Protocol Number:	SGN35-025
Version:	Amendment 4; 23 Jan 2017
Protocol Title:	A phase 1/2 study evaluating brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma after failure of frontline therapy
Investigational Drug:	Brentuximab vedotin; nivolumab
Phase:	1/2
IND Number:	126289
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PROTOCOL SYNOPSIS

Protocol Number SGN35-025 **Version** Amendment 4; 23 Jan 2017 **Phase** 1/2	**Product Name** Brentuximab vedotin; nivolumab **Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A phase 1/2 study evaluating brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma after failure of frontline therapy

Study Objectives

Primary:

- To assess the safety profile of brentuximab vedotin administered in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma (HL)
- To assess the antitumor activity of brentuximab vedotin administered in combination with nivolumab in patients with relapsed or refractory HL

Secondary:

- To assess the objective response rate (ORR)
- To assess the duration of complete response (CR) and objective response (OR)
- To assess progression-free survival (PFS) after autologous stem cell transplant (ASCT)

Additional:

- To assess overall survival (OS)
- To compare the CR rate in patients who relapsed after frontline therapy with the CR rate in patients who were refractory to frontline therapy
- To assess the feasibility of stem cell mobilization and collection after treatment with brentuximab vedotin in combination with nivolumab
- To assess PFS
- To assess pharmacokinetics and incidence of antitherapeutic antibodies (ATA) against each study drug given in combination
- To assess tumor amplification and expression of programmed death-ligand 1/programmed death-ligand 2 (PD-L1/PD-L2) and relationship to response
- To assess tumor microenvironment and peripheral immune status
- To compare safety and efficacy of treatment with staggered versus same-day dosing schemes
- To compare biomarker data obtained with staggered versus same-day dosing schemes
- To explore efficacy in patients who previously received brentuximab vedotin

Study Population

Key eligibility criteria include adult (aged ≥18 years) patients with relapsed or refractory HL following failure of standard frontline chemotherapy for the treatment of classical HL. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and qualifying baseline laboratory data. Patients are excluded if they were previously treated with immuno-oncology agents or previously received an autologous or allogeneic stem cell transplant. Patients with documented history of a cerebral vascular event, history of another invasive malignancy that has not been in remission for at least 3 years, or history of progressive multifocal leukoencephalopathy (PML) are also excluded. There will be 3 parts in this study; each part will be enrolled sequentially. For Parts 1 and 2, patients previously treated with brentuximab vedotin are

excluded; for Part 3, patients who were treated with brentuximab vedotin are eligible under the following conditions: 1) patient's HL was not primary refractory to a brentuximab vedotin-containing regimen in first line, i.e., patient achieved a CR to a brentuximab vedotin-containing regimen and did not progress within 3 months of the last dose of brentuximab vedotin; and 2) brentuximab vedotin was not discontinued due to unacceptable toxicity.

Number of Planned Patients

Approximately 92 patients will be enrolled in this study.

Study Design

This is a phase 1/2, open-label, multicenter study designed to evaluate the safety and antitumor activity of brentuximab vedotin treatment combined with nivolumab.

Patients will be treated for up to four 21-day cycles. In Parts 1 and 2, the first dose of brentuximab vedotin 1.8 mg/kg will be given on Cycle 1 Day 1. The first dose of nivolumab 3 mg/kg will be given on Cycle 1 Day 8. For Cycle 2 and all subsequent cycles, brentuximab vedotin 1.8 mg/kg followed by nivolumab 3 mg/kg will be given on Day 1. In Part 3, both brentuximab vedotin 1.8 mg/kg and nivolumab 3 mg/kg will be administered on Day 1 of all Cycles. For patients in Part 3 who were previously treated with brentuximab vedotin and had a dose reduction, dose assignment must be discussed with the medical monitor.

Patients in Parts 1 and 2 with radiographic evidence of progressive disease (PD) at the Cycle 2 response assessment are not eligible for further treatment on the study. All other patients are eligible to continue treatment on study through Cycle 4. After completion of the end-of-treatment (EOT) response assessments, patients are eligible to undergo ASCT. It is recommended that hematopoietic stem cells (HSC) be mobilized and collected after Cycle 4. However, stem cell collection may occur in prior cycles after discussion with the medical monitor. If patients have an unacceptable toxicity that is attributable to only one agent, as determined by the investigator, they will be eligible to continue on the treatment protocol through Cycle 4 with the tolerated drug as a single agent.

Patients in Part 3 with confirmed, unequivocal PD at the Cycle 2 response assessment are not eligible for further treatment and will proceed to the EOT visit. Patients with stable disease (SD) or better at the Cycle 2 response assessment may continue on treatment through Cycle 4. Patients with an indeterminate response (IR), as defined by the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC; Appendix D) (Cheson 2016), also may continue on treatment through Cycle 4. After completion of the EOT response assessment, patients are eligible to undergo ASCT. It is recommended that HSC be mobilized and collected after Cycle 4. However, stem cell collection may occur in prior cycles after discussion with the medical monitor. If patients have an unacceptable toxicity that is attributable to only one agent, as determined by the investigator, they will be eligible to continue on the treatment protocol through Cycle 4 with the tolerated drug as a single agent.

The safety of combination treatment in Part 1 will be evaluated by a Safety Monitoring Committee (SMC) prior to expansion of enrollment in Part 2 to evaluate treatment effect. In Part 1, after 6 patients have been followed through the end of the dose-limiting toxicity (DLT) period, or at the point that 2 or more patients experience a DLT, whichever comes first, the SMC will review all available data and make a recommendation for one of the following:

1. To proceed to Part 2 of the study, expanding enrollment with additional patients treated with the study drugs at the doses and schedule determined to be safe in Part 1 of the study;

2. To repeat Part 1 of the study and treat up to 6 additional patients at the same drug doses and schedule previously tested or with any of the following modifications that may include, but are not limited to:

    a. Dose reduction of brentuximab vedotin to 1.2 mg/kg and/or nivolumab to 1 mg/kg; of note, doses may not be increased above 1.8 mg/kg brentuximab vedotin or 3 mg/kg nivolumab

    b. Administration of combination treatment on Day 1 of every cycle

3. To close the study to additional enrollment.

For the purpose of this study, DLTs are defined as any study drug-related toxicity (brentuximab vedotin or nivolumab) that requires either a dose reduction or delay of more than 7 days of either study drug in Cycle 2 or delays the Cycle 3 Day 1 administration of combined treatment by more than 7 days. The DLT-evaluation period consists of the first cycle of therapy through the Cycle 3 Day 1 administration of combined treatment.

Part 2 of the study will further characterize safety and evaluate the antitumor activity of brentuximab vedotin combined with nivolumab in patients who have failed standard frontline chemotherapy by enrolling approximately 50 additional patients at the recommended dose schedule determined in Part 1.

