SeattleGenetics

Protocol Number:	SGN35-014
Version:	Amendment 5; 12 December 2018
Protocol Title:	A randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas
Study Name:	ECHELON-2
Investigational Drug:	Brentuximab vedotin
Indication:	Mature T-cell lymphomas
Phase:	3
IND Number:	71634
EudraCT Number:	2012-002751-42
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PROTOCOL SYNOPSIS

Protocol Number SGN35-014 **Version** Amendment 5 **Phase** 3	**Product Name** Brentuximab vedotin **Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas

Study Objectives

Primary:

- To compare the progression-free survival (PFS) as determined by an independent review facility (IRF) between the 2 treatment arms

Secondary:

- To compare the PFS per IRF between the 2 treatment arms for patients with systemic anaplastic large cell lymphoma (sALCL)
- To compare the remission rates per IRF following the completion of study treatment between the 2 treatment arms
- To compare overall survival (OS) between the 2 treatment arms
- To evaluate the safety and tolerability of the 2 treatment arms

Additional:

- To evaluate medical resource utilization (MRU) and calculate utility values
- To characterize the incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin

Study Population

Inclusion Criteria

1. Patients with newly diagnosed, CD30-positive mature T-cell lymphomas per the Revised European-American Lymphoma World Health Organization (WHO) 2008 classification by local assessment. Eligible histologies are limited to the following:
   - ALK-positive sALCL with an International Prognostic Index (IPI) score greater than or equal to 2
   - ALK-negative sALCL
   - Peripheral T-cell lymphoma – not otherwise specified (PTCL-NOS)
   - Angioimmunoblastic T-cell lymphoma (AITL)
   - Adult T-cell leukemia/lymphoma (ATLL; acute and lymphoma types only, must be positive for human T-cell leukemia virus 1)
   - Enteropathy-associated T-cell lymphoma (EATL)
   - Hepatosplenic T-cell lymphoma
2. Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by CT, as assessed by the site radiologist.
3. Age greater than or equal to 18 years.
4. An Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.
5. The following required baseline laboratory data:

- bilirubin ≤1.5X upper limit of normal (ULN) or ≤3X ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3X ULN or ≤5X ULN for patients with document hepatic involvement with lymphoma
- serum creatinine ≤2X ULN
- absolute neutrophil count (ANC) ≥1000/μL (unless documented bone marrow involvement with lymphoma)
- platelet count ≥50,000/μL (unless documented bone marrow involvement with lymphoma)

6. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotrophin (β-hCG) pregnancy test result within 7 days prior to the first dose of study treatment and must agree to use an effective contraception method during the study and for at least 6 months following the last dose of study drug. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.
7. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last dose of study drug.
8. Patients or their legally authorized representative must provide written informed consent.

Exclusion Criteria

1. History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years.
2. Current diagnosis of any of the following:
   - Primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. Cutaneous ALCL with extracutaneous tumor spread beyond locoregional lymph nodes is eligible (previous single-agent treatment to address cutaneous and locoregional disease is permissible).
   - Mycosis fungoides (MF), including transformed MF
3. History of progressive multifocal leukoencephalopathy (PML).
4. Cerebral/meningeal disease related to the underlying malignancy.
5. Prior treatment with brentuximab vedotin.
6. Baseline peripheral neuropathy ≥ Grade 2 (per the NCI CTCAE, Version 4.03) or patients with the demyelinating form of Charcot-Marie-Tooth syndrome.
7. 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.
8. Any active Grade 3 (per the NCI CTCAE, Version 4.03) or higher viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study treatment; any known human immunodeficiency virus (HIV) infection, hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection.
9. Current therapy with other systemic anti-neoplastic or investigational agents.
10. Females who are pregnant or breastfeeding.
11. Patients with a known hypersensitivity to any excipient contained in the drug formulation.
12. Patients with known urinary outflow obstruction.

Number of Planned Patients

Approximately 450 patients (approximately 225 patients per treatment arm) will be randomized in this study.

Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trial designed to evaluate the efficacy and safety of including brentuximab vedotin in the treatment of newly diagnosed, CD30-positive mature T-cell lymphomas. The standard of care in this patient population consists of 6-8 cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Patients will be randomized in a

1:1 manner to receive 21-day cycles of treatment, either: 6-8 cycles of CHOP or 6-8 cycles of brentuximab vedotin plus CHP (A+CHP). A target of 8 cycles of study treatment will be administered, per investigator decision, based on patient-specific characteristics, including stage of disease and IPI risk score.

Brentuximab vedotin or vincristine will be dispensed as a placebo-controlled double-dummy and administered to patients in a blinded manner. Placebo replacements for brentuximab vedotin/vincristine will be prepared by the pharmacist at each study site and a pharmacy blind will be enforced.

Safety will be monitored over the course of the study by an Independent Data Monitoring Committee (IDMC).

Test Product, Dose, and Mode of Administration

Patients will be randomized 1:1 to receive 6-8 cycles of study treatment (number of cycles per investigator decision), either:

Standard-of-care arm: Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, blinded vincristine 1.4 mg/m^2 (dose capped at 2 mg) administered IV on Day 1 of each cycle; prednisone 100 mg daily administered orally on Days 1–5 of each cycle. Placebo replacement for brentuximab vedotin will also be administered IV in a blinded manner on Day 1 of each cycle.

Experimental arm: Blinded brentuximab vedotin 1.8 mg/kg, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, administered IV on Day 1 of each cycle; prednisone 100 mg daily administered orally on Days 1–5 of each cycle. Placebo replacement for vincristine will also be administered IV in a blinded manner on Day 1 of each cycle.

Duration of Treatment

Study treatment consists of 6-8 cycles of multiagent chemotherapy. The maximum total duration of therapy is 8 cycles, or approximately 6 months.

Efficacy Assessments

Lymphoma response and progression will be assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Radiographic disease evaluations, including CT scans of neck, chest, abdomen and pelvis, will be assessed at baseline, after Cycle 4 of treatment, after the completion of study treatment, at 9, 12, 15, 18, 21 and 24 months after initiation of study treatment, and every 6 months thereafter until disease progression, patient death, or analysis of the primary endpoint, whichever comes first. A CT scan will also be performed at the time of suspected clinical progression. A PET scan is required at baseline, after Cycle 4, and after the completion of study treatment. Subsequent restage assessments (CT scans only) will be performed according to the calendar, relative to the first dose of study treatment, to ensure that tumor progression is uniformly assessed between the treatment arms.

Pharmacokinetic/Pharmacodynamic/Immunogenicity Assessments

Serum concentrations of brentuximab vedotin, antitherapeutic antibodies (ATA) to brentuximab vedotin, and free drug (monomethyl auristatin E; MMAE) will be measured. Pharmacodynamic assessments include the measurement of soluble CD30.

Safety Assessments

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

Statistical Methods

[redacted]

[redacted]

Interim Analysis

[redacted] The IDMC will provide recommendations to the sponsor as to appropriate study direction.

Safety Analysis

An IDMC will review safety data on an ongoing basis.

Endpoints

The primary efficacy endpoint of this study is PFS by IRF.

Secondary endpoints are:

- PFS per IRF for patients with sALCL
- Complete remission (CR) rate per IRF following the completion of study treatment
- OS
- Objective response rate (ORR) per IRF following the completion of study treatment
- Type, incidence, severity, seriousness, and relatedness of adverse events
- Laboratory abnormalities

Additional endpoints are:

- Incidence of ATA to brentuximab vedotin
- MRU based on the number of medical care encounters
- Quality of life measured by the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and European Quality of Life 5-Dimensional (EQ-5D)

Analysis Methods

For the primary efficacy analysis, the stratified log-rank test will be used to compare the difference of PFS between the 2 treatment groups. Estimation of the hazard ratio will be based upon the stratified Cox regression model. PFS will also be summarized using the Kaplan-Meier method. Similar methods will be used for the secondary efficacy endpoints of OS and PFS in patients with sALCL. For the primary analysis, PFS will not be censored for post treatment radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT because these interventions are not administered to treat progressive disease.

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

A+CHP	brentuximab vedotin (ADCETRIS®), cyclophosphamide, doxorubicin, and prednisone
ADC	antibody drug conjugate
AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
ATLL	adult T-cell leukemia/lymphoma
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotrophin
CBC	complete blood count
C_{eoi}	concentration at the end of infusion
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHOP-21	cyclophosphamide, doxorubicin, vincristine, and prednisone administered every 21 days
CHP	cyclophosphamide, doxorubicin, and prednisone
C_{max}	maximum concentration
CNS	central nervous system
CR	complete remission
CRF	case report form
CT	computed tomography
C_{trough}	trough concentration
EATL	enteropathy-associated T-cell lymphoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D	European Quality of Life 5-Dimensional
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRA	Health Regulatory Authority
HTLV-1	human T-cell leukemia virus-1
ICH	International Conference on Harmonisation
IV	intravenous
IDMC	Independent Data Monitoring Committee
IPI	International Prognostic Index
IEC	Independent Ethics Committee

IND	investigational new drug
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRF	independent review facility
JCV	John Cunningham virus
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MF	mycosis fungoides
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
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
PR	partial remission
PRO	patient-reported outcome
PTCL	peripheral T-cell lymphoma
QLQ-C30	EORTC core quality of life questionnaire
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SCT	stem cell transplant
TNSn	Total Neuropathy Score-nurse
T_{max}	time at which the maximum concentration occurs
ULN	upper limit of normal
USAN	United States adopted name
USP	United States Pharmacopeia
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.

This is a randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trial designed to evaluate the efficacy and safety of including brentuximab vedotin in the treatment of patients with newly diagnosed, CD30-positive mature T-cell lymphomas. The standard of care in this patient population consists of 6-8 cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Patients will be randomized in a 1:1 manner to receive 21-day cycles of outpatient treatment, either: 6-8 cycles of CHOP or 6-8 cycles of brentuximab vedotin (ADCETRIS®) plus CHP (cyclophosphamide, doxorubicin, and prednisone), known as A+CHP.

