; the microtubule-disrupting agent MMAE; and a protease-cleavable linker that covalently attaches MMAE to cAC10.

In Part 1 of the study, RCHOP, a standard chemotherapy regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, is administered in combination

with brentuximab vedotin in this protocol (A+RCHOP). In Part 2 of the study, an RCHOP regimen omitting vincristine will be administered in combination with brentuximab vedotin in this protocol (A+RCHP). In Part 3 of the study, an RCHOP regimen omitting vincristine will be administered in combination with brentuximab vedotin (A+RCHP) or standard RCHOP chemotherapy (a standard chemotherapy regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) will be administered. See Section 5.3 for information on the description, preparation, administration, and storage of agents contained in the RCHOP and RCHP regimens.

Study Treatment in Each 21-Day Cycle	Part 1	Part 2	Part 3
Brentuximab vedotin 1.2 mg/kg IV on Day 1	X ^a		
Brentuximab vedotin 1.8 mg/kg IV on Day 1	X ^a	X	X ^d
Rituximab 375 mg/m ² IV on Day 1 ^b	X	X	X
Cyclophosphamide 750 mg/m ² IV on Day 1 ^b	X	X	X
Doxorubicin 50 mg/m ² on Day 1 ^b	X	X	X
Vincristine 1.4 mg/m ² on Day 1 ^{b,c}	X		X ^d
Prednisone 100 mg orally 70 mg/m ² on Days 1-5	X	X	X

- a Patients will be randomized to receive treatment with either 1.2 or 1.8 mg/kg brentuximab vedotin in Part 1
- b Administered within approximately 1 hour of completing treatment with brentuximab vedotin administered via IV on Day 1 of each 21-day cycle, as applicable
- c Dose capped at 2 mg total
- d Patients will be randomized to receive treatment with either 1.8 mg/kg brentuximab vedotin combined with RCHP or standard RCHOP in Part 3

5.2 Investigational Study Drug

Detailed information describing the preparation, administration, and storage of brentuximab vedotin is located in the Pharmacy Instructions.

5.2.1 Description

Brentuximab vedotin is a sterile, preservative free, white to off-white lyophilized cake or powder supplied by Seattle Genetics, Inc. in single-use vials for reconstitution for IV administration. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. See the Pharmacy Manual for further information.

5.2.2 Dose and Administration

Brentuximab vedotin (1.2 mg/kg or 1.8 mg/kg) will be administered on Day 1 of each 21-day cycle by IV infusion given over approximately 30 minutes. Brentuximab vedotin should be administered within approximately 1 hour of completing treatment with RCHOP or RCHP (see Section 5.3.3). In the absence of infusion-related reactions, the infusion rate for brentuximab vedotin 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 should not be mixed with other medications.

Dosing is based on patient actual body weight. Doses must be adjusted for patients who experience a $\geq 10\%$ change in weight from baseline. Other dose adjustments for changes in body weight are permitted per institutional standard. An exception to weight-based dosing is

made for patients weighing greater than 100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

5.2.3 Required Premedication and Postmedication

Premedication for rituximab will be given as specified in Section 5.3.4. Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of brentuximab vedotin (after RCHOP or RCHP administration is completed). However, patients who experience a Grade 1 or Grade 2 infusion reaction related to brentuximab vedotin may receive subsequent infusions with premedication as described in Section 5.2.4. 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.

Patients should be individually evaluated to assess the need for tumor lysis prophylaxis prior to the first dose of brentuximab vedotin. Patients should receive prophylaxis as appropriate per the institutional standards.

5.2.4 Management of Infusion Reactions

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. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for infusion-related reactions.

Patients who have experienced an infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30–60 minutes prior to each infusion or according to institutional standards.

If anaphylaxis occurs, brentuximab vedotin administration should be immediately and permanently discontinued.

5.2.5 Management of Suspected PML

Signs and symptoms of PML may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. See the Investigator's Brochure for further details.

If PML is suspected, hold further brentuximab vedotin dosing and undertake a diagnostic work-up including (but not limited to):

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

If PML is confirmed, permanently discontinue treatment with brentuximab vedotin and rituximab.

5.2.6 Dose Modifications

Table 1 describes the recommended brentuximab vedotin and vincristine dose modifications for study treatment-associated neuropathy. Doses reduced for treatment-related neuropathy should not be re-escalated without discussion with the sponsor.

Table 1: Recommended brentuximab vedotin and vincristine dose modifications for treatment-associated neuropathy

Grade of Treatment-Associated Neuropathy	Recommended Dose Modification	
	Sensory Neuropathy	Motor Neuropathy
1	Continue study treatment at same dose level	Continue study treatment at same dose level
2	Reduce dose of brentuximab vedotin ^a	Reduce dose levels of brentuximab vedotin or vincristine ^a
3	Hold brentuximab vedotin and vincristine; restart after recovery to Grade 1 with reduced dose levels of brentuximab vedotin and vincristine ^a	Discontinue treatment with brentuximab vedotin or vincristine
4	Discontinue treatment with brentuximab vedotin and vincristine	Discontinue treatment with brentuximab vedotin or vincristine

^a For patients assigned to 1.8 mg/kg brentuximab vedotin, the reduced dose is 1.2 mg/kg. For patients in Part 1 assigned to 1.2 mg/kg brentuximab vedotin, the reduced dose is 0.8 mg/kg. The reduced dose of vincristine in Part 1 is 1 mg; vincristine dose modifications are not applicable for patients in Part 2.

Brentuximab vedotin dose reductions are also recommended for patients who experience Grade 4 neutropenia despite growth factor support. Patients assigned to 1.8 mg/kg brentuximab vedotin should be dose reduced to 1.2 mg/kg and patients in Part 1 assigned to 1.2 mg/kg brentuximab vedotin should be dose reduced to 0.8 mg/kg.

5.2.7 Storage and Handling

Refrigeration should be set at 2–8°C for storage of vials and solutions containing brentuximab vedotin. The controlled location must be accessible only to the pharmacist, the investigator, or a duly designated person. Brentuximab vedotin does not contain preservatives; therefore, opened and reconstituted vials of brentuximab vedotin should be used as soon as possible. If not used immediately, the in-use storage should not be longer than 24 hours. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use. Reconstituted vials and solutions must not be shaken.

Drug accountability instructions are provided in the Pharmacy Manual.

5.2.8 Packaging and Labeling

Drug product vials may be labeled as brentuximab vedotin, the United States adopted name (USAN) and the International Nonproprietary Name (INN), or as SGN-35, the compound code; the 2 names can be used interchangeably.

5.2.9 Preparation

Brentuximab vedotin vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug disposal procedures.

Brentuximab vedotin should be reconstituted with the appropriate amount of Sterile Water for Injection, United States Pharmacopeia (USP) or equivalent (see Pharmacy Instructions for details). The vial should be gently swirled until the contents are completely dissolved. The vial must not be shaken. The reconstituted drug product should be inspected visually for any particulate matter and discoloration.

The required volume of reconstituted drug product should be diluted into an infusion bag. The bag should be gently inverted to mix the solution. The bag must not be shaken. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

Detailed drug preparation instructions are provided in the Pharmacy Instructions.

5.3 Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

5.3.1 Description

RCHOP is a standard chemotherapy regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RCHP is a modified version that omits vincristine. Rituximab is a CD20-directed cytolytic antibody. Cyclophosphamide is a nitrogen mustard alkylating agent. Doxorubicin is a cytotoxic anthracycline antibiotic. Vincristine is a vinca alkaloid with a mechanism of action related to the inhibition of microtubule formation in the mitotic spindle. Prednisone is a corticosteroid.