Part 3 of the study will further characterize safety and efficacy of the study drug combination administered as same-day dosing in all cycles by enrolling approximately 30 additional patients with relapsed or refractory HL at the recommended doses as followed in Part 2.

Test Product, Dose, and Mode of Administration

Brentuximab vedotin

Parts 1, 2, and 3: 1.8 mg/kg or 1.2 mg/kg will be administered every 3 weeks via outpatient intravenous (IV) infusion on Day 1 of each cycle, as determined by the SMC in Part 1.

Nivolumab

Parts 1 and 2 (Staggered Dosing): 3 mg/kg or 1 mg/kg will be administered every 3 weeks via outpatient IV infusion on Day 8 of Cycle 1 and Day 1 of each subsequent cycle or on Day 1 of each cycle, as determined by the SMC in Part 1.

Part 3 (Same-day Dosing): 3 mg/kg will be administered every 3 weeks via outpatient IV infusion following each brentuximab vedotin dose on Day 1 of all treatment cycles.

Duration of Treatment

Planned treatment duration is 4 cycles (12 weeks).

Efficacy Assessments

Lymphoma response and progression will be assessed by investigators using the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014). Dedicated CT scans of chest, neck, abdomen, and pelvis will be conducted at Cycle 2 response assessments. CT and PET scans will be performed at baseline, at EOT, prior to ASCT, and during long-term follow-up. PET will be performed with CT scans until the patient is in complete metabolic response (CmR) by PET. For patients in Part 3, investigators will conduct response assessments using the Lugano criteria with the incorporation of the Lymphoma Response to Immunomodulatory Therapy Criteria (Cheson 2016).

Cycle-2 CT scans of diagnostic quality will be performed 15 to 21 days after dosing to assess for progression of disease. The window for performing CT/PET scans at the EOT assessment for patients in Parts 1 and 2 is 23 to 37 days post last dose of study drug, but for patients in Part 3, the window for performing CT/PET scans at the EOT assessment is 15 to 30 days post last dose of study drug. Pre-ASCT scans may be waived for patients who have a scan performed within 6 weeks prior. Long-term follow-up assessments will be performed at the following timepoints post-ASCT (or post-EOT for patients who do not undergo ASCT): 100 days and then 6, 9, 12, 18, 24, 30, and 36 months, and then per institutional standard thereafter. A final safety visit will be performed 100 days after the last dose of nivolumab and after the EOT visit to assess for potential immune-mediated adverse events (AEs). Patients will be followed according to this schedule until withdrawal of consent, death, or study closure, whichever occurs first.

Pharmacokinetic and Immunogenicity Assessments

Serum concentrations of brentuximab vedotin and nivolumab, and plasma concentrations of MMAE (unconjugated) will be measured. ATA against brentuximab vedotin and ATA against nivolumab will also be assessed.

Biomarker Assessments

Blood and tumor samples will be collected for measurement of potential biomarkers.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, physical examination findings, pulse oximetry tests, and laboratory tests.

Statistical Methods

Safety and efficacy analyses will be summarized with descriptive statistics. Frequencies and percentages will be used when presenting categorical variables. The primary efficacy endpoint of CR rate will be tested using a one-sided exact binomial test with a null hypothesis of CR rate less than or equal to 30% and α=0.05.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibody
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
β-hCG	beta human chorionic gonadotropin
C_{eoi}	concentration at the end of infusion
C_{max}	maximum concentration
C_{trough}	trough concentration
CBC	complete blood count
CI	confidence interval
CmR	complete metabolic response
CMV	cytomegalovirus
con meds	concomitant medications
CR	complete response
CRF	case report form
CT	computed tomography
DILI	drug-induced liver injury
DLCO	diffusing capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	good clinical practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HRS	Hodgkin Reed-Sternberg
HSC	hematopoietic stem cells
ICH	International Council for Harmonisation
IEC	independent ethics committee
IHC	immunohistochemical
IND	Investigational New Drug
INN	International Nonproprietary Name
IR	indeterminate response
IRB	institutional review board
IV	intravenous
JAK2	Janus kinase 2
LFT	liver function test
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria

MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1/PD-L2	programmed death ligand 1/programmed death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PmD	progressive metabolic disease
PML	progressive multifocal leukoencephalopathy
PR	partial response
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMC	Safety Monitoring Committee
SPD	sum of the products of the largest diameter
TCR	T cell receptor
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USAN	United States adopted name

1 INTRODUCTION

1.1 Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a neoplasm of lymphoid tissue that is histopathologically defined by the presence of malignant Hodgkin Reed-Sternberg (HRS) cells in a background of inflammatory cells. Advances in the use of combined chemotherapy and radiotherapy in HL over the past half century have resulted in a durable remission rate of approximately 70% (Connors 2005). However, these multi-agent regimens are associated with significant morbidity, including secondary malignancies, cardiac disease, pulmonary disease, and infertility (Loge 1999) (Swerdlow 2000). Furthermore, approximately 30–40% of patients presenting with HL will become refractory to initial therapy or will relapse.

1.2 Molecular Targets in the Treatment of Hodgkin Lymphoma

CD30, a cell membrane protein of the tumor necrosis receptor family, is uniformly expressed on HRS cells. However, normal expression of CD30 is restricted to a relatively small population of activated T cells and B cells, making it an excellent surface protein to target with antibody-directed therapy (Falini 1995).

The programmed death-1 (PD-1) cell surface membrane receptor is a member of the CD28 family of T cell co-stimulatory receptors (Pardoll 2003). PD-1 signaling has been shown to inhibit T cell activation, and expansion of previously activated cells. Experimental results suggest that PD-1 blockade has the potential to activate anti-self T cell responses, but these responses are variable and dependent upon various host genetic factors (Sharpe 2007). There is growing evidence that HRS cell-directed PD-1 signaling in tumor infiltrating T cells contributes to the tumor's ability to avoid clearance by the immune system. The PD-1 ligands, PD-L1 and PD-L2, are both expressed by multiple HL cell lines and PD-1 overexpression is found in tumor-infiltrating and peripheral blood T cells of patients with HL (Yamamoto 2008). PD-L1 expression in clinical samples, as detected by immunohistochemical (IHC) staining, is present in more than 80% of cases of HL, with similar rates of expression in all HL pathological subtypes (Chen 2013). There are multiple mechanisms that can account for upregulated expression of PD-L1 and PD-L2 in HRS cells. Many cases of HL are associated with amplification of chromosome 9p24.1 which contains the genes PD-L1, PD-L2, and Janus kinase 2 (JAK2). An increase in JAK2 copy number indirectly contributes to PD ligand overexpression through STAT1 (signal transducer and activator of transcription 1)-mediated transcriptional effects on PD-L1 and PD-L2 (Green 2010). Furthermore, Epstein–Barr virus (EBV) infection of malignant HRS cells, which is implicated in approximately 40% of cases of HL, contributes to overexpression of PD-L1 even in the absence of 9p24.1 amplification. The EBV latent membrane protein 1 exerts direct and indirect effects on PD-L1 promoter and enhancer elements leading to increased PD-L1 protein expression (Green 2012).