1.1 CD30-Positive Mature T-Cell Lymphomas

T-cell lymphomas are a subset of aggressive non-Hodgkin lymphomas (NHL) that comprise approximately 10-15% of all newly diagnosed cases of NHL in the United States. According to the 2008 World Health Organization (WHO) Classification schema, there are 18 subtypes of mature T- and natural killer (NK) cell neoplasms (Swerdlow 2008). Various subtypes of T- and NK-cell lymphomas are known to express the cell surface marker CD30; most notably, sALCL, in which CD30 expression is a hallmark of the diagnosis (Savage 2008).

CD30-positive mature T-cell lymphomas, including sALCL, peripheral T-cell lymphoma – not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and others, are aggressive lymphoid neoplasms that often present with advanced stage, symptomatic disease. These difficult-to-treat lymphomas are often grouped together for enrollment in clinical trials based on their universally dismal outcomes. Five-year overall survival (OS) in the over 1,300-patient International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study was poor and ranged from 12 to 49% depending on histologic subtype (Vose 2008). Five-year failure-free survival, defined as time from initial diagnosis to progression, relapse after response, or death resulting from any cause, ranged from 6 to 36%. Other studies have reported CR rates to CHOP therapy between 40-50% (Mercadal 2008; Simon 2010). These data confirm 2 distinct unmet needs. First, there is a failure to induce a high rate of initial complete remissions (CRs), and second, those patients who do respond to combination chemotherapy experience disease progression at an unacceptably high rate. Increasing the proportion of patients achieving and maintaining CRs may result in a clinically meaningful improvement in progression-free survival (PFS) and OS.

1.2 Frontline Therapy for Mature T-cell Lymphomas

Frontline treatment of mature T-cell and NK-cell neoplasms is dependent on the subtype of disease and often includes clinical trials as the preferred therapeutic option (NCCN 2013). For most subtypes, anthracycline-based multiagent chemotherapy regimens such as CHOP are commonly utilized. The notable exception is extranodal NK/T-cell lymphoma, nasal and non-nasal types, where concurrent chemoradiotherapy regimens are employed.

Although no randomized studies have been conducted to establish the use of CHOP in patients with CD30-positive mature T-cell neoplasms, it is the most commonly used regimen in the frontline treatment of these patients. The International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study results indicate that over 85% of patients were treated with an anthracycline-based multiagent chemotherapy regimen (Vose 2008). In published studies that have compared new treatment approaches to an established standard of care, CHOP administered every 3 weeks (CHOP-21) has been used as the control arm (Simon 2010). In addition, published guidelines recommend enrollment into a clinical trial or CHOP as appropriate frontline treatment options for patients with a diagnosis of "peripheral T-cell lymphoma, noncutaneous" (NCCN 2013). Guidelines support administration of 6 cycles of CHOP therapy for patients with Stage I-II disease and International Prognostic Index (IPI) score of 0–2, and 6–8 cycles of CHOP therapy for Stage I-II patients with an IPI score of 3–5 and all Stage III-IV patients (Schmitz 2010; NCCN 2013). Comparison of non-randomized clinical trials does not support a difference in activity between 6 or 8 cycles of CHOP, with 6–8 cycles commonly employed in clinical practice (Coiffier 2002; Schmitz 2010). As mentioned above, the response to CHOP chemotherapy is suboptimal with CR rates ranging from approximately 40-50%, and overall response rates of approximately 75% (Mercadal 2008; Simon 2010; Dearden 2011). The estimates of long-term outcome in the mature T-cell lymphoma population, regardless of the backbone of anthracycline-based multiagent chemotherapy, are suboptimal with a median EFS or PFS of 12–18 months and a median OS of less than 4 years (depending on histologic subtype and IPI score).

The high rate of subsequent disease progression among patients responding to frontline therapy led some researchers to employ autologous stem cell transplant (SCT) as a means of improving long-term outcomes; however, no randomized studies have been conducted. National and international guidelines support observation, a clinical trial, or the use of autologous SCT as acceptable options for patients who achieve a CR following frontline therapy (Dearden 2011; NCCN 2013).

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 1.8 mg/kg administered every 3 weeks were further evaluated in a pivotal phase 2 study of patients with relapsed or refractory sALCL (Study SG035-0004). In this study, all patients had previously received at least 1 prior regimen of multiagent systemic chemotherapy with curative intent. The majority of patients had a diagnosis of ALK-negative disease (72%); relative to the most recent therapy, 50% of patients were refractory. Additionally, approximately 60% of patients had primary refractory disease, defined as failure to achieve a complete remission (CR) with frontline therapy or progression within 3 months of completing frontline therapy, and 22% of patients had never achieved a response with any previous therapy. In this study of highly refractory patients, the objective response (CR + PR) rate was 86%, with 57% of patients achieving a CR (Pro 2012). The median duration of response was 12.6 months, and in the subset of patients who achieved a CR, the median duration of response was 13.2 months. Brentuximab vedotin was generally well tolerated, with manageable side effects.

The clinical safety and activity of brentuximab vedotin administered sequentially and concurrently with multiagent chemotherapy were evaluated in a phase 1 study in patients with newly diagnosed CD30-positive mature T- and NK-cell neoplasms, including 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. The maximum tolerated dose of brentuximab vedotin was 1.8 mg/kg given concomitantly with CHP. At an interim analysis in this study (data presented at the T-Cell Lymphoma Forum 2012), 20 patients in this study had been treated with brentuximab vedotin 1.2 or 1.8 mg/kg given concomitantly with CHP for 6 cycles, followed by continued brentuximab vedotin every 3 weeks for up to 10 additional cycles for responding patients. The most common adverse events were nausea, fatigue, and peripheral sensory neuropathy. Of the patients who had a response assessment after 6 cycles of brentuximab vedotin plus CHP, 5 of 5 patients achieved a CR.

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

1.4 Rationale for Brentuximab Vedotin in Combination with CHP

Because of the poor outcomes in mature T-cell lymphomas, 2 strategies have been developed in an attempt to improve upon the results of CHOP-21: dose escalation of chemotherapy and new combinations/new agents. Neither approach to modifying CHOP has resulted in short- or long-term benefit to patients. Simon et al. demonstrated in a small randomized study that a more aggressive regimen (etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine; also known as VIP-reinforced-ABVD or VIP-rABVD) was not superior to CHOP-21 in terms of event-free survival. Furthermore, VIP-rABVD resulted in more toxicities than CHOP-21. These data confirm that CHOP remains the reference regimen in these lymphomas. Another strategy to improve outcome has focused on autologous SCT consolidation in patients who achieve CRs at the end of induction therapy. However, many patients are not candidates for SCT, regardless of response to induction

therapy, due to age or intercurrent medical conditions. No randomized studies have been conducted, and results of single-arm studies are mixed.

The results of the pivotal phase 2 study in patients with relapsed or refractory disease (described in Section 1.3) suggest a marked treatment effect of brentuximab vedotin as monotherapy in sALCL that is anticipated to be both clinically meaningful and associated with a positive risk-benefit ratio when introduced into the frontline treatment of patients with CD30-positive mature T-cell lymphomas.

Given the results of treatment with brentuximab vedotin in the relapsed and refractory setting, and its demonstrated safety when combined with CHP, it is hypothesized that a treatment approach in adults that incorporates brentuximab vedotin as part of multiagent frontline induction therapy may yield a PFS and OS benefit. It is also reasonable to evaluate the replacement of vincristine with brentuximab vedotin because of the activity previously observed. By replacing a non-targeted microtubule-disrupting agent with a CD30-directed ADC that delivers a potent microtubule-disrupting agent, the potential overlapping toxicities of peripheral neuropathy that would be inherent to delivering both agents in the same regimen are avoided.

2 OBJECTIVES

2.1 Primary Objective

- To compare the progression-free survival (PFS) as determined by an independent review facility (IRF) between the 2 treatment arms

2.2 Secondary Objectives

- To compare the PFS per IRF between the 2 treatment arms for patients with sALCL
- To compare the remission rates per IRF following the completion of study treatment between the 2 treatment arms
- To compare overall survival (OS) between the 2 treatment arms
- To evaluate the safety and tolerability of the 2 treatment arms

2.3 Additional Objectives

- To evaluate medical resource utilization (MRU) and calculate utility values
- To characterize the incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin

2.4 Endpoints

2.4.1 Primary Endpoint

- Progression-free survival (PFS) by IRF

2.4.2 Secondary Endpoints

- PFS per IRF for patients with sALCL
- Complete remission (CR) rate per IRF following the completion of study treatment
- Overall survival (OS)
- Objective response rate (ORR) per IRF following the completion of study treatment
- Type, incidence, severity, seriousness, and relatedness of adverse events
- Laboratory abnormalities

2.4.3 Additional Endpoints

- Incidence of ATA to brentuximab vedotin
- MRU based on the number of medical care encounters
- Quality of life measured by the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and European Quality of Life 5-Dimensional (EQ-5D)

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trial designed to evaluate the efficacy and safety of including brentuximab vedotin in the treatment of newly diagnosed, CD30-positive mature T-cell lymphomas. The standard of care in this patient population consists of 6-8 cycles of CHOP chemotherapy. Patients will be randomized in a 1:1 manner to receive 21-day cycles of treatment in 1 of the following 2 treatment groups:

1. Standard-of-care arm: 6–8 cycles of CHOP; or
2. Experimental arm: 6–8 cycles of brentuximab vedotin plus CHP (A+CHP)

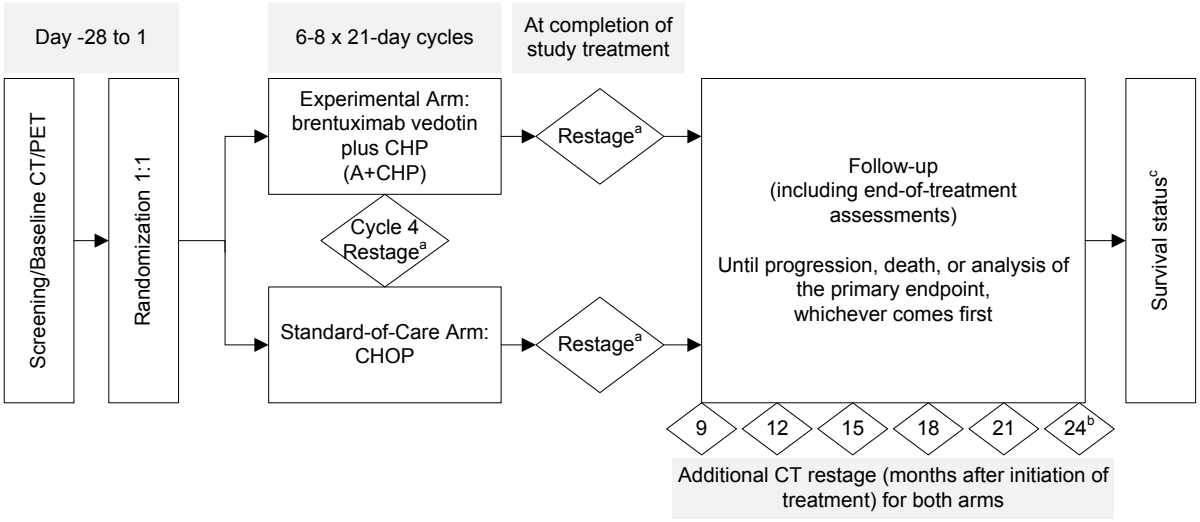
A target of 8 cycles of study treatment will be administered, per investigator decision, based on patient-specific characteristics, including stage of disease and IPI risk score.

Brentuximab vedotin or vincristine will be dispensed as a placebo-controlled double-dummy and administered to patients in a blinded manner (see Table 1 for a list of study treatments by arm). Placebo replacements for brentuximab vedotin/vincristine will be prepared by the pharmacist at each study site and a pharmacy blind will be enforced.

Safety will be monitored over the course of the study by an Independent Data Monitoring Committee (IDMC) as described in Section 9.3.9.

Approximately 450 patients (approximately 225 patients per treatment arm) will be randomized in this study. A study schema is provided in Figure 1. See Appendix A for a schedule of evaluations.

Figure 1: Study design



a CT and PET scans required
b Additional CT scans every 6 months thereafter until progression per investigator, death, or analysis of the primary endpoint, whichever comes first
c For patients with documented progression, continued follow-up for survival every 6 months until death or study closure, whichever comes first

3.2 Discussion and Rationale for Study Design

The primary endpoint of this study, PFS, is one of the endpoints recommended by FDA (FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics") and the EMA ("Guideline on the Evaluation of Anticancer Medicinal Products in Man", CPMP/EWP/205/95/Rev.3/Corr.2) for approval of anticancer drugs. Defined as the time from randomization until objective tumor progression or death, PFS is a direct reflection of tumor growth and can be assessed before determination of a survival benefit. Furthermore, because PFS includes deaths from any cause it may be a correlate to overall survival, a secondary endpoint of this study. An additional advantage of PFS is that its determination is not confounded by subsequent therapy. In this study, post treatment radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT are not considered subsequent new anticancer treatments because they are not administered to treat progressive disease. Standardized criteria will be employed to evaluate progression (Cheson 2007). To ensure consistent unbiased application of these criteria, all imaging studies performed to confirm disease status and to assess progression during the study will be submitted to an independent third-party imaging core laboratory for blinded review and all patients will have evaluations for progression performed on the same schedule.

The current standard of care, CHOP chemotherapy administered for 6-8 cycles followed by either observation and best supportive care, a clinical trial, or an SCT, results in long-term disease-free survival in only a minority of patients. Despite this, CHOP is the best available therapy in this population, and the use of CHOP administered for 6-8 cycles is therefore considered appropriate and ethical. The randomized, blinded design of this trial is based on the considerations outlined in the FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics", which states that PFS is ideally evaluated in a randomized and blinded study.

3.2.1 Method of Assigning Patients to Treatment Groups

Following informed consent and screening assessments, patients will be randomly assigned to study treatment in a 1:1 ratio. Randomization will be performed centrally using a system that will assign a unique patient randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the Study Manual.

[redacted]

3.2.2 Rationale for Selection of Doses

In a phase 1 dose-escalation study of brentuximab vedotin (Study SG035-0001), the MTD was defined as 1.8 mg/kg IV administered every 3 weeks. This dose and schedule was further evaluated in two pivotal phase 2 studies (Studies SG035-0003 and SG035-0004) in patients with CD30-positive hematologic malignancies.

In a phase 1 study of brentuximab vedotin (Study SGN35-011), the MTD was defined as 1.8 mg/kg IV administered concomitantly with CHP every 3 weeks.

3.2.3 Blinding

A pharmacy blind will be employed in this trial. The adverse event profile of brentuximab vedotin 1.8 mg/kg administered IV once every 3 weeks is not anticipated to be discernable from vincristine in this population of aggressive CD30-positive mature T-cell lymphomas.

Maintaining the blind of the study is crucial for achieving the study objectives. Investigators, patients, IRF, and the sponsor will be blinded to treatment assignments, unless otherwise specified in the Study Manual.

Individual treatment assignment will remain blinded even after the primary analysis is conducted. Unblinding an individual patient treatment assignment will only occur when one of the following circumstances is applicable:

1. At the time of disease progression, a patient's treatment assignment may be unblinded upon request. A formal unblinding procedure will be followed to provide the study

treatment assignment directly to the patient for the purpose of further treatment planning (see Study Manual).

2. At the time of study closure, after the primary analysis is completed, the study treatment assignment will be provided directly to the patient.

3. Unblinding a patient's treatment assignment prior to study closure or disease progression must be limited to emergency circumstances where knowledge of the treatment assignment would affect decisions regarding the management of the patient. In the event of such an emergency circumstance, a formal unblinding procedure, carried out by a third party organization, will be followed to allow the investigator to immediately access a patient's treatment assignment (see Study Manual). Information on study treatment assignment should not be distributed to any other personnel involved in the clinical trial. In the event of any emergency unblinding, Seattle Genetics is to be notified within 24 hours of the occurrence.

4 STUDY POPULATION

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 (HRA) inspection. Any questions regarding a patient's eligibility should be discussed with the sponsor's study management group prior to enrollment.

Patients must meet **ALL** of the following inclusion criteria to be eligible for this study:

4.1 Inclusion Criteria

1. Patients with newly diagnosed, CD30-positive mature T-cell lymphomas per the Revised European-American Lymphoma WHO 2008 classification by local assessment. See Section 7.1.1 for details on definition of CD30 positivity. Eligible histologies are limited to the following:

   - ALK-positive sALCL with an IPI score greater than or equal to 2
   - ALK-negative sALCL
   - PTCL-NOS
   - AITL
   - Adult T-cell leukemia/lymphoma (ATLL; acute and lymphoma types only, must be positive for human T-cell leukemia virus 1)
   - Enteropathy-associated T-cell lymphoma (EATL)
   - Hepatosplenic T-cell lymphoma

2. Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by CT, as assessed by the site radiologist.

3. Age greater than or equal to 18 years.

4. An Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.

5. The following required baseline laboratory data:
    - bilirubin ≤1.5X upper limit of normal (ULN) or ≤3X ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma
    - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3X ULN or ≤5X ULN for patients with document hepatic involvement with lymphoma
    - serum creatinine ≤2X ULN
    - absolute neutrophil count (ANC) ≥1000/μL (unless documented bone marrow involvement with lymphoma)
    - platelet count ≥50,000/μL (unless documented bone marrow involvement with lymphoma)
6. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotrophin (β-hCG) pregnancy test result within 7 days prior to the first dose of study treatment and must agree to use an effective contraception method during the study and for at least 6 months following the last dose of study drug. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.
7. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last dose of study drug.
8. Patients or their legally authorized representative must provide written informed consent.

4.2 Exclusion Criteria

1. History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years.
2. Current diagnosis of any of the following:
    - Primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. Cutaneous ALCL with extracutaneous tumor spread beyond locoregional lymph nodes is eligible (previous single-agent treatment to address cutaneous and locoregional disease is permissible)
    - Mycosis fungoides (MF), including transformed MF
3. History of progressive multifocal leukoencephalopathy (PML).
4. Cerebral/meningeal disease related to the underlying malignancy.
5. Prior treatment with brentuximab vedotin.
6. Baseline peripheral neuropathy ≥ Grade 2 (per the NCI CTCAE, Version 4.03) or patients with the demyelinating form of Charcot-Marie-Tooth syndrome.

7. 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.
8. Any active Grade 3 (per the NCI CTCAE, Version 4.03) or higher viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study treatment; any known human immunodeficiency virus (HIV) infection, hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection.
9. Current therapy with other systemic anti-neoplastic or investigational agents.
10. Females who are pregnant or breastfeeding.
11. Patients with a known hypersensitivity to any excipient contained in any of the drug formulations of study treatments.
12. Patients with known urinary outflow obstruction.

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). If a patient discontinues study treatment, every attempt should be made to follow the patient until progression, death, or administrative study closure. Final assessments will be performed before any other therapeutic intervention if possible. Additionally, any subsequent treatments should be documented on the patient's medical records and 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
- 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 until withdrawal from the study (reasons for study discontinuation listed in Section 4.3.2).

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

The study treatments to be administered are described in Table 1.