5.3.2 Method of Procurement

Agents contained in the RCHOP regimen are commercially available and approved by the United States FDA and other regulatory agencies for use in treating patients with multiple types of cancer.

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone will be supplied by the study site and billed to patients and/or their third-party payer (insurance, a healthcare provider, or applicable government program).

5.3.3 Dose and Administration

In Part 1 of the study, rituximab 375 mg/m^2 , cyclophosphamide 750 mg/m^2 , doxorubicin 50 mg/m^2 , and vincristine 1.4 mg/m^2 (dose capped at 2 mg total) will be administered IV on

Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle. In Part 2 of the study, rituximab 375 mg/m², cyclophosphamide 750 mg/m², and doxorubicin 50 mg/m², will be administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle.

In Part 3, patients will be randomized to receive either:

- Rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (dose capped at 2 mg total) administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle or
- Rituximab 375 mg/m², cyclophosphamide 750 mg/m², and doxorubicin 50 mg/m² administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1–5 of every 21-day cycle.

The order of RCHOP or RCHP administration should be according to the institutional standard. If part of the combination treatment, brentuximab vedotin should be administered within approximately 1 hour of completing treatment with the other agents.

Dosing should be based on the patient's baseline (predose, Cycle 1 Day 1) height and weight or per institutional standards at the site.

5.3.4 Required Premedication and Postmedication

Acetaminophen and an antihistamine should be given within 30 to 60 minutes prior to initiating the rituximab infusion. Additional premedications, including steroids, may be given prior to the rituximab infusion in accordance with the rituximab package insert, institutional standard of care, or as clinically indicated.

There are no protocol-required pre- or post-medications for cyclophosphamide, doxorubicin, vincristine or prednisone. Routine anti-emetic prophylaxis should be administered per institutional standard.

5.3.5 Management of Infusion Reactions

Infusion reactions related to rituximab should be managed according to the package insert and/or institutional standard of care.

5.3.6 Dose Modifications

See [Table 1](#) for vincristine dose modifications related to neuropathy. Dose modifications of rituximab, cyclophosphamide, doxorubicin, vincristine (if applicable) or prednisone due to hematologic and non-hematologic toxicity are allowed per institutional standards and according to the product specific United States Prescribing Information (USPI) at the discretion of the investigator. Permitted dose modifications include discontinuation of a treatment component.

5.3.7 Storage and Handling

Rituximab, cyclophosphamide, doxorubicin, vincristine (if applicable), and prednisone should be stored and handled per institutional guidelines.

5.3.8 Packaging and Labeling

Supplies of rituximab, cyclophosphamide, doxorubicin, vincristine (if applicable), and prednisone are commercially available.

5.3.9 Preparation

Rituximab, cyclophosphamide, doxorubicin, vincristine (if applicable), and prednisone should be prepared per institutional guidelines.

5.4 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be collected from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent.

5.4.1 Required Concomitant Therapy

Patients with a negative hepatitis PCR assay who also tested positive for hepatitis B surface antigen and/or hepatitis B core antibody must begin antiviral prophylaxis prior to receiving study treatment and for at least 6 months following the completion of study treatment, per institutional standard. Patients receiving antiviral prophylaxis should be regularly monitored for viral reactivation by PCR per institutional standard.

See Section [5.3.4](#) for required rituximab premedications.

5.4.2 Allowed Concomitant Therapy

Routine premedication for infusion reactions should not be administered prior to the first dose of brentuximab vedotin. However, patients who experience an infusion-related reaction may receive subsequent treatment with premedication as described in Section [5.2.3](#).

The use of corticosteroids to treat conditions other than DLBCL is permitted per institutional standard. Systemic corticosteroids may be used to keep DLBCL symptoms under control prior to Cycle 1 Day 1 as long as the duration of steroid use is no longer than 14 days.

Routine infectious prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP) should be considered for all patients. In addition, the NCCN 2012 guideline for the prevention and treatment of cancer-related infections is recommended ([NCCN 2012](#)).

Routine prophylaxis with vaccines that do not contain live micro-organisms is permitted.

The use of transfusions, platelet and/or colony-stimulating factors per the American Society of Clinical Oncology (ASCO) guideline for the use of white blood cell growth factors is recommended for the management of neutropenia and febrile neutropenia ([Smith 2006](#)).

Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the investigator.

The use of colony-stimulating factors and/or chemotherapy for stem-cell collection to enable a future autologous stem cell transplant (SCT) is permitted per institutional standard. Chemo-mobilization of stem cells is only permitted after end of treatment (EOT) procedures are completed.

Consolidative radiotherapy or SCT may be given at the investigator's discretion after EOT procedures are completed. At least 6 cycles of study treatment should be given prior to initiating post-treatment consolidative radiotherapy or SCT.

Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions.

5.4.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy from Day 1 through EOT. Exceptions are noted in Section [5.4.2](#).

5.5 Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF.

6 STUDY ACTIVITIES

6.1 Schedule of Events

Adverse events and concomitant medications will be collected from Day 1 (predose) through the safety reporting period (see Section [7.6.1.3](#)). Any study protocol-related adverse event should be recorded from the time of informed consent as well as any concomitant medications given for treatment of the adverse event. A schedule of events is provided in [Appendix A](#). Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section [7](#).

6.2 Screening Visit (Days -28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria (see Section [4](#))
- Medical history
- Collection/acquisition of tumor specimen for central pathology review (see Section [7.1.1](#))
- Patient International Prognostic Index (IPI) score (see [Appendix B](#))
- Echocardiogram or multigated acquisition (MUGA) scan
- Serology for hepatitis B surface antigen and anti-hepatitis B core antibody; if positive, PCR for hepatitis B viremia must also be performed (see Section [5.4.1](#))

- CT of diagnostic quality of neck, chest, abdomen, and pelvis
- PET (Note: a combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning)
- Bone marrow biopsy (Note: must be collected within 60 days of the first dose of brentuximab vedotin). Results of the bone marrow biopsy must be available prior to enrollment.
- B symptom assessment
- IHC staining for CD30 expression on tumor tissue will be performed in Parts 2 and 3 of the study, using a local pathology laboratory; a tumor specimen will be collected for an additional central pathology review to confirm CD30 expression

6.2.1 Baseline Visit (Days -7 to Day 1)

- Physical exam including focused lymphoma assessment (see Section [7.2](#))
- Height and weight
- Electrocardiogram (ECG)
- Pregnancy test for females of childbearing potential
- ECOG Performance Status (see [Appendix C](#))
- Serum chemistry panel (see Section [7.6.2](#))
- Complete blood count (CBC) with differential (see Section [7.6.2](#))

6.3 Treatment Period (Day 1 to Day 21)

6.3.1 Cycle 1 Day 1 (-1 day)

- B symptom assessment
- Serum chemistry panel (see Section [7.6.2](#))
- CBC with differential (see Section [7.6.2](#))
- Blood samples for PK and biomarkers (see Sections [7.3](#) and [7.4](#))
- RCHOP (Parts 1 and 3) or RCHP (Parts 2 and 3) administration (prednisone on Days 1–5)
- Brentuximab vedotin administration (if applicable for patients in Part 3)

If Baseline Visit activities occur within 1 day prior to Cycle 1, Day 1, the following assessments do not need to be repeated at Visit 1: serum chemistry panel and CBC with differential.