1.3 Study Treatments

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

1.3.1 Brentuximab Vedotin

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 primary mechanism of anticancer activity of brentuximab vedotin is 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. Possible additional mechanisms of anticancer activity include bystander effects on nearby cells in the tumor microenvironment, immunogenic cell death, and antibody-dependent cellular phagocytosis (Oflazoglu 2007; Li 2014; Muller 2014; Gardai 2015; Kim 2015).

In a pivotal phase 2 study of 102 patients with relapsed or refractory HL following autologous stem cell transplant (ASCT), treatment with brentuximab vedotin 1.8 mg/kg every 3 weeks resulted in an objective response rate (ORR) of 75% (95% confidence interval [CI], 64.9%–82.6%). The complete response (CR) rate was 34% (95% CI, 25.2%–44.4%) and the median progression-free survival (PFS) for all patients on study was 5.6 months (95% CI, 5.0–9.0 months) (Younes 2012).

The activity of brentuximab vedotin in patients who had previously received it was demonstrated in the SGN35-006 study of patients with hematologic malignancies who initially responded to brentuximab vedotin and then subsequently progressed (Bartlett 2014). In this open-label, multicenter, phase 2 study of patients with HL or systemic anaplastic large cell lymphoma who had responded to brentuximab vedotin monotherapy during a previous clinical trial (Bartlett 2014), patients were eligible if they had achieved a partial response (PR) or better to initial treatment with brentuximab vedotin, discontinued treatment while in remission, and subsequently developed disease progression or relapse. In the retreatment study, patients received brentuximab vedotin 1.8 mg/kg on Day 1 of each 21-day treatment cycle. Patients whose dose was reduced to 1.2 mg/kg for any reason during their initial therapy were given 1.2 mg/kg on Day 1 of each 21-day treatment cycle upon retreatment. Of the 21 patients with HL enrolled, the median time between the last brentuximab vedotin dose from initial treatment and the first dose at retreatment was 11.4 months (range 4–45 months). The ORR and CR rates with brentuximab vedotin retreatment were 60% and 30%, respectively. The median duration of response was 9.2 months (range 0.0+ to 19.5+ months). For patients who achieved a CR, the median duration of response was 9.4 months (range 1.7–14.2 months). The median PFS was 9.9 months, and the median overall survival (OS) had not been reached at the time of study closure. The most common adverse events (AEs) were peripheral sensory neuropathy (59%), fatigue and nausea (41% each), diarrhea (38%), and

arthralgia, headache, peripheral motor neuropathy, and pyrexia (28% each). The most common AEs that were ≥ Grade 3 consisted of anemia (17%), fatigue (14%), and hyperglycemia, hypophosphatemia, and thrombocytopenia (10% each). No serious AEs leading to death were attributed to brentuximab vedotin.

1.3.2 Nivolumab

Nivolumab is a fully-human monoclonal antibody (immunoglobulin G4 [IgG4]) that targets PD-1. In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39 to 2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Nivolumab blocks the PD-1 pathway and results in a reproducible enhancement of both proliferation and interferon gamma (IFN-γ) release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen-specific recall response indicates that nivolumab augments IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the antitumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) (Wolchok 2009).

A recent report from a phase 1 study of nivolumab in patients with advanced hematological malignancies demonstrated a high response rate in patients with relapsed or refractory HL, with an ORR of 87% (20/23) and a CR rate of 17% (4/23). The responses obtained were durable with a 6-month PFS of 86% and no significant difference in the ORR in the subset of 18 patients who had previously failed brentuximab vedotin (Ansell 2015).

1.4 Clinical Study Rationale

High dose chemotherapy with ASCT provides the best chance to achieve a durable remission in patients with HL who have relapsed or refractory disease after standard frontline combination chemotherapy (Schmitz 2002). Salvage chemotherapy is typically given prior to delivering high-dose chemotherapy/ASCT to maximally debulk disease. Patients achieving a metabolic CR after salvage chemotherapy have a long-term relapse-free survival of ~75% post-ASCT. In contrast, patients with evidence of residual disease prior to high dose chemotherapy/ASCT have a long-term relapse-free survival that is only ~25% (Moskowitz 2010). Because results from salvage therapy directly influence long-term event-free survival post-ASCT, it is critical to develop well-tolerated regimens that increase CR rates pre-ASCT (Moskowitz 2012).

Given that brentuximab vedotin and nivolumab both have documented high single-agent response rates in HL and also work through distinct mechanisms of action, it is expected that combination therapy could potentially be more effective in the salvage treatment setting than administration of either agent alone. Moreover, both agents are well tolerated, have few overlapping toxicities, and can be infused in the outpatient setting. This study will evaluate

the safety and antitumor activity of combination therapy with brentuximab vedotin combined with nivolumab in a population of patients who have failed standard frontline chemotherapy.

2 OBJECTIVES

2.1 Primary Objectives

- To assess the safety profile of brentuximab vedotin administered in combination with nivolumab in patients with relapsed or refractory HL
- To assess the antitumor activity of brentuximab vedotin administered in combination with nivolumab in patients with relapsed or refractory HL

2.2 Secondary Objectives

- To assess the ORR
- To assess the duration of CR and objective response (OR)
- To assess PFS after ASCT

2.3 Additional Objectives

- To assess OS
- To compare the CR rate in patients who relapsed after frontline therapy with the CR rate in patients who were refractory to frontline therapy
- To assess the feasibility of stem cell mobilization and collection after treatment with brentuximab vedotin in combination with nivolumab
- To assess PFS
- To assess pharmacokinetics (PK) and incidence of antitherapeutic antibodies (ATA) against each study drug given in combination
- To assess tumor amplification and expression of PD-L1/L2 and relationship to response
- To assess tumor microenvironment and peripheral immune status
- To compare safety and efficacy of treatment with staggered versus same-day dosing schemes
- To compare biomarker data obtained with staggered versus same-day dosing schemes
- To assess efficacy in patients who previously received brentuximab vedotin

2.4 Endpoints

2.4.1 Primary Endpoints

- Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities
- CR rate following the completion of study treatment