Table 1: Study treatment by study arm

Study Treatment in Each 21-Day Cycle		Experimental Arm A+CHP	Standard-of-Care Arm CHOP
Blinded Study Drug A[a]	Brentuximab vedotin 1.8 mg/kg IV on Day 1	X	
	Placebo dosing solution IV on Day 1[b]		X
Cyclophosphamide 750 mg/m^2 IV on Day 1		X	X
Doxorubicin 50 mg/m^2 IV on Day 1[c]		X	X
Prednisone 100 mg po daily on Days 1-5 (±1 day window)		X	X
Blinded Study Drug B	Vincristine 1.4 mg/m^2 (dose capped at 2 mg) IV on Day 1		X
	Placebo saline IV on Day 1[b]	X	

a Administered within 1 hour of completing treatment with other agents administered via IV
b Prepared by the site pharmacist; pharmacy blind to be maintained
c May be administered over up to 48 hours according to institutional standards

5.2 Investigational Study Drug

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.

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 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 Instructions for further information.

5.2.2 Method of Procurement

Brentuximab vedotin will be provided by the sponsor.

5.2.3 Dose and Administration

The investigational agent will be administered on Day 1 of every 21-day cycle by IV infusion given over approximately 30 minutes (see Table 1) and within 1 hour of completing treatment with other agents administered via IV. In the absence of infusion-related reactions, the infusion rate for all patients should be calculated in order to achieve a 30-minute infusion period. Investigational agent must not be administered as an IV push or bolus. Investigational agent should not be mixed with other medications.

Dosing is based on patient weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. 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.

Dose modifications of the investigational agent are described in Section 5.5.

5.2.4 Required Premedication and Postmedication

Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of study treatment. However, patients who experience a infusion-related reaction may receive subsequent infusions of study treatment with premedication as described in Section 5.2.5. Patients who experience a Grade 3 or Grade 4 infusion-related reaction may potentially continue to receive treatment 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 investigational agent. Patients should receive prophylaxis as appropriate per the institutional standards.

5.2.5 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of study treatment. 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, study treatment administration should be immediately and permanently discontinued.

5.2.6 Management of Suspected PML

Signs and symptoms of progressive multifocal leukoencephalopathy (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 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, brentuximab vedotin should be permanently discontinued.

5.2.7 Storage and Handling

In this trial, brentuximab vedotin is provided in a blinded study treatment kit, and the guidelines for the storage of this kit should be followed per the Pharmacy Manual.

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 or a duly designated person. Brentuximab vedotin does not contain preservatives; therefore, opened and reconstituted vials should be used immediately. If not used immediately, reconstituted vials and solutions must be stored no longer than 24 hours from vial reconstitution under refrigeration at 2–8°C. It is recommended that 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.

In this study, vials of brentuximab vedotin will be provided in a blinded kit, which will be labeled to meet country-specific regulatory requirements.

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 standard. 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.

For the standard-of-care arm, the pharmacy at the study site must prepare an IV bag containing only diluent (e.g., normal saline). This placebo replacement for brentuximab vedotin is to be administered in the same manner as described above and in the Pharmacy Instructions.

Detailed drug preparation instructions are provided in the Pharmacy Instructions.

5.3 Vincristine

5.3.1 Description

Vincristine is a vinca alkaloid. The mechanism of action is related to the inhibition of microtubule formation in the mitotic spindle.

5.3.2 Method of Procurement

Vincristine is commercially available and approved by the United States FDA and other regulatory agencies for use in patients with multiple types of cancer. Globally, vincristine will be supplied to study sites by the sponsor.

5.3.3 Dose and Administration

Vincristine is typically administered as an IV push (see Table 1 for dose), and will be given on Day 1 of each 21-day cycle. Dosing should be based on the patient's baseline (predose, Cycle 1 Day 1) height and weight or per institutional standards at the site.

Dose modification guidelines for vincristine are described in Section 5.5.

5.3.4 Required Premedication and Postmedication

There are no required pre- or postmedications for vincristine. Routine anti-emetic prophylaxis should be administered per institution standard.

5.3.5 Storage and Handling

In this trial, vincristine is provided in a blinded study treatment kit, and the guidelines for the storage of this kit should be followed per the Pharmacy Manual and as described in Section 5.2.7. Institutional guidelines for the handling of vincristine are to be followed.

5.3.6 Packaging and Labeling

Vials of vincristine will be labeled in a blinded kit to meet country-specific regulatory requirements.

5.3.7 Preparation

Vincristine should be prepared per institutional guidelines.

For the experimental arm, the site pharmacist will prepare a placebo replacement for vincristine (e.g., normal saline) to be administered in the same manner as vincristine.

5.4 Cyclophosphamide, Doxorubicin, and Prednisone

5.4.1 Description

All patients in the study will be administered the cyclophosphamide, doxorubicin, and prednisone components of the CHOP regimen.

Cyclophosphamide is a nitrogen mustard alkylating agent. Doxorubicin is a cytotoxic anthracycline antibiotic. Prednisone is a corticosteroid.

5.4.2 Method of Procurement

Cyclophosphamide, doxorubicin, and prednisone are commercially available and approved by the United States FDA and other regulatory agencies for use in treating patients with multiple types of cancer.

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

In Japan, cyclophosphamide and doxorubicin will be supplied by the study site. Prednisone will be supplied to study sites by the sponsor.

In regions outside of the United States, Canada, and Japan, cyclophosphamide, doxorubicin, and prednisone will be supplied to study sites by the sponsor.

5.4.3 Dose and Administration

Refer to Table 1 for specific doses. Administration of study treatment should be according to the institutional standard. Dosing should be based on the patient's baseline (predose, Cycle 1 Day 1) height and weight or per institutional standards at the site.

Dose modification guidelines for cyclophosphamide, doxorubicin, or prednisone are described in Section 5.5.

5.4.4 Required Premedication and Postmedication

There are no protocol-required pre- or postmedications for cyclophosphamide, doxorubicin, and prednisone. Routine anti-emetic prophylaxis should be administered per institution standard.

5.4.5 Packaging and Labeling

In the United States and Canada, supplies of cyclophosphamide, doxorubicin, and prednisone are commercially available. Outside of the United States and Canada, supplies will be labeled to meet country-specific regulatory requirements.

5.4.6 Preparation

Cyclophosphamide, doxorubicin, and prednisone should be prepared per institutional guidelines.

5.4.7 Storage and Handling

Cyclophosphamide, doxorubicin, and prednisone should be stored and handled per institutional guidelines.

5.5 Dose Modifications

Table 2 describes the recommended dose modifications for study treatment-associated neuropathy.

Doses reduced for treatment-related neuropathy should not be re-escalated without discussion with the sponsor.

Table 2: Recommended 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	Continue study treatment at the same dose level.	Reduce dose levels of brentuximab vedotin/vincristine[a].
3	Reduce dose levels of brentuximab vedotin/vincristine[a].	Discontinue treatment with brentuximab vedotin/vincristine.
4	Discontinue treatment with brentuximab vedotin/vincristine.	Discontinue treatment with brentuximab vedotin/vincristine.

a To maintain the study blind, dose levels of both blinded study treatments must be reduced as follows: 1.2 mg/kg brentuximab vedotin and 1 mg vincristine. No further dose reductions are permitted.

Dose modifications of blinded study treatment (brentuximab vedotin/vincristine), cyclophosphamide, doxorubicin, or prednisone due to hematologic and non-hematologic toxicity are allowed per institutional standards at the discretion of the investigator. Permitted dose modifications include discontinuation of a treatment component. For blinded study treatment, the reduced dose levels are 1.2 mg/kg brentuximab vedotin and 1 mg vincristine. No further dose reductions of brentuximab vedotin or vincristine are permitted.

5.6 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.

5.6.1 Required Concomitant Therapy

There are no required concomitant therapies.

5.6.2 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 5.2.5.

Routine infectious prophylaxis for Pneumocystis jiroveci pneumonia (PCP) should be considered for all patients.

The use of transfusions, platelet and/or colony-stimulating factors per institutional practice is permitted. 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 SCT is permitted per institution standard. Chemomobilization of stem cells is only permitted after EOT procedures are completed.

Consolidative SCT or radiotherapy 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 SCT or radiotherapy.

5.6.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy from Day 1 through EOT. In addition, other prohibited concomitant therapies should be excluded in accordance with the approved prescribing information for each agent. Exceptions are noted in Section 5.6.2.

5.7 Treatment Compliance

Study drug administration is 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. 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 (Day -28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- CD30/histological confirmation – submission of tumor specimen for central pathology confirmation of histology, CD30 expression, and ALK status (see Section 7.1.1)
- Human T-cell leukemia virus-1 (HTLV-1) status (see Section 7.1)
- IPI score (see Section 7.1)
- Hemoglobin (Hgb) A1c (see Section 7.6.2)
- CT of chest, neck, abdomen, pelvis (see Section 7.2)
- PET scan (see Section 7.2)
- Bone marrow biopsy (may be obtained within 60 days of the first dose of study treatment; see Section 7.2)
- Echocardiogram or multi-gated acquisition (MUGA) scan (may be obtained up to 6 months prior to the first dose of study treatment)

6.2.1 Baseline Visit (Day -7 to Day 1)

- Height and weight
- Electrocardiogram (ECG)
- Pregnancy test for females of childbearing potential (see Section 7.6.2)
- ECOG performance status (see Section 7.6.3)
- Serum chemistry panel (see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Randomization – to occur after eligibility is determined and within 1 business day of planned first dose of study treatment

6.3 Treatment Period (21-day cycles)

6.3.1 Every Cycle: Day 1

- Lymphoma assessment (see Section 7.2; conducted within ≤48 hours prior to study treatment in Cycle 1)
- ECOG performance status (not required in Cycle 1)
- Serum chemistry
- CBC with differential
- Patient-reported outcome (PRO) questionnaires – EQ-5D, QLQ-C30, and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-NTX; see Section 7.5)

- Medical resource utilization (MRU) data collection (see Section 7.4)
- Total Neuropathy Score-nurse (TNSn) assessment; every odd-numbered cycle only (see Section 7.6.4)
- Blood samples for pharmacokinetic (PK), pharmacodynamic (PD) assessment (see Section 7.3 for details)
- Blood sample for ATA assessment (Cycles 1-4 only; see Section 7.3 for details)
- Study treatment; administered after all assessments have been conducted

6.3.2 Cycles 1 and 2 Only: Day 3

- Blood sample for PK assessment

6.3.3 Cycle 4 Only: Day 15-21

- CT of chest, neck, abdomen, pelvis
- PET scan
- Bone marrow biopsy to confirm response (if positive at baseline)

6.3.4 Last Planned Cycle of Treatment: Day 15-21

The following assessments must be obtained for patients who complete the last planned cycle of treatment. Patients who discontinue treatment prior to the planned last cycle of treatment should have an EOT visit, as described in Section 6.4.