6.3.2 Cycle 1 Day 2

- Blood samples for PK (first 10 enrolled patients in Part 1 only; see Section [7.3](#))

6.3.3 Cycle 1 Day 3 (\pm 1 day)

- Optional malignant lymphoma biopsy (for patients who consent to the procedure)

6.3.4 Cycles 2–6 Day 1 (\pm 1 day)

- Physical exam including focused lymphoma assessment (see Section 7.2)
- ECOG Performance Status (see [Appendix C](#))
- B symptom assessment
- Serum chemistry panel (see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Blood samples for PK and biomarkers (see Sections 7.3 and 7.4)
- RCHOP (Parts 1 and 3) or RCHP (Parts 2 and 3) administration (prednisone on Days 1–5)
- Brentuximab vedotin administration (if applicable for patients in Part 3)

6.3.5 Cycle 3 Day 2

- Blood samples for PK (first 10 enrolled patients in Part 1 only; see Section 7.3)

6.4 End of Treatment Visit (30 to 37 days after last dose of study treatment)

End of Treatment (EOT) visits should occur 30 to 37 days after the last dose of study drug. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the patient will be contacted 30 to 37 days following the last treatment to assess for adverse events.

- Physical examination including focused lymphoma assessment (see Section 7.2)
- ECOG Performance Status (see [Appendix C](#))
- Serum chemistry panel (see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Pregnancy test for females of childbearing potential
- Blood samples for PK and biomarkers (see Sections 7.3 and 7.4)
- B symptom assessment

6.5 End of Treatment Response Assessment (5 weeks [\pm 1 week] after last dose of study treatment)

- CT of diagnostic quality of neck, chest, abdomen, and pelvis
- PET (Note: a combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning)
- Physical examination including focused lymphoma assessment (see Section 7.2)
- Optional malignant lymphoma biopsy (Note: only for patients who experience progressive disease and who consent to the procedure)
- Bone marrow (BM) biopsy (required to confirm CR if BM positive at baseline; should be obtained within 4 weeks after documentation of CR)

6.6 Long-Term Follow-Up Visit (every 4 months [\pm 1 week] after last scan for the first 2 years, and every 6 months thereafter)

Patients who discontinue from study treatment will remain on the study for follow-up until they withdraw from the study (see Section 4.3.2).

- All patients who receive at least one dose of study drug will be followed for survival and disease status at 4-month intervals after their last scan for the first 2 years, and at 6 month intervals thereafter until death or study closure, whichever comes first.
- Patients who discontinue study treatment for any reason other than disease progression or initiation of a non-protocol therapy for treatment of lymphoma will have CT and PET scans of the neck, chest, abdomen, and pelvis every 4 months after the last scan for the first 2 years and every 6 months thereafter until disease progression, death, or study closure, whichever comes first. If PET scan negativity was previously achieved during the course of the study, PET scans are not required during long-term follow-up and/or can be discontinued once PET scan negativity is achieved during long-term follow-up.
- Information will also be collected regarding subsequent anticancer therapies received
- Optional malignant lymphoma biopsy (Note: only for patients who experience progressive disease and who consent to the procedure)

6.7 End of Study/End of Follow-up

The date the patient met criteria for study discontinuation and the reason for study discontinuation will be collected.

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

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

Patient IPI scores should be calculated based on the International Non-Hodgkin Lymphoma Prognostic Factors Project (Shipp 1993) to determine eligibility (see Appendix B), and used for randomization into study arms. The IPI is calculated by scoring 5 prognostic factors: age, stage of disease, lactate dehydrogenase (LDH) level, ECOG score, and number of extranodal sites. Patient aaIPI scores should be calculated based on the method initially published by Shipp et al to be used for randomization. The aaIPI is calculated by scoring 3 prognostic factors: stage of disease, lactate dehydrogenase (LDH) level, and ECOG score. Refer to the Study Manual for details and scoring sheets.

Patient disease stage is to be calculated to determine eligibility, per the Cotswolds Modification of Ann Arbor Staging System (Lister 1989).

Cardiac function will be determined by performing either an echocardiogram or MUGA scan and an ECG.

Patient medical history includes a thorough review of significant past medical history, and current conditions, any treatment for prior malignancies, and any concomitant medications.

7.1.1 CD30 Expression and Histologic Subtype

Histologically confirmed DLBCL must be determined by local pathology assessment.

Submission of the tumor block or approximately 14 unstained slides is required for central pathology evaluation.

In Part 2 of the study, assessment of CD30 expression to determine eligibility will be performed by the institutional or central lab. Tissue samples will be sent to the central pathology lab (selected by the sponsor) for further evaluation of CD30 expression.

Details and shipping instructions are provided in the Research Specimen Laboratory Manual.

7.2 Response/Efficacy Assessments

Lymphoma assessments are to be performed at the timepoints outlined in Section [6](#) and [Appendix A](#). An adequate focused lymphoma assessment consists of:

- Patient medical history, including a thorough review of:
 - The patient's current signs and symptoms, including B symptoms (fever, night sweats, or weight loss >10%)
 - Concomitant medications
- Physical examination, including evaluation of skin, HEENT (head, eyes, ears, nose, and throat), lymph nodes, heart, lungs, abdomen, back, extremities, and neurology

Radiographic assessments (CT of chest, neck, abdomen, and pelvis) will be performed at protocol-specified time points or if disease progression is suspected. 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. Assessment of lymphoma progression will be made according to the Revised Response Criteria for Malignant Lymphoma ([Cheson 2007](#)). Treatment decisions by the investigator will be based on these assessments. CT and PET scans are required per protocol as directed in Section [6](#) and [Appendix A](#). A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning when both are required per protocol, as long as the CT scan is of diagnostic quality. CT and/or PET scans may also be obtained throughout the study if clinically indicated.

A bone marrow biopsy is required at baseline. Information from an assessment performed within 60 days of the first dose of study treatment, as part of clinical care, may be used to satisfy the baseline bone marrow biopsy requirement. Postbaseline biopsies are required to confirm CR if bone marrow is positive at baseline; this confirmation is to be obtained within 4 weeks of documentation of CR by radiographic assessment.

If cutaneous lesions are the sole site of progressive disease, a biopsy must be obtained to histologically confirm progression.

Patients' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee), upon request.

7.3 Pharmacokinetic Assessments

Serum or plasma concentrations of brentuximab vedotin ADC and MMAE will be measured at the timepoints shown in [Table 2](#) and at the end of treatment. If brentuximab vedotin is discontinued, PK assessments are not required at subsequent visits. If patients in Part 3 are randomized to standard RCHOP chemotherapy, PK assessments are not required.

Trough serum ADC and plasma MMAE concentrations (C_{trough}), as well as 24-hour post-dose plasma MMAE concentrations in a subset of patients, will be determined. The relationship between these concentrations and safety or efficacy of brentuximab vedotin will be explored.

Refer to the Research Specimen Manual for information on collection, processing, storage, and shipment of samples.

Table 2: Pharmacokinetic sampling timepoints

Cycle	Study Day	Time	Window	Relative Time
1 and 3 only	Day 1	Predose	Within 24 h prior to start of infusion	Start of infusion
	Day 2 ^a	24 h	± 4 h	Start of infusion
2 and subsequent cycles	Day 1	Predose	Within 8 h	Start of infusion

a Samples collected in the first 10 patients in Part 1 of the study for measurement of MMAE only

7.4 Biomarker Analysis

7.4.1 Pharmacodynamic Biomarkers

Protein Markers in Blood

Blood samples will be collected predose prior to each cycle for measurement of pharmacodynamic biomarkers, which may include markers such as sCD30 and other disease-related biomarkers and brentuximab vedotin-related species.