2.4.2 Secondary Endpoints

- ORR

- Duration of CR and OR
- PFS post-ASCT

2.4.3 Additional Endpoints

- OS
- PFS
- Selected PK, ATA, and biomarker endpoints

3 INVESTIGATIONAL PLAN

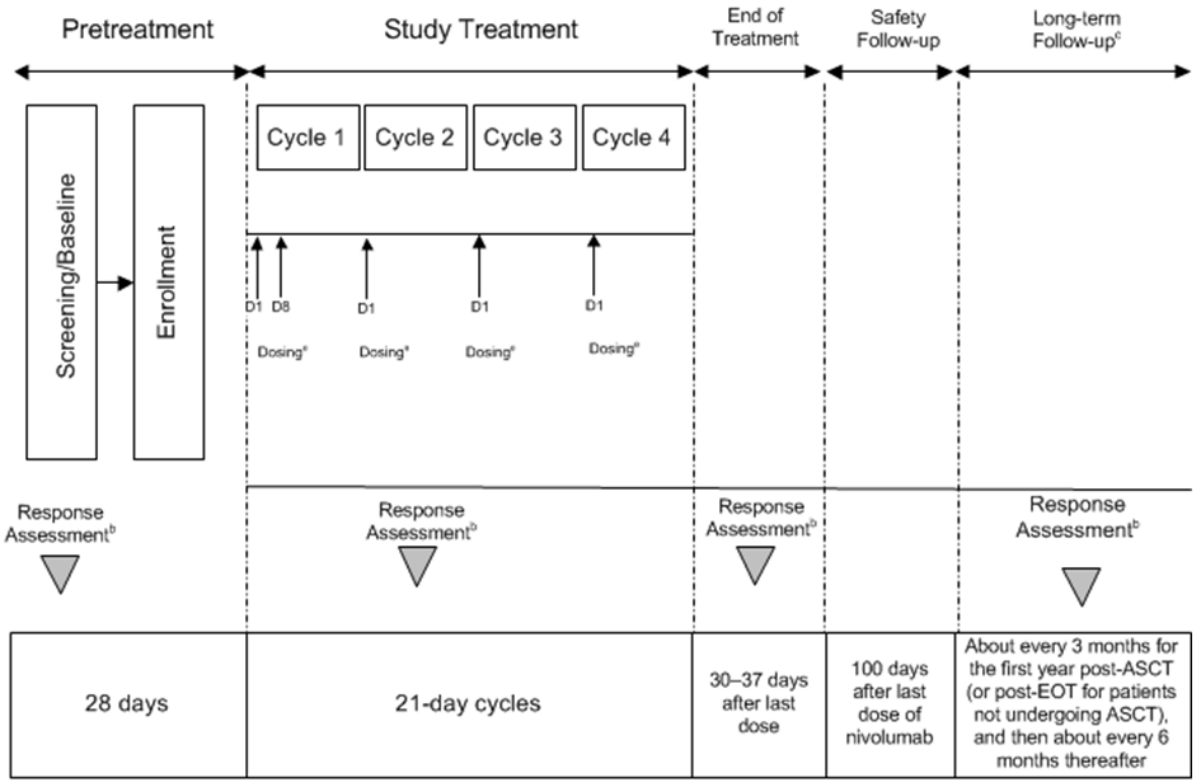
3.1 Summary of Study Design

This is a phase 1/2, open-label, multicenter study designed to evaluate the safety and antitumor activity of brentuximab vedotin treatment combined with nivolumab. The study will be conducted in 3 parts.

3.1.1 Study Design Parts 1 and 2

Patients in Parts 1 and 2 will be treated for up to four 21-day cycles. The first dose of brentuximab vedotin will be given on Cycle 1 Day 1. The first dose of nivolumab will be given on Cycle 1 Day 8. For Cycle 2 and all subsequent cycles, both brentuximab vedotin and nivolumab will be administered on Day 1. Nivolumab will be administered at least 30 minutes after infusion of brentuximab vedotin is complete (Figure 1).

Figure 1: Study design: Staggered dosing in Cycle 1 (Parts 1 and 2)



a Each cycle consists of 21-days. At Cycle 1, 1.8 mg/kg brentuximab vedotin is administered on Day 1, followed by 3 mg/kg nivolumab on Day 8. At subsequent cycles, 1.8 mg/kg brentuximab vedotin and 3 mg/kg nivolumab are both administered on Day 1.

b Response assessment performed at Screening/Baseline, between Days 15–21 at Cycle 2, and at EOT. CT only at Cycle 2 to assess for progressive disease. CT/PET at Screening/Baseline, EOT (23–37 days post last dose of study drug), and during long-term follow-up until a patient has achieved CmR by PET assessment; once a patient has achieved CmR by PET assessment, responses will be followed by CT scans of diagnostic quality only.

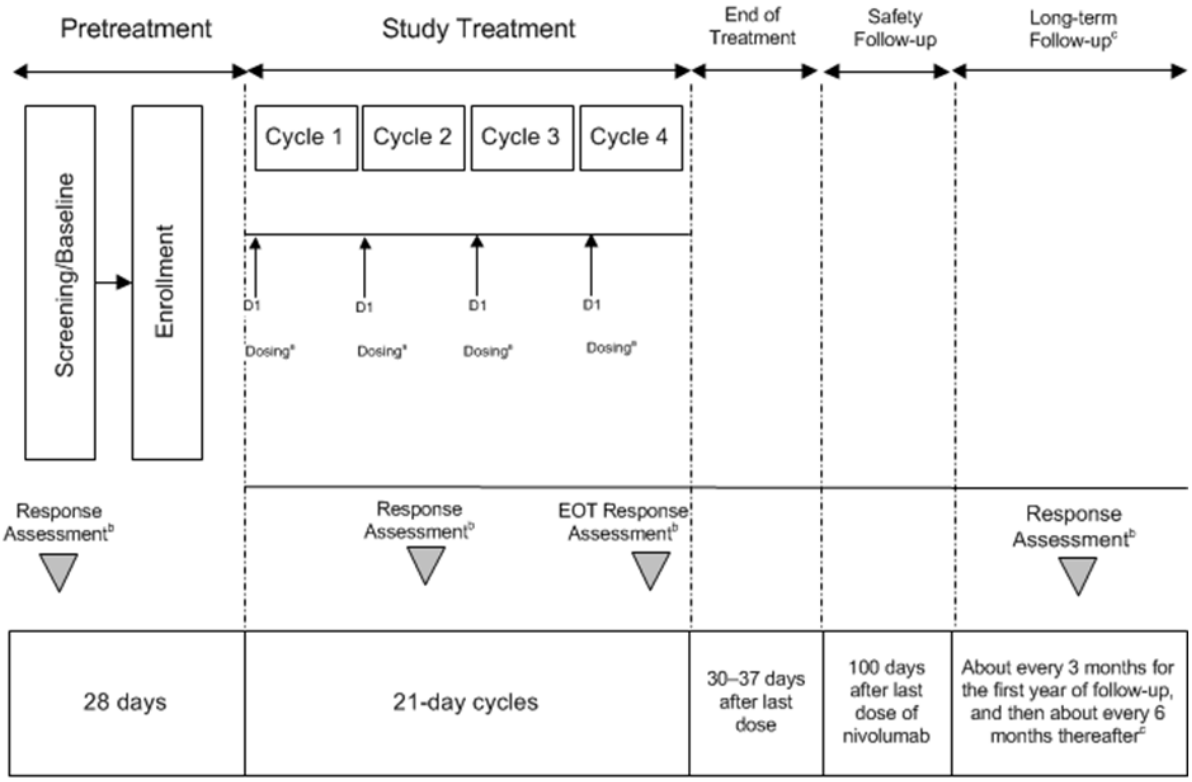
c All patients who receive at least one dose of brentuximab vedotin will have long-term follow-up assessments at the following time points post-ASCT (or for patients who do not undergo ASCT, post-EOT): 100 days and then 6, 9, 12, 18, 24, 30, and 36 months, and then per institutional standard thereafter. A final safety visit will be performed 100 days after the last dose of nivolumab and after the EOT to assess for potential immune-mediated adverse events. Patients will be followed at this schedule until withdrawal of consent, death, or study closure, whichever occurs first.