- Lymphoma assessment
- CT of chest, neck, abdomen, pelvis
- PET scan
- Bone marrow biopsy to confirm response (if positive at baseline and not found to be negative at a prior restage)

6.4 End-of-Treatment Visit (30-37 days after last dose of study drug)

If EOT evaluations are completed before 30 days after the last study treatment, the patient will be contacted by phone 30-37 days following the last treatment to assess for adverse events.

EOT assessments will be performed before any other therapeutic intervention, if possible.

- Pregnancy test for females of childbearing potential
- Performance status
- Serum chemistry
- CBC with differential
- Blood samples for PK, PD, and ATA assessment
- PRO questionnaires: EQ-5D, QLQ-C30, and FACT/GOG-NTX
- MRU data collection
- TNSn assessment

The following response assessments are required if they were not conducted at last cycle of treatment:

- Lymphoma assessment
- CT of chest, neck, abdomen, pelvis
- PET scan
- Bone marrow biopsy to confirm response (if positive at baseline and not found to be negative at a prior restage)

6.5 Follow-up

The following assessments are required during follow up at the time points described. Months are relative to the first dose of study treatment. Assessments are to be conducted until death or study closure unless otherwise specified. Assessments occurring after 24 months from first dose may be conducted via a phone call.

- Survival status and subsequent anticancer therapies received – every 6 months (+/-1 week up to month 30, +/-1 month after month 30) starting at month 12 and after disease progression
- TNSn assessment and FACT/GOG NTX – every 3 months (+/-1 week) month 9 through month 24 or until disease progression or initiation of new anticancer therapy; only performed for patients with treatment-emergent neuropathy (a treatment-emergent event is one that is newly occurring or worsening following study treatment; see Section 9.3.8.2)
- QLQ-C30 questionnaire – every 3 months (+/-1 week) month 9 through month 24 and at month 30, or until disease progression
- MRU data collection – every 3 months (+/-1 week) month 9 through month 24 and at month 30
- EQ-5D questionnaire – every 3 months (+/-1 week) month 9 through month 24 and every 6 months (+/-1 week) thereafter; not required at months 9, 15, and 21 for patients with disease progression

In addition, (prior to Amendment 5), patients who have not yet experienced disease progression per investigator assessment [based on the Revised Response Criteria for Malignant Lymphoma (Cheson 2007)], the following assessments must be obtained at 9, 12, 15, 18, 21, and 24 months (+/-1 week) after the first dose of study treatment, and every 6 months thereafter (+/-1 week) until progression per investigator, death, or analysis of the primary endpoint, whichever comes first.

- CT of chest, neck, abdomen, pelvis
- Lymphoma assessment

After the analysis of the primary endpoint (Amendment 5 and later), patients who have not yet experienced disease progression should continue to be scanned according to the site's

standard of care schedule. If progression occurs, it should be recorded in the CRF. Scans should not be sent to BioClinica.

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

Cardiac function will be determined by performing either an echocardiogram or MUGA scan (may be obtained up to 6 months prior to the first dose of study treatment).

HTLV-1 status must be obtained by local laboratory assessment to inform the diagnosis.

IPI score must be determined based on the International Non-Hodgkin Lymphoma Prognostic Factors Project (Shipp 1993).

7.1.1 CD30 Expression and Histologic Subtype

Histologically confirmed CD30+ disease and histologic subtype must be determined by local pathology assessment in a CD30-qualified laboratory to enable enrollment. Local pathology will also assess ALK status for patients with a diagnosis of sALCL.

By local assessment, tissue from the diagnostic biopsy must confirm CD30 positivity by immunohistochemistry. The 3 following criteria must be met to declare CD30 positivity:

1. CD30 detected in 10% or greater of neoplastic cells (in cases where enumeration of neoplastic cells is not possible, total lymphocytes may be used).
2. CD30 staining at any intensity above background.
3. Membranous, cytoplasmic, and/or golgi pattern of expression of the CD30 antigen.

Submission of the tumor block or approximately 15 unstained slides from a diagnostic biopsy is required prior to randomization for subsequent central confirmation of CD30 expression, disease subtype, and ALK status for patients with a diagnosis of sALCL. The diagnostic specimen must be from a malignant lymph node or extranodal tissue obtained by core or excisional/incisional biopsy. Cutaneous, bone, or bone marrow samples alone are unacceptable. Fine needle aspirate and cytology samples are also unacceptable.

[redacted]

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 time points 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. 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; if scans are performed at non-protocol specified time points, results will be collected in the patient's CRF and images will be submitted for central review.

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 response if bone marrow is positive at baseline; this confirmation is to be obtained within 4 weeks of documentation of response by radiographic assessment. Repeat bone marrow biopsies are not required once bone marrow is found to be negative.

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

All patients' clinical data and tumor images must be available for CRF source verification. Copies of all imaging studies must be made available for review by the sponsor (or its designee) and the third party imaging core laboratory. Refer to the Study Manual for details (instructions on collecting and submitting tumor imaging studies for third-party imaging core laboratory review).

7.3 Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments

Sensitive, qualified assays will be used to measure drug analytes including brentuximab vedotin ADC and MMAE concentrations in serum or plasma. These assays will include enzyme linked immunosorbent assays (ELISA) and liquid chromatography/tandem mass spectrometry (LC-MS/MS) assays, as well as other assays if further characterization is required.

Blood samples for PK testing will be collected at selected time points in Cycles 1 and 2 and at predose in subsequent cycles (see Table 3). ATA to brentuximab vedotin will also be measured predose at Cycles 1 through 4 and at EOT using an appropriate qualified assay.

Selected PK parameters to be estimated include concentration at 48 hours from the start of infusion, concentration at the end of infusion for brentuximab vedotin (C_{eoi}), and trough concentration (C_{trough}). PK, demographic, and clinical laboratory data may be incorporated into the brentuximab vedotin population PK model for further model refinement and parameter estimation. The incidence of ATA to brentuximab vedotin will also be assessed.

Blood samples will be collected (predose at each cycle) for measurement of PD biomarkers such as sCD30.

Table 3 presents the PK/PD and immunogenicity sample collection time points. All sampling times are relative to the start of brentuximab vedotin infusion, except for the end of infusion concentrations. Refer to the Research Specimen Manual for information on collection, processing, storage, and shipment of samples.

Table 3: Pharmacokinetic, pharmacodynamic, and immunogenicity sampling time points

Cycle	Study Day	Time	Window	Relative Time[a]	PK	PD	ATA
1-2	Day 1	Pre-dose	Within prior 24 hr	Start of infusion	X	X	X
		End of infusion (30 min)	Within 30 min post end of infusion	End of infusion	X		
	Day 3	48 hr	± 24 hr	Start of infusion	X		
3+	Day 1	Pre-dose	Within prior 24 hr	Start of infusion	X	X	X[b]
EOT					X	X	X

a Relative to infusion of Blinded Study Drug A (brentuximab vedotin or placebo replacement)
b Cycles 3 and 4 only

7.3.1 Biopsy Tissue for Exploratory Correlative Studies

Patients will be asked to participate in optional exploratory correlative studies involving tumor tissue. The tumor tissue will be used to conduct exploratory correlative studies such as CD30 expression. [redacted] These optional studies will be conducted on the following tissues:

- Leftover unstained slides or tumor tissue from the diagnostic biopsy

- Unstained slides or leftover tissue from a core biopsy obtained as part of standard-of-care clinical interventions while a patient is participating in the study (e.g., for treatment failure at any time)

No additional procedures will be conducted to obtain these research tissues, and thus no additional patient risk is introduced with these optional exploratory correlative studies.

7.3.2 Biospecimen Samples for Future Research

In the United States, remaining de-identified unused blood and tissue will be retained by Seattle Genetics and used for future research for patients who provide additional consent. [redacted] Blood and tissue samples donated for future research will be retained for a period of 25 years.

For patients treated outside of the United States, or if additional consent is not granted, any blood and tissue samples remaining after all study testing is completed will be destroyed following study closure.

[redacted]

7.4 Medical Resource Utilization Data Collection

All medical care encounters related to lymphoma, treatment for lymphoma, or lymphoma-related assessments will be collected for all patients. See Appendix A and Section 6 for timing of MRU data collection and see the Study Manual for detailed guidance.

7.5 Patient-Reported Outcomes

Questionnaires will be administered as specified in Appendix A and Section 6 and must be completed prior to administration of study treatment on treatment days. Questionnaires may be collected by phone once a patient experiences disease progression per investigator [based on the Revised Response Criteria for Malignant Lymphoma (Cheson 2007)] and is in survival follow-up.

7.5.1 EQ-5D – Utility Measurement

The European Quality of Life (EuroQOL) EQ-5D is a 5-item questionnaire with a "thermometer" visual analog scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

7.5.2 FACT/GOG-NTX

The FACT/GOG-NTX is a self-administered questionnaire for assessing changes in quality of life and assessment of treatment-induced neurologic symptoms (sensory, hearing, motor, and dysfunction). Patients score their well-being by selecting the frequency with which they

associate with a given statement (0 being “not at all”, up to 4 being “very much”). The neurotoxicity subscale consists of 11 questions.