7.4.2 Exploratory Correlative Studies

Characterization of Tumor Tissue

CD30 expression will be evaluated on baseline tumor specimens by multiple modalities which may include both protein and mRNA-based assays.

On Cycle 1 Day 3 (±1 day), an optional malignant lymphoma biopsy will be obtained for patients with accessible sites of disease and in instances where obtaining a fresh biopsy

would not pose an unnecessary risk to the patient. An optional malignant lymphoma biopsy will also be requested from patients who experience PD.

All samples will be used to evaluate disease-related biomarkers, including but not limited to characterization of the tumor microenvironment as well as determination of the presence of brentuximab vedotin-related species. This evaluation may include both protein and mRNA-based assays.

Cell of origin (COO) and molecular characterization of tumor biopsies

By gene expression profiling DLBCL can be classified based on COO into germinal center B-cell (GCB) and activated B-cell (ABC) subtypes which have different prognoses. In addition, a number of somatic mutations such as Myc, Bcl-6, and EZH2 have been identified in DLBCL in both GCB and ABC subtypes and represents different oncogenic pathways. Patients with Myc and Bcl-2 translocation have particularly poor outcome. If samples are available, correlation of response to brentuximab vedotin with rates of these known mutations, as well as immune cell infiltrates, may be evaluated.

Minimal Residual Disease (MRD)

MRD evaluation may also be carried out to understand the depth of response to therapy and to correlate the depth of response with ORR and other patient outcomes. Molecular MRD status may be analyzed using the Adaptive ClonoSEQ assay.

7.5 Biospecimen Repository

In the US only, for patients who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seattle Genetics and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and to identify predictive pharmacodynamic biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed following study completion.

7.6 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs), recording of concomitant medication and measurements of protocol-specified physical examination findings and laboratory tests.

Safety will be monitored over the course of the study by an SMC as described in Section 9.3.8.

7.6.1 Adverse Events

7.6.1.1 Definitions

Adverse Event

According to the International Conference on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.6.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a serious adverse event (SAE), or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a

	hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	Resulted in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Adverse Event Severity

AE severity should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for Serious Adverse Events).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (brentuximab vedotin, RCHOP) should be evaluated by the investigator using the following criteria:

Related:	<p>There is evidence to suggest a causal relationship between the drug and the AE, such as:</p> <ul style="list-style-type: none"> • an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	<p>Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible</p>

7.6.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met serious criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction.' Instead, record each sign or symptom as an individual adverse event. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and the SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Cancer

Do not use the term 'disease progression' when reporting an AE because it is too general. Instead, report the specific disease (clinical) manifestation of the progression (e.g., 'malignant pleural effusion', 'spinal bone metastases', 'lymphadenopathy from underlying non-Hodgkin lymphoma', 'brain metastases').

Pregnancy

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 12 months after the last dose of study drug(s), including any pregnancies that occur in the partner of a male study patient. Only report pregnancies that occur in a male patient's partner if the estimated date of conception is after the male patient's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events and Pre-Existing Conditions CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.6.1.1) should be reported as SAEs.

7.6.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment (brentuximab vedotin or combination therapy), whichever is later. However, all study protocol-related AEs are to be collected from the time of informed consent. All SAEs that occur after the safety reporting period and are considered related to any component of RCHOP or brentuximab vedotin in the opinion of the investigator should also be reported to the sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the patient dies or withdraws consent, or study closure. All non-serious AEs will be followed through the safety reporting period. Certain AEs of interest may be followed until resolution, return to baseline, or study closure.

7.6.1.4 Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Patient number
- Date of event onset
- Description of the event
- Study treatment, if known

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor's or contract research organization's Drug Safety Department (see email address or fax number included on the SAE report form) within 24 hours.

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.6.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section [7.6.1.4](#)).

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity as well as other SAEs that are not study endpoints, but are known consequences of the underlying disease or condition that are anticipated to occur in the study population should not be reported to the Food and Drug Administration (FDA) as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's final guidance Safety Reporting Requirements for INDs and Bioavailability (BA) and Bioequivalence (BE) Studies (December 2012).

In this study, the SAE that does not require individual IND safety reports to the FDA is progression of the underlying cancer. This anticipated SAE will be reviewed periodically by the Seattle Genetics Drug Safety Department. If, upon review, an SAE is occurring at a higher rate than that which would be expected for the study population, then an IND safety report for the SAE will be submitted to the FDA.

7.6.2 Clinical Laboratory Assessments

Samples will be drawn for central and local labs. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions. The following assessments will be performed by the central lab to evaluate safety at scheduled timepoints (see [Appendix A](#)) during the course of the study:

- Chemistry panel: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, chloride, glucose, lactate dehydrogenase (LDH), potassium, sodium, total bilirubin, and uric acid
- Hematology panel: white blood cell (WBC) count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, platelet count, hematocrit, and hemoglobin.

The following laboratory assessment will be performed by local laboratories at scheduled timepoints (see [Appendix A](#)) during the course of the study:

- A serum or urine β -hCG pregnancy test for females of childbearing potential
- Hepatitis B surface antigen or anti-hepatitis B core antibody testing

7.6.3 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Measurements of height obtained within the prior 12 months may be utilized.

7.7 Appropriateness of Measurements

Internationally accepted criteria for the evaluation of lymphoma will be employed to assess tumor lesion size and extent of disease in the determination of response rate and PFS in this study ([Cheson 2007](#)). The schedule for tumor imaging is consistent with general oncological practice and appropriately balances measurement of tumor control with the expense and patient inconvenience associated with CT and PET scanning.

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Pharmacokinetic and pharmacodynamic assessments for drug activity are also common in clinical studies.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of patients at the site, Seattle Genetics or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's Brochure/ package insert
- Recording and reporting AE and SAE
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval process
- Informed consent process
- Good Clinical Practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities

- Investigational product storage, accountability, labeling, dispensing and record keeping
- Patient coding and randomization (if applicable)
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seattle Genetics representative will review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study patients, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Seattle Genetics or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for electronic CRF (eCRF) data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed during monitoring. The CRFs and related source documents will be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.

- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5 Quality Assurance Procedures

The Clinical Quality Assurance group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Clinical Quality Assurance group of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and Institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seattle Genetics.

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size

9.1.1 Part 1

In order to guarantee enrollment of no less than 25 patients per cohort, approximately 50 patients will be randomized in Part 1 of this study. The null hypothesis is assumed to be a 70% CR rate in both cohorts combined. The alternative hypothesis is that the CR rate is

≥84%. A sample size of 50 patients provides the study with 73% power to reject the null hypothesis when the true CR rate is 84%.

For safety evaluations, with a sample size of 50 patients, the study would provide an 88% chance of observing at least 3 occurrences (6%) of a clinically relevant AE with a true event rate of 10%. Within each cohort, at least 25 patients would provide a 93% chance of observing at least 1 occurrence (5%) of a clinically relevant AE with a true event rate of 10%.

9.1.2 Part 2

In order to guarantee enrollment of no fewer than 25 evaluable patients, approximately 25 patients will be enrolled in Part 2 of this study. Although there is no formal statistical hypothesis, a sample size of 25 patients is considered adequate to detect antitumor activity of A+RCHP within this group of CD30-positive DLBCL patients. For safety evaluations within Part 2, a sample size of 25 would provide a 93% probability of observing at least 1 (5%) occurrence of a clinically relevant AE with a true event rate of 10%.