Patients in Parts 1 and 2 with radiographic evidence of progressive disease (PD) at the Cycle 2 response assessment are not eligible for further treatment on the study. All other patients in Parts 1 and 2 are eligible to continue treatment on study through Cycle 4. After completion of the end-of-treatment (EOT) response assessments, patients are eligible to undergo ASCT. It is recommended that hematopoietic stem cells (HSC) be mobilized and collected after Cycle 4. However, stem cell collection may occur in prior cycles after discussion with the medical monitor. If patients have an unacceptable toxicity that is attributable to only one agent, as determined by the investigator, they will be eligible to continue on the treatment protocol through Cycle 4 with the tolerated drug as a single agent.

3.1.2 Study Design Part 3

In Part 3, patients will be treated for up to four 21-day cycles. Both brentuximab vedotin and nivolumab will be administered on Day 1 of all cycles (Figure 2); nivolumab will be administered at least 30 minutes after infusion of brentuximab vedotin is complete.

Figure 2: Study design: Same-day dosing in all treatment cycles (Part 3)



a On Day 1 of each 21-day cycle, both brentuximab vedotin 1.8 mg/kg and nivolumab 3 mg/kg will be administered.
b Response assessment performed at Screening/Baseline, between Days 15–21 at Cycle 2, and at EOT. CT only at Cycle 2 to assess for progressive disease. CT/PET at Screening/Baseline, at EOT (15–30 days post last dose of study drug) and during long-term follow-up until a patient has achieved CmR by PET assessment; once a patient has achieved CmR by PET assessment, responses will be followed by CT scans of diagnostic quality only.
c All patients who receive at least one dose of either study drug will have long-term follow-up assessments at the following time points post-ASCT (or post-EOT for patients who do not undergo ASCT): 100 days and then 6, 9, 12, 18, 24, 30, and 36 months, and then per institutional standard thereafter. A final safety visit will be performed 100 days after the last dose of nivolumab and after the EOT to assess for potential immune-mediated adverse events. Patients will be followed at this schedule until withdrawal of consent, death, or study closure, whichever occurs first.

Patients in Part 3 with confirmed, unequivocal PD at Cycle 2 are not eligible for further treatment and will proceed to the EOT visit. Patients with stable disease (SD) or better at the Cycle 2 response assessment may continue on treatment through Cycle 4. Patients with an indeterminate response (IR), as defined by the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC; Appendix D) (Cheson 2016), also may continue on treatment through Cycle 4. After completion of the EOT response assessment, patients are eligible to undergo ASCT. It is recommended that HSC be mobilized and collected after Cycle 4. However, stem cell collection may occur in prior cycles after discussion with the medical monitor. If patients have an unacceptable toxicity that is attributable to only one agent, as determined by the investigator, they will be eligible to continue on the treatment protocol through Cycle 4 with the tolerated drug as a single agent.

3.1.3 Safety Monitoring Committee

In Part 1, the safety of combination treatment will be evaluated by a Safety Monitoring Committee (SMC) prior to expansion of enrollment to evaluate treatment effect in Part 2, as detailed in Section 9.3.9. In Part 1, after 6 patients have been followed through the end of the dose-limiting toxicity (DLT) period, or at the point that 2 or more patients experience a DLT, whichever comes first, the SMC will review all available data and make a recommendation for one of the following:

1. To proceed to Part 2 of the study, expanding enrollment with additional patients treated with the study drugs at the doses and schedule determined to be safe in Part 1 of the study
2. To repeat Part 1 of the study and treat up to 6 additional patients at the same drug doses and schedule previously tested or with any of the following modifications that may include, but are not limited to:
    a. Dose reduction of brentuximab vedotin to 1.2 mg/kg and/or nivolumab to 1 mg/kg; of note, doses may not be increased above 1.8 mg/kg brentuximab vedotin or 3 mg/kg nivolumab
    b. Administration of combination treatment on Day 1 of every cycle
3. To close the study to additional enrollment.

Part 2 of the study will further characterize safety and evaluate the antitumor activity of brentuximab vedotin combined with nivolumab in patients who have failed standard frontline chemotherapy by enrolling approximately 50 additional patients at the recommended dose schedule determined in Part 1.

Part 3 of the study will further characterize safety and efficacy of the study drug combination administered as same-day dosing in all cycles by enrolling approximately 30 additional patients with relapsed or refractory HL at the recommended doses as followed in Part 2. If any safety signals are observed after the first 6 patients in Part 3 have been treated for 2 cycles, then an SMC meeting will be convened.

Details of the SMC will be documented in an SMC charter.

3.1.4 Dose-Limiting Toxicities

DLTs are only assessed during Part 1 of the study. For the purpose of this study, DLTs are defined as any study drug-related toxicity (brentuximab vedotin or nivolumab) that requires either a dose reduction or delay of more than 7 days of either study drug in Cycle 2 or delays the Cycle 3 Day 1 administration of combined treatment by more than 7 days. The DLT-evaluation period consists of the first cycle of therapy through the Cycle 3 Day 1 administration of combined treatment. The Investigator's Brochures for brentuximab vedotin and nivolumab individually describe AEs commonly observed relative to either agent (i.e., neutropenia or peripheral neuropathy with brentuximab vedotin; immune-mediated AEs with nivolumab), as well as less common serious findings. The respective Investigator's Brochures should be referenced when attributing causality; however, the final decision regarding causality is at the discretion of the investigator.