7.5.3 QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. The QLQ-C30 incorporates 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality of life scale (Aaronson 1993).

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 IDMC as described in Section 9.3.9.

7.6.1 Adverse Events

7.6.1.1 Definitions

Adverse Event

According to the International Conference on Harmonization (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an adverse event 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 case report form (CRF):

- From the time of informed consent through the day prior to study Day 1, only study protocol-related adverse events should be recorded.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All adverse events (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 adverse events, 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 adverse event unless it is associated with clinical signs or symptoms, requires an intervention, results in a serious adverse event, or results in study termination or interruption/discontinuation of study treatment. When recording an adverse event 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 adverse event should be classified as a serious adverse event (SAE) if it meets one of the following criteria:

Fatal:	Adverse event resulted in death
Life threatening:	The adverse events placed the patient at immediate risk of death. This classification does not apply to an adverse event 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 serious adverse events 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 adverse event 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 adverse event to each study treatment [blinded study treatment (brentuximab vedotin or vincristine) or any component of CHP] should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the adverse event, such as: • 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:	Another cause of the adverse event 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 adverse event and administration of the study treatment, or a causal relationship is considered biologically implausible

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 adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of the investigational agent. 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 primary event on both the CRF and an SAE form; events occurring secondary to the primary event should be described on the SAE form in the narrative description of the case.

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: Based on the estimated date of conception, complete a Pregnancy Report Form for all pregnancies that occur from the time of informed consent to the end of the protocol-defined contraception period, including any pregnancies that occur in the partner of a male study patient. Fax the form to the sponsor's Drug Safety Department within 48 hours of becoming aware of the pregnancy. All pregnancies that occur during this time period 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: Based on the estimated date of conception, all pregnancies that occur from time of informed consent to within 30 days of last study drug dose, including any pregnancies that occur in the partner of a male study patient, 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 (blinded study treatment or any component

of CHP), 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 study treatment-related 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. 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.

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 (or designee), 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 faxed to the sponsor's Drug Safety Department at **(425) 527-4308** within 24 hours, unless otherwise instructed on the sponsor's SAE form.

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

7.6.1.5 Sponsor Safety Reporting Requirements in the United States

According to the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA draft guidance Safety Reporting Requirements for INDs and BA/BE Studies (September 2010), endpoints that assess disease-related mortality or major morbidity as well 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 FDA as individual IND safety reports.

In this study, SAEs of disease progression do not require individual IND safety reports.

These anticipated SAEs will be reviewed periodically by an Independent Data Monitoring Committee and/or Seattle Genetics Drug Safety Department. If, upon review, an SAE is occurring at a higher rate than that which would be expected for the experimental arm, then an IND safety report for the SAE will be submitted to the FDA by the sponsor.

These safety reporting requirements apply only to the process by which the sponsor reports SAEs to the FDA. Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor. In addition, the sponsor will report all SAEs to international authorities as required per local regulatory reporting requirements.

7.6.2 Clinical Laboratory Tests

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

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, uric acid, and glucose.
- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count, platelet count, and hemoglobin/hematocrit.
- Hgb A1c will be obtained at baseline.

The following laboratory assessment will be performed by local laboratories at scheduled time points (see Appendix A) during the course of the study:

- A serum or urine β-hCG pregnancy test for females of childbearing potential

7.6.3 ECOG Performance Status

ECOG performance status (see Appendix B) will be evaluated at protocol-specified time points.

7.6.4 TNSn

The Total Neuropathy Score-nurse is a tool used in the assessment of neuropathy, including an examination conducted by a healthcare professional. A composite neuropathy score is calculated which includes subjective sensory symptoms, subjective report of symptoms and amount of difficulty with daily activities, deep tendon reflexes, manual muscle testing, and pin sensibility.

7.6.5 Monitoring of Patients with Hepatitis

Carriers of chronic hepatitis C should be closely monitored for clinical and laboratory signs of active infection during study treatment.

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 PFS and response rate 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.

The QLQ-C30 is a validated questionnaire developed by the EORTC to assess the quality of life of cancer patients (Aaronson 1993). In this study, the neurotoxicity subscale of the FACT/GOG-NTX questionnaire was selected as a measure to enable assessment of the effect of neurotoxicity on patients in the study. The EQ-5D is a validated instrument for use as a measure of health outcome. These PROs have been incorporated into previous clinical trials that seek to quantify the quality of life in patients. The TNSn is a tool that will allow precise measurement of the onset, resolution, and characterization of peripheral neuropathy.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to brentuximab vedotin. Pharmacokinetic 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
- GCP 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, FDA representatives, or representatives of other regulatory agencies.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for 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 information contained in the CRFs, such as past history, secondary diagnoses, disease assessment records, adverse events, and concomitant medications. 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 the FDA or other regulatory agencies.

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.

The investigator should retain records of the changes and corrections, written and/or electronic.

Data handling procedures for this trial have been designed to permit data changes so that they are documented by an audit trail. Data changes may only be made by those individuals so authorized.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records, copies of CRFs (or electronic files), 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

Approximately 450 patients (~225 patients per treatment arm) will be randomized in this study. The target proportion of patients with a diagnosis of sALCL per central pathology assessment will be 75% (+/-5%), i.e., 338 (+/-23) patients. The sponsor will monitor the proportion of sALCL and non-sALCL patients per central pathology assessment to ensure that the enrollment targets are reached and not exceeded.

[redacted]

9.2 Study Endpoint Definitions

9.2.1 Primary Endpoint: PFS per IRF

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of first documentation of PD, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurs first. Note that receipt of post treatment radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will not be considered as disease progression or as having started new anticancer therapy. Patients without documentation of PD/relapse, subsequent anticancer therapy for residual or progressive disease, or death at the time of analysis, will be censored at the date of last radiographic disease assessment. In the absence of a PFS event, patients receiving post treatment radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will be censored at the most recent tumor assessment before the data cutoff or study withdrawal, whichever occurs first.

If PD is not documented, no subsequent anticancer chemotherapy to treat residual or progressive disease has been initiated, and the patient is alive at the time of the data cutoff or study withdrawal, PFS will be censored as follows:

If there is no radiographic postbaseline tumor assessment, PFS will be censored at the date of randomization.

If there are radiographic postbaseline tumor assessments, PFS will be censored at the most recent tumor assessment before the data cutoff or study withdrawal, whichever occurs first.

Detailed methodology, including handling rules for missing assessments and censoring approaches for the analysis of PFS, is provided in the Statistical Analysis Plan (SAP).

9.2.2 Secondary Efficacy Endpoints

9.2.2.1 PFS per IRF in Patients with sALCL

PFS per IRF in patients with sALCL is defined in the same manner as the primary endpoint of PFS per IRF. For this endpoint, PFS per IRF will be analyzed in the subset of patients with a central pathology confirmed diagnosis of sALCL

9.2.2.2 Complete Remission (CR) Rate per IRF

Complete remission (CR) rate is defined as the proportion of patients with CR at the end of treatment per IRF according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Patients whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate.

9.2.2.3 Overall Survival

Overall survival (OS) is defined as the time from randomization to death due to any cause. Specifically,

OS = Date of death – Date of randomization + 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 will have their survival time censored on the date of randomization (i.e., OS duration of 1 day).

9.2.2.4 Objective Response Rate per IRF

ORR per IRF is defined as the proportion of patients with CR or partial remission (PR) per IRF following the completion of study treatment (at EOT) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Patients whose disease response cannot be assessed will be scored as non-responders for calculating the ORR.

9.2.3 Additional Endpoints

9.2.3.1 Incidence of ATA

The ATA incidence rate is defined as the proportion of patients that develop ATA at any time during the study.

9.2.3.2 Medical Resource Utilization

Medical resource utilization data include medical care encounters (e.g., hospital admissions or major diagnostic procedures) related to study treatment or treatment for lymphoma.

9.2.3.3 Quality of Life

Changes in quality of life will be measured based on PROs according to the QLQ-C30, FACT/GOG-NTX subscale, and EQ-5D.

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 was finalized prior to first patient visit. 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

9.3.1.1 Randomization and Blinding

This is a randomized, double-blind, placebo controlled comparative study that will enroll approximately 450 patients. Patients will be randomized in a 1:1 manner to receive either CHOP or brentuximab vedotin plus CHP. Brentuximab vedotin or vincristine will be administered as a placebo-controlled double-dummy and provided to sites in a blinded manner.

Randomization will be performed centrally using a system that will assign a unique patient randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the Study Manual.

9.3.1.2 Adjustments for Covariates

This is a phase 3 study. Stratified analyses will include adjustment for the stratification factors as recorded at randomization (described in Section 9.3.1.1). Covariates may be considered for adjustment in exploratory regression 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 (see Sections 9.2.1 and 9.2.2.3).

9.3.1.4 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

[redacted]

9.3.1.6 Data Transformations and Derivations

The date of progression will be the earliest of all radiologic scan dates for the given disease assessment. No other data transformation is planned for the primary or secondary efficacy endpoints.

9.3.1.7 Analysis Sets

Intent-to-Treat (ITT) Analysis Set: The ITT analysis set will include all randomized patients. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.

Safety Set: The safety analysis set will include all patients who receive any amount of brentuximab vedotin or any component of CHOP. Treatment group will be determined using the actual treatment received, regardless of the randomization treatment assignment. Patients receiving any dose of brentuximab vedotin will be grouped into the experimental group. Patients who do not receive brentuximab vedotin but receive any dose of any component of CHOP will be grouped into the standard-of-care group.

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.

[redacted]

[redacted]

9.3.2 Patient Disposition

An accounting of study patients by disposition will be tabulated by treatment group. The number of patients in each analysis population will be summarized by treatment group. Patients who discontinue study treatment and patients who withdraw from the study will be summarized by treatment and reason for discontinuation or withdrawal and listed.