9.1.3 Part 3

In order to guarantee enrollment of no fewer than 50 evaluable patients, approximately 25 patients will be randomized to each arm in Part 3 of this study. The null hypothesis is assumed to be a 70% CR rate in the RCHOP arm. The alternative hypothesis is that the CR rate is ≥90% in the A+RCHP arm. A sample size of 50 patients provides the study with 70% power to reject the null hypothesis when the true CR rate is 90%.

For safety evaluations, with a sample size of 50 patients, the study would provide an 88% chance of observing at least 3 occurrences (6%) of a clinically relevant AE with a true event rate of 10%. Within each cohort, at least 25 patients would provide a 93% chance of observing at least 1 occurrence (5%) of a clinically relevant AE with a true event rate of 10%.

9.2 Study Endpoint Definitions

9.2.1 Primary Efficacy Endpoint

CR rate is defined as the proportion of patients with CR at the end of treatment according to the Revised Response Criteria for Malignant Lymphoma ([Cheson 2007](#)), as assessed by the investigator. Patients whose disease response cannot be assessed will be scored as nonresponders for calculating the CR.

9.2.2 Secondary Efficacy Endpoints

9.2.2.1 Objective Response Rate (ORR) per Investigator

ORR is defined as the proportion of patients with CR or partial remission (PR) at the end of treatment according to the Revised Response Criteria for Malignant Lymphoma ([Cheson 2007](#)), as assessed by the investigator. Patients whose disease response cannot be assessed will be scored as non-responders for calculating the ORR.

9.2.2.2 Progression-Free Survival (PFS)

PFS is defined as the time from randomization or enrollment (for those patients who are not randomized) to first documentation of disease progression (PD), death due to any cause, or receipt of subsequent lymphoma chemotherapy other than the components of the study treatment regimen (excludes post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, and consolidative autologous or allogeneic SCT), whichever comes first.

PFS data will be censored as described below:

- Patients who do not have disease progression and are still on study at the time of an analysis will be censored on the date of the last disease assessment documenting absence of PD
- Patients who do not have disease progression and are given post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will be censored on the date of the last disease assessment documenting absence of PD
- Patients who are removed from study prior to documentation of disease progression will be censored on the date of the last disease assessment documenting absence of PD

Patients lacking an evaluation of tumor response after their first dose will have their event time censored at one day.

9.2.2.3 Overall Survival (OS)

OS is defined as the time from randomization or enrollment to death due to any cause. Specifically,

OS = Date of death – Date of randomization or enrollment + 1.

For a patient who is not known to have died by the end of study follow-up, observation of OS is censored on the date the patient was last known to be alive (i.e., date of last contact).

Patients lacking data beyond the day of randomization or enrollment will have their survival time censored on the date of randomization or enrollment (i.e., OS duration of 1 day).

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

Parts 1 and 3 of this study are phase 2, randomized, open-label studies with formal statistical hypotheses for the primary efficacy endpoint. Part 2 of this study is a phase 2, non-

randomized, open-label study with no formal statistical hypothesis for the primary efficacy endpoint. For all parts of the study, there are no formal pre-specified statistical hypotheses for the primary safety objective.

Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be used to describe continuous variables. Frequencies and percentages will be used to describe categorical variables.

All analyses will be evaluated separately for each part of this study; Part 1 will be evaluated by dosing cohort, Part 2 will be evaluated as a single dose cohort, and Part 3 will be evaluated by treatment arm.

9.3.1.1 Randomization and Blinding

In Part 1, approximately 50 patients will be randomized in a 1:1 manner to receive either 1.2 mg/kg or 1.8 mg/kg of brentuximab vedotin plus RCHOP.

In Part 3, approximately 50 patients will be randomized in a 1:1 manner to receive either 1.8 mg/kg brentuximab vedotin combined with RCHP or RCHOP alone.

Randomization for Parts 1 and 3 will be stratified by high-intermediate versus high risk group.

- High-intermediate risk includes patients with either:
 - IPI Score: 3
 - Age-adjusted IPI Score: 2
- High risk includes patients with either:
 - IPI Score: 4–5
 - Age-adjusted IPI Score: 3

Randomization will be centrally performed using a system that will assign a unique patient randomization number and specify the actual treatment assignment.

Part 2 is a non-randomized study that will enroll approximately 25 patients who will receive 1.8 mg/kg brentuximab vedotin plus RCHP.

9.3.1.2 Adjustments for Covariates

Stratified analyses will include adjustment for the stratification factor as recorded at randomization (described in Section 9.3.1.1). Covariates may be considered for adjustment in exploratory analyses.

9.3.1.3 Handling of Dropouts and Missing Data

Missing data will not be imputed, with the exception of AE start dates while calculating duration of events. Patients with missing values of a variable other than the time-to-event endpoints (PFS and OS) will be excluded from the analysis of that endpoint. Censoring rules will be applied to the estimation of the distribution of the time-to-event endpoints.

9.3.1.4 Multicenter Studies

Site-to-site variation will not be adjusted for in the analyses.

9.3.1.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed because only 1 primary endpoint will be summarized in this study.

9.3.1.6 Data Transformations and Derivations

No data transformations are planned for the primary endpoints.

Age in years will be calculated using informed consent date and birth date as (informed consent date - birth date)/365.25 truncated to the whole number.

Other time variables based on 2 dates, e.g., start date and end date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

9.3.1.7 Analysis Sets

Modified Intent-to-Treat (mITT) Analysis Set: The mITT analysis set will include all patients who receive any amount of brentuximab vedotin or any component of RCHOP. Randomized patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.

Safety Analysis Set: The safety analysis set will include all patients who receive any amount of brentuximab vedotin or any component of RCHOP. For randomized patients, the treatment group will be determined using the actual treatment received, regardless of the randomization treatment assignment.

CD30-positive Analysis Set: The CD30-positive analysis set will include all patients in Part 1 who receive any amount of brentuximab vedotin or any component of RCHOP and who are CD30-positive ($\geq 1\%$ CD30-expression) per the central laboratory.

9.3.1.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.9 Timing of Analyses

There are no formal interim analyses planned for this study.

The final primary analysis of CR per investigator will occur after all patients have completed treatment on each part of the study. The database cutoff date for this analysis will be determined once all study patients have completed treatment.

9.3.2 Patient Disposition

An accounting of study patients by disposition will be tabulated by study part. The number of patients in each analysis set will be summarized by study part. Patients who discontinue

study treatment and patients who withdraw from the study will be summarized by study part and reason for discontinuation or withdrawal and listed.

9.3.3 Patient Characteristics

Demographics, other baseline characteristics, and concomitant medications will be summarized by study part and listed.

9.3.4 Treatment Compliance

The dose administered at each cycle for each study part and cohort or arm will be assessed and dose intensity will be summarized. Details will be provided in the SAP.

9.3.5 Efficacy Analyses

9.3.5.1 Primary Efficacy Analyses

CR rate at the end of treatment will be summarized by study part and cohort or arm using the mITT analysis set. An exact two-sided 95% CI using the Clopper-Pearson method ([Clopper 1934](#)) will be calculated.

9.3.5.2 Secondary Efficacy Analyses

ORR at the end of treatment will be summarized by study part and cohort or arm using the mITT analysis set. An exact two-sided 95% CI using the Clopper-Pearson method ([Clopper 1934](#)) will be calculated.