If any patient enrolled in Part 1 discontinues the study during the DLT period, that patient will be replaced unless discontinuation is for DLT.

3.2 Discussion and Rationale for Study Design

The endpoints of this study are appropriate for evaluating the safety of brentuximab vedotin treatment in combination with nivolumab for patients with relapsed or refractory HL. The DLT evaluation in Part 1 of the study will provide an opportunity to assess safety and tolerability of combination treatment, the components of which have previously been assessed for safety in other settings. Expanded enrollment in Part 2 is designed to assess the efficacy of the combination treatment based on CR rate with staggered dosing of nivolumab and to provide additional safety data. The sample size is chosen to provide satisfactory power to exclude the previously demonstrated CR rate of single-agent brentuximab vedotin in a similar patient population in the case that the true CR rate of the combination treatment meets a clinically compelling threshold.

3.2.1 Rationale for Study Design of Same-day Dosing

On interim analysis, patients in Parts 1 and 2 had an ORR of 90% (95% CI 72.6%, 97.8%; 26/29 patients) and a CR rate of 62% (95% CI 42.3%, 79.3%; 18/29 patients). Similar results were reported by the ECOG-ACRIN Cancer Research Group study (E4412 Arms D and E) (ORR 100%, 8/8 evaluable patients; CR rate 62.5%, 5/8 patients), which enrolled patients with relapsed refractory HL for treatment with both brentuximab vedotin and nivolumab on Day 1 beginning with Cycle 1 (Diefenbach 2016). Based on results from both studies, a decision was made to amend the protocol to evaluate the safety and efficacy of same-day dosing of the study-drug combination beginning with Cycle 1. This new cohort, Part 3, will enroll patients with relapsed or refractory HL and will permit patients previously treated with brentuximab vedotin to explore activity of the combined regimen in brentuximab vedotin-exposed patients.

3.2.2 Method of Assigning Patients to Treatment Groups

In this open-label study, each part of the trial will enroll sequentially. Enrollment and treatment in Part 1 will be completed before enrollment begins in Part 2, which will evaluate a staggered dosing schedule of brentuximab vedotin and nivolumab in Cycle 1 followed by same-day dosing of both drugs in Cycles 2 through 4.

After enrollment in Part 2 is complete, approximately 30 patients will be enrolled in Part 3 to evaluate same-day dosing of brentuximab vedotin and nivolumab in all treatment cycles.

3.2.3 Rationale for Selection of Doses

The recommended dose for brentuximab vedotin per its prescribing information is 1.8 mg/kg via intravenous (IV) infusion administered every 3 weeks. This dose and schedule were evaluated in two pivotal phase 2 studies (SG035-0003 and SG035-0004) in patients with CD30-positive hematologic malignancies. This dose and schedule for retreatment with brentuximab vedotin monotherapy were similarly evaluated in a separate phase 2 study (SGN35-006) with the caveat that patients enrolled for retreatment who had a dose reduction for any reason to 1.2 mg/kg during their initial therapy would receive brentuximab vedotin retreatment at the reduced dose of 1.2 mg/kg.

The dose for nivolumab for this study is 3 mg/kg via IV infusion administered every 3 weeks. The approved dose for nivolumab as monotherapy is 3 mg/kg every 2 weeks for the treatment of melanoma and metastatic squamous non-small cell lung cancer. However, nivolumab has been studied as monotherapy and in combination treatment in several tumor types with dosing every 3 weeks. It was recently reported that nivolumab dose levels of 0.3, 2, and 10 mg/kg every 3 weeks yielded similar ORR, PFS, and OS in a phase 2 trial of patients with metastatic renal cell carcinoma (Motzer 2015). Moreover, nivolumab dose levels of 0.1, 0.3, 1, 3, and 10 mg/kg every 2 weeks were associated with very similar (median 64%–70%) PD-1 receptor occupancy and comparable ORR and PFS in patients with advanced melanoma (Topalian 2012). These findings indicate a flat dose-response relationship for nivolumab across a wide dose range for both 2- and 3-week dosing schedules, suggesting that dosing nivolumab at 3 mg/kg every 3 weeks is appropriate in the current study. These results further suggest that reduction of the nivolumab dose level to 1 mg/kg every 3 weeks is appropriate if the combination of 3 mg/kg nivolumab with brentuximab vedotin results in an unfavorable safety profile.

The rationale for staggered dosing of brentuximab vedotin and nivolumab in Cycle 1 is supported by the reasoning that, by delivering brentuximab vedotin, a directly cytotoxic agent, 1 week prior to nivolumab in Cycle 1, it is anticipated that tumor-associated antigens will be released and available for presentation to resident cytotoxic T cells at the same time that these cells become activated through PD-1 blockade. However, because of the long half-life of nivolumab, there is no rationale to continue staggered dosing beyond Cycle 1.

Same-day dosing in all treatment cycles is supported by data from the ECOG-ACRIN study (E4412) (Diefenbach 2016). In that study, patients in Arms D and E with relapsed or refractory HL were treated with brentuximab vedotin and nivolumab administered on Day 1

of 21-day cycles. The regimen was well-tolerated in the 10 patients who were evaluable for safety, with only 1 infusion-related reaction observed. The ORR was 100% in 8 efficacy-evaluable patients, with a CR rate of 62.5%. Based on the low rate of infusion-related reactions and promising activity observed in the E4412 study, the protocol was amended to explore same-day dosing in Part 3 of the SGN35-025 study.

3.2.4 Blinding

This is an open-label study. Blinding will not be implemented.

4 STUDY POPULATION

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

4.1 Inclusion Criteria

1. Documented histopathological diagnosis of classical HL, excluding nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)
2. Patients must have biopsy-proven (see Section 6.2) relapsed or refractory disease after failure of standard frontline chemotherapy for the treatment of classical HL
   - Relapsed disease is defined as achieving a CR to frontline therapy but then progressing 3 months or more after completing frontline therapy
   - Refractory disease is defined as never achieving a CR to frontline therapy or having a CR but then progressing within 3 months of completing frontline therapy
3. Patients must have fluorodeoxyglucose positron emission tomography- (FDG-PET) avid and bidimensional measureable disease of at least 1.5 cm in longest axis as documented by radiographic technique (spiral computed tomography [CT] preferred)
4. Patients must have confirmation of diffusing capacity of the lung for carbon monoxide (DLCO) over 60% (adjusted for hemoglobin) by a pulmonary function test
5. Age 18 years and older
6. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1
7. Patients must be considered eligible to undergo autologous stem cell transplant
8. Patients must have the following required baseline laboratory data:
   - Absolute neutrophil count (ANC) ≥1000/µL
   - Platelet count ≥50,000/µL (no platelet transfusions for prior 14 days)
   - Hemoglobin ≥8.5 g/dL (no red blood cell [RBC] transfusions for prior 7 days)
   - Serum bilirubin ≤1.5 x upper limit of normal (ULN) (except patients with Gilbert Syndrome, who can have total bilirubin <3.0 x ULN)
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN

- Calculated creatinine clearance of ≥30 mL/min

9. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 7 days prior to the first dose of brentuximab vedotin. Females with false positive results and documented verification that the patient is not pregnant are eligible for participation. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy

10. Females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraceptive methods during the study and for 6 months following the last dose of brentuximab vedotin or 8 months following the last dose of nivolumab, whichever is later

11. Patients or their legally authorized representative must provide written informed consent

4.2 Exclusion Criteria

1. Patient has received prior salvage therapy, including salvage radiotherapy, for relapsed or refractory classical HL

2. Chemotherapy or biologics therapy that is not completed 4 weeks prior to the first dose of study drug(s), unless documented progression of underlying disease on treatment

3. Prior radiation therapy within 3 weeks, or chest radiation ≤12 weeks prior to first dose of the study drug(s)

4. For patients in Parts 1 and 2, previous treatment with brentuximab vedotin; for Part 3, patients with HL that is refractory to a brentuximab vedotin-containing regimen in first line, or patients who discontinue brentuximab vedotin due to unacceptable toxicity are ineligible. Refractory disease is defined as never achieving a CR to frontline therapy or having a CR but then progressing within 3 months of completing frontline therapy

5. Has received any prior immuno-oncology therapy (e.g., therapies affecting the PD-1, CTLA4, or CD137 pathways)

6. Previously received an allogeneic and/or autologous stem cell transplant for HL

7. Current therapy with other systemic antineoplastic or investigational agents

8. Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment

    - Inhaled or topical steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

9. History of another primary invasive malignancy that has not been in remission for at least 3 years

10. History of progressive multifocal leukoencephalopathy (PML)

11. Known cerebral/meningeal disease related to the underlying malignancy
12. Pre-existing neuropathy of Grade 2 or greater
13. Any active Grade 3 or higher (per the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of brentuximab vedotin; routine antimicrobial prophylaxis is permitted
14. Females who are pregnant or breastfeeding
15. Known hypersensitivity to any excipient contained in the drug formulation of brentuximab vedotin or nivolumab
16. Positive for hepatitis B by surface antigen expression, or any other positive test for hepatitis B virus indicating acute or chronic infection
17. Active hepatitis C infection (positive by serology and confirmed by polymerase chain reaction [PCR] or on antiviral therapy for hepatitis C within the last 6 months)
18. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
19. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV (Appendix C) within 6 months prior to their first dose of study drug(s)
20. Previous history of known or suspected autoimmune disease
    - Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted
21. Active interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
22. Known history of pancreatitis
23. Other serious underlying medical condition that, in the opinion of the investigator, would impair the ability to receive or tolerate the planned treatment and follow-up

4.3 Removal of Patients from Therapy or Assessment

Seattle Genetics or their designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and case report form (CRF).

4.3.1 Discontinuation of Study Drug

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

- Completed treatment
- Progressive disease
- AE
- Investigator decision
- Patient decision, non-AE
- Study termination by sponsor
- Other, Non-AE

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent. Dose delays of both brentuximab vedotin and nivolumab resulting in treatment interruption of all therapy for >6 weeks require patient discontinuation from study treatment.

4.3.2 Patient Withdrawal from Study

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

- Completed study per protocol
- Patient withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

There are two investigational agents under study in this protocol. Brentuximab vedotin 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. Nivolumab is a fully human IgG4 monoclonal antibody that acts as an immunomodulator by blocking ligand activation of the PD-1 receptor on activated T cells.

5.2 Brentuximab Vedotin

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

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 Binder for further information.

5.2.2 Dose and Administration

Brentuximab vedotin 1.8 mg/kg (or 1.2 mg/kg, if recommended by the SMC during Part 1) will be administered every 21 days by IV infusion given over approximately 30 minutes. For patients in Part 3 who were previously treated with brentuximab vedotin and had a dose reduction, dose assignment must be discussed with the medical monitor.

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. Brentuximab vedotin must not be administered as an IV push or bolus. Brentuximab vedotin should not be mixed with other medications. When both drugs are administered on Day 1 of the cycle, brentuximab vedotin administration should be completed at least 30 minutes prior to starting administration of nivolumab.

Dosing is based on patient actual body weight. Doses must be adjusted for patients who experience a ≥10% change in weight from baseline. Other dose adjustments for changes in body weight are permitted per institutional standard. An exception to weight-based dosing is made for patients weighing greater than 100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

5.2.3 Dose Modifications

Table 1 describes the recommended dose modifications for brentuximab vedotin treatment-associated toxicity.

Doses reduced for brentuximab vedotin-related toxicity should not be re-escalated without discussion with the sponsor. Patients who discontinue nivolumab due to an AE may continue treatment with brentuximab vedotin monotherapy to complete the allowable 4 cycles of treatment. If brentuximab vedotin is withheld at the time a cycle of nivolumab is given, once the AE causing the delay of brentuximab vedotin has resolved, administration of brentuximab vedotin should resume on the same schedule with the next cycle of combination therapy. Dose delays of both brentuximab vedotin and nivolumab resulting in treatment interruption of all therapy for >6 weeks require patient discontinuation from study treatment.

Table 1: Recommended dose modifications for brentuximab-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral neuropathy	Continue at same dose level	Reduce dose to 1.2 mg/kg and resume treatment[a]	Withhold until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at 1.2 mg/kg[a]	Discontinue treatment
Non-hematologic (except peripheral neuropathy)	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume treatment at the same dose level[b]	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the investigator[a,b,c]
Hematologic[d]	Continue at same dose level	Continue at same dose level	Withhold until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at the same dose level[e]. Growth factor support (G-CSF or GM-CSF) should be considered for subsequent cycles. If Grade 4 neutropenia recurs despite growth factor support, consider discontinuation or dose reduction to 1.2 mg/kg.[a]	

G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte macrophage colony-stimulating factor.
a Dose reductions below 1.2 mg/kg are not allowed, and toxicities should be managed with dose delays.
b Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.
c Treatment should be discontinued for patients who experience Grade 4 infusion-related reactions.
d Support with blood product transfusions allowed per institutional standard of care.
e Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

5.2.4 Storage and Handling

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

Drug accountability instructions are provided in the Pharmacy Binder.

5.2.5 Packaging and Labeling

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

5.2.6 Preparation

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

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

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

Detailed drug preparation instructions are provided in the Pharmacy Binder.