9.3.3 Patient Characteristics

Demographics, other baseline characteristics, and concomitant medications will be summarized by treatment group and listed.

9.3.4 Treatment Compliance

The dose administered at each cycle for each treatment agent 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

Kaplan-Meier methods will be used to assess PFS. The stratified log-rank test without adjustments for covariates will be used in the primary evaluation of PFS differences between the experimental arm and the standard-of-care arm in the ITT analysis set using a one-sided, $\alpha = 0.025$ level test. All events entered in the database at the time of analysis that have been source data-verified will be included in the analysis of PFS, even if there are more than the prespecified number of events.

Kaplan-Meier Curves depicting PFS in the 2 arms will be generated. Additionally, median PFS and probability of PFS from 3 months to the end of the follow-up period will be reported at 3-month intervals. The two-sided 95% confidence intervals (CI) for the median and 3-month intervals will be calculated using the complementary log-log transformation method (Collett 1994). Detailed methodology is provided in the SAP.

9.3.5.2 Secondary Efficacy Analyses

ORR and CR rate will be summarized by treatment group using the ITT analysis set. An exact two-sided 95% confidence interval using the Clopper-Pearson method (Clopper 1934) will be calculated.

OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by treatment group using the ITT analysis set. The median OS and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated by treatment group.

9.3.6 Pharmacokinetic and Pharmacodynamic Analyses

Antibody drug-conjugate (brentuximab vedotin) and unconjugated drug (MMAE) levels in serum or plasma will be summarized with descriptive statistics at each PK sampling time point. Any additional PK and PK/PD analyses may be described in a separate analysis plan and presented in a separate report.

9.3.7 Health Outcomes Analyses

EQ-5D scores and MRU data will be summarized using descriptive statistics by treatment group.

Quality of life total and subscale scores will be summarized with descriptive statistics by treatment group and visit using the ITT analysis set. In addition, change from baseline will be tabulated by treatment group and visit. Descriptive summaries of individual items may also be presented.

Additional statistical modeling for MRU and PRO measures may be performed separately in post hoc analyses.

9.3.8 Safety Analyses

9.3.8.1 Extent of Exposure

Duration of treatment, number of cycles, total dose and dose intensity will be summarized by treatment arm using the safety analysis set. Dose modifications will also be summarized.

Details will be provided in the SAP.

9.3.8.2 Adverse Events

Adverse events will be defined as treatment emergent if they are newly occurring or worsen following treatment with brentuximab vedotin, cyclophosphamide, doxorubicin, vincristine, or prednisone. The incidence of all AEs, treatment-emergent AEs, and treatment-related AEs will be tabulated by treatment group using the safety analysis set. 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 treatment group, MedDRA preferred term, severity, and relationship to study drug using the safety analysis set. 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 treatment group. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner.

9.3.8.3 Deaths and Serious Adverse Events

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

9.3.8.4 Clinical Laboratory Results

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by treatment group and scheduled visit using the safety analysis set. Patients with laboratory values outside of the normal reference range at any postbaseline assessment will be listed by treatment group.

9.3.9 Interim Analysis

An Independent Data Monitoring Committee (IDMC) will periodically monitor the trial for safety and will review expedited SAEs as they arise.

[redacted]

The IDMC conduct of ongoing safety reviews [redacted] will be documented in the IDMC Charter.

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 (e.g. 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 federal, state, and local laws, rules, and regulations.

All data recorded in the CRF for patients participating in this study will be transcribed from medical records or other source documents.

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

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator until notified by the sponsor in writing that retention is no longer necessary.

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 the requirements of the Health Information Portability and Accountability Act (HIPAA) Privacy Rule 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, case report forms 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: STUDY SCHEDULE

		Baseline/Screening		Enrollment	Cycle 1	Cycles 2+	Cycle 4 only	Last planned cycle of tx	EOT visit	Long-term F/U						
										Months after first dose						
										9	12	15	18	21	24	>24
Visit Window		D-28 to 1	D-7 to 1	D-7 to 1	D1	D1±1	Day 15-21	Day 15-21	30-37 days post last dose[f]	±1 wk						Every 6 mos ±1 wk
Screening/ Baseline Assessments	Informed consent	X		Eligibility documentation submitted to sponsor prior to study start; randomization[j]												
	Inclusion/exclusion	X														
	Medical history	X														
	CD30/histology[a]	X														
	HTLV-1 status	X														
	Hgb A1c	X														
	IPI score	X														
	Echocardiogram or MUGA scan	X[o]														
	Height & weight		X													
	Electrocardiogram		X													
	Pregnancy test		X						X							
Treatment	Study treatment administration				X	X										
ATA/PK/PD	Samples for ATA/PK/PD				See Section 7.3											
Response Assessment	Lymphoma assessment[b]				X[l]	X		X	X[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
	CT (chest, neck, abdomen, pelvis)	X					X	X	X[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
	PET[c]	X					X	X	X[f]							
	Bone marrow biopsy	X[d]					X[e]	X[e]	X[e,f]							
	Survival status										X[h]		X[h]		X[h]	X[h]
Safety Assessments	ECOG performance status		X			X			X							
	Serum chemistry		X		X	X			X							
	CBC with differential		X		X	X			X							
	Con meds & AEs	Collect any related to study protocol procedures			Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later											
	TNSn assessment				X	X[m]			X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
PRO/MRU	QLQ-C30				X	X			X	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]
	Medical Resource Utilization				X	X			X	X	X	X	X	X	X	X (30 mo post first dose only)
	FACT/GOG-NTX subscale				X	X			X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
	EQ-5D				X	X			X	X[p]	X	X[p]	X	X[p]	X	X[k]

a Locally assessed to enable enrollment (see Section 7.1.1 for definition of CD30-positivity); tumor specimen must be submitted for central pathology review before randomization to confirm histology (and ALK status, if applicable) and CD30 expression

b Consists of the following: physical examination, patient medical history, including a thorough review of the patient's current signs and symptoms, B symptoms, and concomitant medications. See Section 7.2

c A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as a diagnostic quality CT scan is obtained; PET scans may also be obtained any time during the study if clinically indicated

d Obtained within 60 days of first dose of study treatment

e Bone marrow biopsy is required to confirm response if bone marrow is positive at baseline and should be obtained within 4 weeks after documentation of response; does not need to be repeated once bone marrow is negative

f Response assessments at EOT required if not performed at last cycle of treatment. EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30-37 days following the patient's last study treatment to ensure that no changes in AE profile have occurred

g After 24 months following the first dose of study drug, required every 6 months. Obtain until patient experiences PD per investigator assessment, death, or analysis of the primary endpoint, whichever comes first

h Once a patient experiences PD per investigator assessment, survival status is required every 6 months until death or study closure, whichever comes first. After 30 months, the window for the assessment is ±1 month. Collect information regarding subsequent anticancer therapies

i Collect until patient experiences PD per investigator assessment or 30 months post first dose of study treatment, whichever comes first

j Randomization to occur after eligibility is determined and within 1 business day of planned first dose of study treatment

k Required every 6 months until death or study closure, whichever comes first

l Within ≤48 hours prior to study treatment

m Every odd-numbered cycle only

n Only for patients with treatment-emergent peripheral neuropathy; collect until patient experiences PD per investigator, initiates a subsequent anticancer therapy, or until 24 months post first dose, whichever comes first

o May be obtained up to 6 months prior to first dose of study treatment

p Not required if patient has experienced PD per investigator assessment

APPENDIX B: 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 C: INTERNATIONAL PROGNOSTIC INDEX FOR NHL

Score

	Score	
Risk Factor	0 point	1 point
Age	≤60 years	>60 years
Serum LDH	≤1 x ULN	>1 x ULN
ECOG Performance Status	0 or 1	2, 3, or 4
Stage	I or II	III or IV
Extranodal Involvement	≤1 site	>1 site

LDH = lactate dehydrogenase
ECOG = Eastern Cooperative Oncology Group
ULN = upper limit of normal

Risk Category

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

Based on The International Non-Hodgkin's Lymphoma Prognostic Factors Project (Shipp 1993)

APPENDIX D: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "A randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas".

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	28-Jun-2012
Amendment 1	27-Sep-2012
Amendment 2	31-Jan-2013
Amendment 3	05-Mar-2015
Amendment 4	15-May-2018
Amendment 5	12-Dec-2018

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Title page, Synopsis, Appendix D	Removed mention of ARROVEN from the protocol title.	Sponsor decision to remove ARROVEN as the study identifier.
Synopsis, 4.2	Added known human immunodeficiency virus infection, hepatitis B surface antigen-positive status, and known or suspected active hepatitis C infection to the exclusion criteria.	Additional safety precaution
[redacted]	[redacted]	[redacted]
Synopsis, 9.3.9	The IDMC will review, but not conduct the interim analysis for futility "The IDMC conduct of ongoing safety reviews and review of the planned interim analysis for futility will be documented in the IDMC Charter."	Clarification.
5.2.9	Removed listing of infusion bags that have no known incompatibilities with brentuximab vedotin: "~~There are no known incompatibilities between brentuximab vedotin and polyvinylchloride (PVC) ethylene vinyl acetate (EVA), polyolefin, or polyethylene bags.~~"	This information will be provided in the Pharmacy Instructions.
6.2, 7.1, Appendix A	Added echocardiogram or MUGA scan up to 6 months prior to the first dose of study treatment to the screening assessment.	Specific screening assessment required to assess left ventricular ejection fraction for exclusion criterion 7 in Section 4.2.
6.4, Appendix A	Response assessment at EOT is not required if assessment was conducted at last cycle of treatment. "The following response assessments are required if they were not conducted ~~within 4 weeks prior to EOT~~ at last cycle of treatment: • CT of chest, neck, abdomen, pelvis • PET scan • Bone marrow biopsy to confirm response (if positive at baseline and not found to be negative at a prior restage)"	To allow for more flexibility in response assessment.
[redacted]	[redacted]	[redacted]