PFS and OS will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median survival time and its two-sided 95% CI using the log-log transformation method ([Collett 1994](#)) will be calculated.

9.3.6 Pharmacokinetic and Pharmacodynamic Analyses

Antibody drug-conjugate (brentuximab vedotin) and unconjugated drug (MMAE) PK in serum or plasma will be summarized with descriptive statistics.

Relationships of biomarker and pharmacodynamic parameters (e.g. baseline values, absolute and relative changes from baseline) to efficacy, safety and pharmacokinetic parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. Details of this analysis will be described separately.

9.3.7 Safety Analyses

9.3.7.1 Extent of Exposure

Exposure of each treatment agent, including duration of treatment, number of cycles, total dose, and dose intensity will be summarized by study part and cohort or arm using the safety analysis set. Dose modifications will also be summarized.

Details will be provided in the SAP.

9.3.7.2 Adverse Events

Adverse events will be defined as treatment emergent if they are newly occurring or worsen following study treatment. The incidence of all AEs, treatment-emergent AEs, and treatment-related AEs will be tabulated by study part and cohort or arm. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by study part and cohort or arm, MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one patient, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and cohort or arm. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

9.3.7.3 Deaths and Serious Adverse Events

Serious adverse events will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.7.4 Clinical Laboratory Results

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by study part and cohort or arm and scheduled visit. Patients with laboratory values outside of the normal reference range at any postbaseline assessment will be listed by study part.

9.3.8 Interim Analyses

In Part 1 of the study, an SMC will monitor the trial for safety and efficacy and will convene periodically during the study. The SMC will review accumulating safety data after 10 patients in each cohort (N=20) have completed treatment and after all patients in both dose cohorts have completed treatment (N=50). If Grade 3 neuropathy (sensory or motor) is observed in >20% of patients in either dosing cohort, that dose level will have exceeded the stopping criteria. If the 1.8 mg/kg brentuximab vedotin cohort exceeds the stopping criteria, but acceptable safety is observed at 1.2 mg/kg during the first SMC review, patients receiving treatment at 1.8 mg/kg will be dose reduced to 1.2 mg/kg, randomization will cease, and all remaining patients will be enrolled and treated at 1.2 mg/kg brentuximab vedotin. If the SMC determines that the risks outweigh the benefits of study treatment at both dose levels, no further patients will be enrolled.

In Part 2 of the study, the SMC will review accumulating safety data after 10 patients have completed treatment and after all patients have completed treatment. If the SMC determines that the risks outweigh the benefits of study treatment with 1.8 mg/kg A+RCHP, no further patients will be enrolled in Part 2 and the study will be halted. For those patients still receiving therapy, treatment with standard of care or appropriate treatment will continue outside of the study at the discretion of the investigator.

In Part 3 of the study, the SMC will review accumulating safety and efficacy data after 12 patients (approximately equal numbers of patients in each arm) have completed treatment. If the SMC determines that the risks outweigh the benefits of study treatment with 1.8 mg/kg A+RCHP, no further patients will be enrolled in Part 3 and the study will be halted. For those patients still receiving therapy, treatment with standard of care or appropriate treatment will continue outside of the study at the discretion of the investigator.

An ongoing real-time review of serious AEs (SAEs) in both parts of the study and all cohorts or arms will also be conducted by the Seattle Genetics Program Safety Monitoring Team.

Additionally, interim data from the study may be presented at scientific meetings such as the annual meetings of the American Society of Clinical Oncology and the American Society of Hematology.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

10.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring patients are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each patient, or legally authorized representative, if applicable, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a legally authorized representative for a patient who is unable to provide informed consent at study entry, but the patient is later able to provide informed consent, the investigator must obtain written informed consent from the patient.

10.2 Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (eg quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1 Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4 Study Documentation, Privacy and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the patient authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of patient identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5 Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS

SCHEDEULE OF EVENTS		D-28 to 1	Screening	D-7 to 1	Baseline	Enrollment						Long-term follow-up																																	
Visit Window		D-28 to 1	D-7 to 1	D-7 to 1						D1 (-1 day)		C1		D3 (± 1 day)		D1 (± 1 day)		C2		D2		C3		D1 (± 1 day)		C4		D1 (± 1 day)		C5		D1 (± 1 day)		C6		D1 (± 1 day)		30 \pm 7 days post last dose		EOT ^H		EOF ^I Response Assessment		Q4 mos after last scan for 1st 2 yrs then Q6 mos	
Screening/ Baseline Assessments	Informed consent	X																																											
	Inclusion/exclusion	X																																											
	Medical history	X																																											
	Tumor Specimen Submission	X ^K																																											
	IPI or age-adjusted IPI score	X																																											
	Height & weight		X																																										
	Electrocardiogram		X																																										
	Pregnancy test		X																											X															
Treatment ^R	Echo or MUGA scan	X																																											
	Serology for hepatitis B ^M	X																																											
Research Samples ^A	Brentuximab vedotin					X												X	X	X	X	X	X																						
	RCHOP or RCHP					X												X	X	X	X	X	X																						
	ADC PK sample					X												X	X	X	X	X	X																						
	MMAE PK sample					X												X	X	X	X	X	X																						
	CD30 status ^N	X				X	X ^{D,L}										X	X	X ^{D,L}	X	X	X	X																						
	Soluble CD30					X												X	X	X	X	X	X																						
Response Assessments	MRD ^Q					X											X	X	X	X	X	X	X																						
	Malignant lymphoma biopsy							X ^{I,L}																				X ^I	X ^I																
	CT ^B	X																											X ^G	X															
	PET ^C	X																											X ^{F,G}	X ^O															
	BM biopsy	X																											X ^E																
Safety Assessments	B symptoms	X							X									X	X	X	X	X	X						X																
	Survival status																																												
	Phys exam/focused lymph assess		X															X	X	X	X	X	X						X ^P																
	ECOG		X															X	X	X	X	X	X																						
	Serum chemistry		X															X	X	X	X	X	X																						
Safety Assessments	CBC with differential		X															X	X	X	X	X	X																						
	Con meds & AEs	Collect any related to study procedures																																											

A Refer to Sections 7.3 and 7.4 for detailed schema; PK is not required for Part 3 patients randomized to standard RCHOP chemotherapy

B CT of chest, neck, abdomen, and pelvis

C A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning

D First 10 enrolled patients in Part 1 only

E Bone marrow (BM) biopsy required to confirm CR if BM positive at baseline; should be obtained within 4 weeks after documentation of CR

F Once negative PET or CT/PET is documented, no further PET or CT/PET is required; CT scans only are acceptable

G Should be repeated if not done within the previous 6 weeks

H EOT evaluations should be done before initiation of non-protocol therapy. If done <30 days post last study treatment, conduct a phone screen 30-37 days post last treatment to ensure no change in AE profile has occurred.

I Optional malignant lymphoma biopsy for accessible nodes, and in instances where obtaining a fresh biopsy would not pose an unnecessary risk to the patient

J Optional malignant lymphoma biopsy (for patients who experience PD)

K Archived tumor specimen must be submitted for central pathology review

L Relative to timing of brentuximab vedotin administration

M Hepatitis B surface antigen and anti-hepatitis B core antibody; if positive, PCR for hepatitis B viremia must also be performed

N For patients enrolled in Parts 2 and 3 only; determined using IHC staining

O If PET scan negativity was previously achieved during the course of the study, PET scans are not required during long-term follow-up and/or can be discontinued once PET scan negativity is achieved during long-term follow-up.

P The EOT physical exam and the EOT response assessment physical exam may be combined.

Q Minimal residual disease (MRD) predose all cycles and at EOT.

R In Part 3, patients will be randomized to receive either brentuximab vedotin and RCHP or RCHOP alone.

APPENDIX B: INDEX SCALES

International Prognostic Index (IPI, for patients >60 years of age)

1 point for any of the following:

- Age >60
- Serum LDH $>1 \times$ ULN
- ECOG Performance Status ≥ 2
- Stage III or IV
- Extranodal involvement ≥ 2 sites

Risk Category:

- Low: 0–1
- Low-intermediate: 2
- High-intermediate: 3
- High: 4–5

From the International Non-Hodgkin's Lymphoma Prognostic Factors Project ([Shipp 1993](#)).

Age-adjusted International Prognostic Index (aaIPI, for patients ≤ 60 years of age)

1 point for any of the following:

- Serum LDH $>1 \times$ ULN
- ECOG Performance Status ≥ 2
- Stage III or IV

Risk Category:

- Low: 0
- Low-intermediate: 1
- High-intermediate: 2
- High: 3

Based on ([Shipp 1993](#); [Moskowitz 1999](#); [Hamlin 2003](#)).

APPENDIX C: ECOG PERFORMANCE STATUS

Score	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX D: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled “A Phase 2 Study of Brentuximab Vedotin in Combination with Standard of Care Treatment (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone [RCHOP]) or RCHP (Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone) as Front-line Therapy in Patients with Diffuse Large B-cell Lymphoma (DLBCL)”

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature

Date

Investigator Name, Printed

APPENDIX E: DOCUMENT HISTORY

Version	Date
Original	27-Mar-2013
Amendment 1	19-June-2013
Amendment 2	04-Nov-2013
Amendment 3	26-Feb-2014
Amendment 4	14-Jan-2015
Amendment 5	10-Aug-2015

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Synopsis, 3.2.1, 6.2, 7.1.1, 9.3.1.1, 9.3.1.2, Appendix A	Removed CD30 expression by local pathology laboratory as a screening assessment. In addition, patients will no longer be stratified by CD30 expression.	For operational ease because CD30 staining is not part of the routine immunostaining panel for DLBCL patients at local pathology laboratories. Central pathology evaluation will still be performed. Randomization will no longer be stratified by CD30 expression because it is unlikely that significant imbalances will be observed between treatment arms.
6.5, 6.6, 7.4.2, Appendix A	Clarified that the optional malignant lymphoma biopsy may be requested for patients who progress at any time during their participation on the study.	Clarification.
9.2.2.2	Clarified the definition of PFS and associated censoring rules.	Clarification.

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Protocol cover page	The sponsor's medical monitor has been changed.	Administrative change.
Synopsis, 4.2	12. Known human immunodeficiency virus (HIV) infection, <u>positive for hepatitis B surface antigen positive status or anti-hepatitis B core antibody</u> , or known or suspected active hepatitis C infection.	To exclude patients who are positive for either hepatitis B surface antigen or anti-hepatitis B core antibody because of the risk of hepatitis B reactivation in patients treated with rituximab.
5.4.2	<p>The use of corticosteroids to treat conditions other than DLBCL is permitted per institutional standard. <u>Systemic corticosteroids may be used to keep DLBCL symptoms under control prior to Cycle 1 Day 1 as long as the duration of steroid use is no longer than 14 days.</u></p> <p>Routine infectious prophylaxis for Pneumocystis jiroveci pneumonia (PCP) should be considered for all patients. In addition, the NCCN 2012 guideline for the prevention and treatment of cancer-related infections is recommended (NCCN 2012).</p> <p><u>Routine prophylaxis with vaccines that do not contain live micro-organisms is permitted.</u></p>	To clarify permissible use of corticosteroids prior to first dose and to clarify that routine vaccination is permitted as long as the vaccine does not contain live micro-organisms.
6.2 and Appendix A	Removed the requirement for tumor specimen slides to be submitted between Day -28 and Day 14.	For operational ease.
6.2 and Appendix A	Added serology for hepatitis B surface antigen and anti-hepatitis B core antibody to the screening assessments	To ensure exclusion of patients who are positive for either hepatitis B surface antigen or anti-hepatitis B core antibody because of the risk of hepatitis B reactivation in patients treated with rituximab.
7.1.1	Increased the number of tumor specimen slides required for central pathology evaluation from approximately 12 to approximately 14.	To ensure adequate tissue is available for exploratory correlative studies.
7.6.1.3	The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment (brentuximab vedotin or combination therapy), whichever is later. However, all study protocol-related AEs are to be collected from the time of informed consent. All SAEs that occur after the safety reporting period and are considered <u>study treatment-related to any component of RCHOP or brentuximab vedotin</u> in the opinion of the investigator should also be reported to the sponsor.	To clarify the definition of study treatment-related and to clarify that certain AEs of interest may be followed until resolution, return to baseline, or study closure.

Section(s)	Change	Rationale
	SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the patient dies or withdraws consent, or study closure. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.	
Synopsis, 9.1	<p><u>In order to guarantee enrollment of no less than 25 patients per cohort.</u> <u>A</u>pproximately 50 patients (<u>approximately 25 patients in each cohort</u>) will be randomized in this study. <u>The null hypothesis is assumed to be a 70% CR rate in both cohorts combined. The alternative hypothesis is that the CR rate is ≥84%. A sample size of 50 patients provides the study with 73% power to reject the null hypothesis when the true CR rate is 84%. With a sample size of 50, observing 42 complete remissions (CR; 84%) at the end of treatment across both cohorts would allow us to state with 95% confidence (lower limit one-sided exact 95% confidence interval [CI], 73.0%) and 73% power that the true CR is greater than 70%.</u></p> <p>For safety evaluations, with a sample size of 50 patients, the study would provide an 88% chance of observing at least 3 occurrences (6%) of a clinically relevant AE with a true event rate of 10%. Within each arm, at least <u>4225</u> patients would provide a <u>72</u> <u>93%</u> chance of observing at least 1 occurrence (5%) of a clinically relevant AE with a true event rate of 10%.</p>	To clarify the sample size, state the null and alternative hypotheses, and clarify the power calculation for safety based on each 25-patient cohort.
Appendix A	<p>Footnotes added:</p> <p><u>L</u> <u>Relative to timing of brentuximab vedotin administration</u></p> <p><u>M</u> <u>Hepatitis B surface antigen and anti-hepatitis B core antibody</u></p>	Clarification.

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Synopsis, 1.1, 1.2, 1.4, 2.1, 3.1, 3.2, 3.2.1, 4, 4.1, 7.1, 9.3.1.1, Appendix A, Appendix B	Text throughout the protocol has been revised to define high-intermediate and high risk patients based on standard IPI (score ≥ 3 for patients >60 years of age) or age-adjusted IPI (score 2 or 3 for patients ≤ 60 years of age).	It is standard for younger patients to be evaluated using an age-adjusted IPI scoring system rather than the traditional IPI scoring system; including younger patients with high-intermediate or high risk disease better represents this patient population.
Abbreviations	Added aaIPI and sCD30	For consistency with abbreviations in the document.
Title page, 7.6.1.4	Added new information for the SAE fax number.	A new fax number for SAEs is provided on the SAE form.
7.4.2	Text revised for exploratory correlative studies as follows: <u>These All</u> samples will be used to evaluate disease-related biomarkers <u>on treatment</u> , including but not limited to characterization for the tumor microenvironment as well as determination of the presence and/or binding properties of brentuximab vedotin-related species.	Clarification to show that all samples provided by patients may be used to evaluate disease-related biomarkers, including baseline tumor specimens and not just those specimens taken on treatment.
7.6.1.5	Included the final date of guidance.	To update the referenced guidance as final.
11	New references added.	To update the references for age-adjusted IPI scores.