Section(s)	Change	Rationale
	[redacted]	
7.6.1.2	Pregnancy Report Forms should be completed for all pregnancies that occur from the time of informed consent to the end of the protocol-defined contraception period (ie, 30 days for female patients and 6 months for female partners of male patients). ~~"Complete~~ Notification to Drug Safety: Based on the estimated date of conception, complete a Pregnancy Report Form ~~and fax~~ for all pregnancies that occur from the time of informed consent to the end of the protocol-defined contraception period, including any pregnancies that occur in the partner of a male study patient. Fax the form to the sponsor's Drug Safety Department ~~(or sponsor's designee as specified on form)~~ within 48 hours of becoming aware of ~~a~~ the pregnancy. ~~On~~ All pregnancies that occur during this time period will be monitored for the ~~Adverse Events~~ full duration; all perinatal and ~~Pre-Existing Conditions CRF, record~~ neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks. Collection of data: Based on the estimated date of conception, all pregnancies that occur from time of informed consent to within 30 days of last study drug dose ~~(i.e., based on the estimated date of conception),~~ including any pregnancies that occur in the partner of a male study patient~~.~~, 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. ~~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."~~	To align the required submission of Pregnancy Report Forms with the protocol-defined contraception period.
7.6.5	Due to the addition of hepatitis B surface antigen-positive status as an exclusion criterion, monitoring of hepatitis B carriers is no longer relevant. As only patients with known or suspected active hepatitis C infection are excluded, carriers of chronic hepatitis C should still be closely monitored. "Carriers of ~~hepatitis B and~~ chronic hepatitis C should be closely monitored for clinical and laboratory signs of active infection during study treatment."	Clarification.

Section(s)	Change	Rationale
Schedule of Events	EQ-5D assessments at months 9, 15, and 21 of long-term follow up are not required if patient has experience progressive disease per investigator assessment	Clarification

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Title Page	Added study name, ECHELON-2	Study has been given the name ECHELON-2
Synopsis, 2.2	Changed secondary objective to refer to remission rates rather than CR: To compare the ~~complete~~ remission ~~(CR) rate~~ rates per IRF following the completion of study treatment between the 2 treatment arms	To pre-specify the analysis of both the complete remission rate and objective response rate per IRF
Synopsis, 4.1	Added the following additional baseline laboratory inclusion criteria: • absolute neutrophil count (ANC) ≥1000/µL (unless documented bone marrow involvement with lymphoma) • platelet count ≥50,000/µL (unless documented bone marrow involvement with lymphoma)	Additional safety precaution to address a doxorubicin contraindication for myelosuppression
Synopsis, 4.1	Female contraception period increased from 30 days to at least 6 months following the last dose of study drug	Additional safety precaution
Synopsis, 4.2	Excluded patients with the demyelinating form of Charcot-Marie-Tooth syndrome	Additional safety precaution to address a vincristine contraindication
Synopsis, 4.2	Excluded patients who have had previous treatment with complete cumulative doses of doxorubicin or other anthracyclines	Additional safety precaution to address a doxorubicin contraindication
Synopsis, 4.2	Excluded patients with known urinary outflow obstruction	Additional safety precaution to address a cyclophosphamide contraindication
Synopsis, 2.4.2	Added new secondary endpoint: Objective response rate (ORR) per IRF following the completion of study treatment	Additional secondary endpoint related to the modified secondary objective
Synopsis, 9.3.1.9	Added estimated duration of study through final primary analysis and through final analysis of OS	To provide greater clarity regarding the estimated duration of the study
1.2, 11	Updated NCCN non-Hodgkin lymphoma guidelines to version 1.2013	To reference current NCCN guideline document
5.2.9	Brentuximab vedotin should be reconstituted with the appropriate amount of Sterile Water for Injection, United States Pharmacopeia (USP), or equivalent standard.	To allow for equivalent standards of sterile water for injection in regions outside the United States
5.4.2	Specified that in Japan, cyclophosphamide and doxorubicin will be supplied by the study site and prednisone will be supplied by the sponsor	Clarification
5.6.3	Specified that concomitant therapies should be excluded in accordance with approved prescribing information for each agent	Additional safety precaution

Section(s)	Change	Rationale
7.1.1	Submission of the tumor block or approximately 15 unstained slides from a diagnostic biopsy is required prior to randomization for subsequent central confirmation of CD30 expression, disease subtype, and ALK status for patients with a diagnosis of sALCL. The diagnostic specimen must be from a malignant lymph node or extranodal tissue obtained by core or excisional/incisional biopsy. Cutaneous samples alone are unacceptable. Fine needle aspirate and cytology samples are also unacceptable.	Clarification
7.3	Specified that blood samples for PK testing will be collected at selected time points in Cycles 1 and 2 and at predose in subsequent cycles	Clarification
7.3	ATA to brentuximab vedotin will be measured predose at Cycles 1 through 4 and at EOT.	Clarification
7.6.1.3	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~~.	Additional safety precaution
9.2.1	~~If death or PD occurs after 2 or more consecutively missed radiographic tumor assessments, censoring will be as above, where the most recent tumor assessment is the last radiologic tumor assessment prior to the missed assessments.~~ Detailed methodology ~~is~~, including handling rules for missing assessments and censoring approaches for the analysis of PFS, is provided in the Statistical Analysis Plan (SAP). ~~Details of differing censoring approaches are also presented in the SAP.~~	Handling rules for missed events and censoring approaches will be provided in the SAP
9.2.2.4	Added definition of ORR per IRF endpoint	To characterize the new secondary endpoint
9.3	Specified that the SAP was finalized prior to first patient visit	Clarification
9.3.1.5	Added the key secondary endpoint, ORR per IRF, to the analysis plan in fourth position after PFS per IRF in patients with sALCL, CR rate per IRF, and OS	Addition of ORR per IRF to analysis plan
9.3.5.2	~~Complete response~~ ORR and CR rate will be summarized by treatment group using the ITT analysis set. An exact two-sided 95% confidence interval using the Clopper-Pearson method (Clopper 1934) will be calculated.	Clarification that ORR will also be summarized in the secondary efficacy analyses
Schedule of Events	Specified that the TNSn assessment will also be performed during odd-numbered cycles from cycle 2 onwards	Clarification
Schedule of Events	Removed footnote ‘d’ from Cycle 2 (Day 1 ±1) that specified “Obtained within 60 days of first dose of study treatment”	Correction

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Title Page	Name and contact information for previous medical monitor replaced with those of the current medical monitor	Administrative change
Synopsis, 3.1, 9.1, 9.3.1.1	Approximately ~~300~~450 patients (~~150~~225 patients per treatment arm) will be randomized in this study. The target proportion of patients with a diagnosis of sALCL per central pathology assessment will be 75% (+/-5%), i.e., ~~225~~338 (+/- ~~15~~23) patients.	Enrollment increase [redacted] and to increase the likelihood of observing the specified number of PFS events for the final analysis of the primary study endpoint; the 75% (+/-5%) sALCL cap will be maintained
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
6.4, Schedule of Events	Specified that the end-of-treatment lymphoma assessment is required if not conducted at last cycle of treatment	In response to investigator requests—this is to permit the lymphoma assessment to be conducted at either the last cycle of treatment or the end-of-treatment visit
6.5	Specified that MRU data collection should continue following progression through 30 months after the first dose of study treatment	Clarification
7.1.1	Cutaneous, bone, or bone marrow samples alone are unacceptable.	To clarify acceptable diagnostic biopsy tissue in response to site feedback [redacted]
7.4	All medical care encounters related to lymphoma, treatment for lymphoma, ~~including study treatment,~~ or lymphoma-related assessments will be collected for all patients. ~~Each time an AE or unscheduled physician visit occurs (directly related to a patient's participation in the study), MRU data will be captured. Examples of data to be collected are number of medical care encounters, such as hospital admissions or major diagnostic procedures.~~ See Appendix A and Section 6 for timing of MRU data collection and see the Study Manual for detailed guidance.	In a response to site feedback, information regarding MRU data collection has been clarified and a reference to the Study Manual has been added

Section(s)	Change	Rationale
9.2.1	If there is no radiographic postbaseline tumor assessment, PFS will be censored at ~~Study Day 1~~ the date of randomization.	Clarification
Schedule of Events	Removed footnote that indicated that QLQ-C30 should only be collected at EOT if patient has not experienced disease progression	Correction

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
9.2.1	Progression-free survival (PFS) is defined as the time from the date of randomization to the date of first documentation of PD, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurs first. Note that receipt of post treatment radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will not be considered as disease progression or as having started new anticancer therapy. Patients without documentation of PD/relapse, subsequent anticancer therapy for residual or progressive disease, or death at the time of analysis, will be censored at the date of last radiographic disease assessment. In the absence of a PFS event, patients receiving post treatment radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will be censored at the most recent tumor assessment before the data cutoff or study withdrawal, whichever occurs first. If PD is not documented, no subsequent anticancer chemotherapy to treat residual or progressive disease has been initiated, and the patient is alive at the time of the data cutoff or study withdrawal, ~~whichever occurs first~~, PFS will be censored as follows:	Clarification
[redacted]	[redacted]	[redacted]

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Synopsis	[redacted] The IDMC will provide recommendations to the sponsor~~'s Steering Committee~~ as to appropriate study direction.	Correction. Recommendations were to be provided to the sponsor, not the sponsor's Steering Committee.
6.5	Reorganized section for clarity. Specified that patients who have not progressed by the time of the primary analysis should get scanned per standard of care. Corrected inconsistencies with Appendix A.	Clarify assessments for the long-term follow up period, including assessments for patients who have not progressed by the time of the primary analysis
6.5 and Appendix A	Changed the window for survival assessments to ± 1 month after 30 months from first dose	To provide additional flexibility