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Synopsis and Section 2	<p>Updated the objectives:</p> <ul style="list-style-type: none"> • To assess the antitumor activity of brentuximab vedotin administered in combination with RCHOP <u>or</u> RCHP as measured by the complete remission (CR) rate at the end of treatment per investigator assessment in treatment-naïve patients with high-intermediate or high risk systemic DLBCL • To assess the safety profile of brentuximab vedotin administered at dose levels of 1.2 mg/kg versus 1.8 mg/kg in combination with RCHOP <u>or</u> brentuximab vedotin 1.8 mg/kg <u>in combination with RCHP</u> in treatment-naïve patients with high-intermediate or high risk systemic DLBCL • To assess the antitumor activity of brentuximab vedotin administered in combination with RCHOP <u>or</u> RCHP as measured by the objective response rate (ORR) at the end of treatment per investigator assessment • To assess the progression-free survival (PFS) associated with brentuximab vedotin administered in combination with RCHOP <u>or</u> RCHP • To assess survival associated with brentuximab vedotin administered in combination with RCHOP <u>or</u> RCHP • To assess the pharmacokinetics (PK) of brentuximab vedotin administered in combination with RCHOP <u>or</u> RCHP 	To reflect the addition of a modified RCHOP regimen to be studied in combination with brentuximab vedotin.
Synopsis and Section 3.1	The overall study design was updated to reflect the addition of Part 2 (1.8 mg/kg A+RCHP).	To reflect the revised study design and objectives.
Section 1.5	Added background and rationale for treatment of CD30-positive DLBCL patients with 1.8 mg/kg A+RCHP. Rationale includes an overview of the safety and efficacy of current treatment, as well as a discussion of known vincristine toxicities.	Phase 1 studies of brentuximab vedotin included treatment with CHP; it is reasonable to add this dose cohort.
Synopsis and Section 4.1	A new inclusion criterion was added for Part 2, requiring patients to have confirmed CD30-positive disease.	To restrict the added patient population to CD30-positive patients, which are expected to benefit more from treatment with brentuximab vedotin.
Section 6.2 and 7.1.1	Procedures for determining CD30 status were added for patients in Part 2.	To address the new requirement for patients enrolled in Part 2 of the study.
Section 6.6 and Appendix A	The following sentence was added to long-term follow-up visits:	To clarify that PET is required during follow-up until confirmed to be negative.

	<u>PET is required during long-term follow-up if PET-negativity is not previously documented and the patient has achieved at least SD, and has not received additional treatment (excluding consolidative treatment).</u>	
Section 7.3	The following sentence was added to the sampling timepoints: <u>If brentuximab vedotin is eliminated, PK is not required at subsequent visits.</u>	To clarify that once brentuximab vedotin has been discontinued, PK sampling is no longer required.
Section 9.1	Sample size was updated to include Part 2.	To provide rationale for adding 25 patients to Part 2 of the study.
Sections 9.2.2.2 and 9.2.2.3	Revised definitions for PFS and OS.	PFS and OS now include Part 2 patients who were not randomized; the definition has been updated to include these patients in the censoring.
Section 9.3	Section has been revised to include patients in Part 2.	To reflect the change in sample size and differentiate between randomization procedures for Part 1 and Part 2.
Section 9.3.8	Section has been updated to include an SMC for Part 2.	To clarify that an SMC will review data for patients in Part 2.
Appendix A	Footnotes have been added.	To clarify timing of and need for assessments.
Throughout protocol	References to RCHOP chemotherapy and components of RCHOP chemotherapy were revised as needed to distinguish between Part 1 and Part 2 of the study. Editorial changes have also been made for clarity and consistency.	To reflect the change to the combination therapy from brentuximab vedotin and RCHOP to brentuximab vedotin and RCHP.

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Synopsis and Section 2	<p>Added objectives for Part 3:</p> <ul style="list-style-type: none"> • To assess the antitumor activity of brentuximab vedotin administered in combination with RCHP versus RCHOP alone as measured by the CR rate at the end of treatment per investigator assessment in treatment-naïve patients with high-intermediate or high risk systemic DLBCL • To assess the safety profile of brentuximab vedotin administered at 1.8 mg/kg in combination with RCHP in treatment-naïve patients with high-intermediate or high risk systemic DLBCL • To assess the antitumor activity of brentuximab vedotin administered in combination with RCHP versus RCHOP alone as measured by the objective response rate (ORR) at the end of treatment per investigator assessment • To assess the progression-free survival (PFS) associated with brentuximab vedotin administered in combination with RCHP versus RCHOP alone • To assess survival associated with brentuximab vedotin administered in combination with RCHP versus RCHOP alone 	To reflect the addition of a randomized part of the trial that will study brentuximab vedotin in combination with a modified RCHOP regimen versus standard RCHOP chemotherapy.
Synopsis and Section 3.1	The overall study design was updated to reflect the addition of Part 3.	To describe a new study part.
Section 3.2	Added language explaining how patients will be randomized into Part 3 and how sites will be expected to enroll patients.	To reflect the revised study design.
Section 4.1	Revised Inclusion criterion #7 to clarify patients must use 2 effective contraception methods during the study.	To reflect additional concerns of pregnancy during a clinical trial.
Section 4.2	Revised Exclusion criterion #12 to allow patients with negative PCR assay.	To allow patients on study if they have a negative PCR assay and receive effective anti-viral prophylaxis.
Sections 5.4.1, 6.2, and 7.6.2	Added language regarding patients with a negative hepatitis B PCR assay.	To include additional instructions regarding testing for hepatitis B PCR assay and concomitant therapy with antiviral prophylaxis.
Section 7.3	<p>The following sentence was added to the sampling timepoints:</p> <p><u>If patients in Part 3 are randomized to standard RCHOP chemotherapy, PK assessments are not required.</u></p>	To clarify patients who are not receiving brentuximab vedotin in Part 3 do not require PK sampling.

Section 7.4	<u>Added text regarding the testing of cell of origin and molecular characterization of tumor biopsies and minimal residual disease. Also clarified that the biospecimen repository will be utilized for US patients only.</u>	To include additional biomarker testing and clarification for retaining samples.
Section 9.1	Sample size was updated to include Part 3.	To provide rationale for adding 50 patients to Part 3 of the study.
Section 9.3	Section has been revised to include patients in Part 3.	To reflect the change in sample size and differentiate between randomization procedures for all parts of the study.
Section 9.3.6	Section has been revised to include a summary of the biomarker analyses to be performed.	To provide a summary of the biomarker and pharmacodynamic parameters to be explored.
Section 9.3.8	Section has been updated to include an SMC for Part 3 and to describe what will happen to patients if the study is stopped due to safety concerns.	To clarify that an SMC will review data for patients in Part 3 and what will happen to patients in treatment if the study is halted.
Appendix A	Footnotes have been added and revised.	To clarify timing of and need for assessments.
Throughout protocol	References to combination (A+RCHP) and standard RCHOP chemotherapy were revised as needed to distinguish between all parts of the study. Editorial and administrative changes have also been made for clarity and consistency.	To reflect the addition of Part 3.