5.3 Nivolumab

Detailed information describing the preparation, administration, and storage of nivolumab is located in the Pharmacy Binder.

5.3.1 Description

Nivolumab is a sterile, preservative free, clear to opalescent, colorless to pale-yellow solution supplied by Seattle Genetics in single-use vials for dilution for IV administration. Each single-use vial of the product contains 100 mg/10 mL solution. See the Pharmacy Binder for further information.

5.3.2 Method of Procurement

Nivolumab will be provided by Bristol-Myers Squibb and supplied to the study sites by Seattle Genetics.

5.3.3 Dose and Administration

For patients in Parts 1 and 2, nivolumab will be administered on Day 8 of Cycle 1 and Day 1 of Cycles 2 through 4 of each 21-day treatment cycle. For patients in Part 3, nivolumab will be administered on Day 1 of all 21-day treatment cycles. Patients will receive nivolumab at a dose of 3 mg/kg (or 1 mg/kg, if recommended by the SMC during Part 1) as a 60-minute infusion. When both drugs are administered on Day 1 of the cycle, nivolumab should be administered at least 30 minutes after completing treatment with brentuximab vedotin. Nivolumab infusions should be administered through an IV line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Other drugs should not be co-administered through the same IV line (e.g., brentuximab vedotin).

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to recalculate subsequent doses if the patient weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram.

The Pharmacy Binder contains specific instructions for nivolumab dose calculation, dilution, preparation of the infusion fluid, and administration.

5.3.4 Dose Modifications

Based on available information, autoimmune complications are the most likely AEs attributable to nivolumab. Dose modifications for AEs are described in this section as well as in Appendix 2 of the nivolumab Investigator's Brochure.

There will be no dose escalations or reductions of nivolumab allowed, unless determined by the SMC to enroll patients to be treated at 1 mg/kg throughout the trial (see Section 3.1.3). Patients who discontinue brentuximab vedotin due to an AE may continue treatment with nivolumab monotherapy to complete the allowable 4 cycles of treatment. If nivolumab is held at the time a cycle of brentuximab vedotin is given, once the AE causing the delay of nivolumab has resolved, administration of nivolumab should resume on the same schedule with the next cycle of combination therapy. Dose delays of both brentuximab vedotin and nivolumab resulting in treatment interruption of all therapy for >6 weeks require patient discontinuation from study treatment. See Section 7.6.1.1 for determining causality.

5.3.4.1 Dose Delays

Dose delays for nivolumab-related liver function test (LFT) abnormalities are described in Section 5.3.4.3. Otherwise, nivolumab administration should be delayed for the following:

- Any ≥ Grade 2 non-skin, nivolumab-related AE, with the following exception:
  - Grade 2 nivolumab-related fatigue or laboratory abnormalities, other than LFT abnormalities (see Section 5.3.4.3), do not require a treatment delay
- Any Grade 3 skin, nivolumab-related AE
- Any Grade 3 nivolumab-related laboratory abnormality, other than LFT abnormalities (see Section 5.3.4.3), with the following exceptions for lymphopenia or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay
  - Any ≥ Grade 3 nivolumab-related amylase or lipase abnormality that has been evaluated clinically and radiographically and is without evidence of pancreatitis does not require dose delay. The medical monitor should be consulted for such ≥ Grade 3 amylase or lipase abnormalities
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of nivolumab

Patients who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated. Nivolumab may be resumed at the next scheduled treatment cycle if the AE recovers to ≤ Grade 1 or baseline, with the following exceptions:

- Patients may resume nivolumab treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 nivolumab-related skin AE may resume nivolumab treatment in the presence of Grade 2 skin toxicity
- Nivolumab-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before nivolumab treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for continued nivolumab treatment if discussed with and approved by the medical monitor
- Nivolumab-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume nivolumab treatment after consultation with the medical monitor

5.3.4.2 Dose Discontinuation

Dose discontinuations for LFT abnormalities are described in Section 5.3.4.3. Otherwise, nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 nivolumab-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 6 weeks or requires systemic treatment
- Any Grade 3 non-skin, nivolumab-related AE lasting more than 7 days, with the following exceptions for laboratory abnormalities other than LFT abnormalities (see Section 5.3.4.3), nivolumab-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 nivolumab-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 nivolumab-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 nivolumab-related thrombocytopenia lasting more than 7 days or associated with bleeding; other Grade 3 nivolumab-related laboratory abnormalities other than LFT abnormalities (see Section 5.3.4.3), do not require treatment discontinuation
- Any Grade 4 nivolumab-related AE or laboratory abnormality other than LFT abnormalities (see Section 5.3.4.3), except for the following events:
    - Grade 4 neutropenia ≤7 days
    - Grade 4 lymphopenia or leukopenia

- Isolated Grade 4 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis; consult the medical monitor for Grade 4 amylase or lipase abnormalities
- Isolated Grade 4 electrolyte imbalances/abnormalities not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 nivolumab-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with the medical monitor

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing

Any event that leads to delay in nivolumab dosing lasting >6 weeks from the previous nivolumab dose requires discontinuation of nivolumab treatment, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage nivolumab-related AEs are allowed. Prior to re-initiating nivolumab treatment in a patient with a nivolumab dosing delay lasting >6 weeks from the previous nivolumab dose, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if nivolumab dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Dosing delays lasting >6 weeks from the previous nivolumab dose that occur for non-nivolumab-related reasons may be allowed if approved by the medical monitor. Prior to re-initiating nivolumab treatment in a patient with a nivolumab dosing delay lasting >6 weeks, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if nivolumab dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

5.3.4.3 Dose Modifications for Liver Function Test Abnormalities

Doses of nivolumab should be delayed for the following LFT abnormalities:

- If a patient has a baseline AST/ALT that is within the normal limits, delay dosing for nivolumab-related Grade 2 (>3 to 5 x ULN) elevations
    - Nivolumab may be resumed if the value improves to Grade 1 (≤3 x ULN) or better

- If a patient has a baseline AST/ALT in the Grade 1 range (ULN to ≤3 x ULN), delay dosing for nivolumab-related Grade 3 (>5 to 8 x ULN) elevations
    - Nivolumab may be resumed if the value improves to Grade 2 (>3 to 5 x ULN) or better
- If a patient has a baseline total bilirubin that is within normal limits, delay dosing for nivolumab-related Grade 2 elevations (>1.5 to 3 x ULN)
    - Nivolumab may be resumed if the bilirubin improves to Grade 1 or better (≤1.5 x ULN)
- If a patient has a baseline Grade 1 elevation of total bilirubin (ULN to ≤1.5 x ULN), delay dosing for nivolumab-related Grade 3 elevations in the range of >3 to 5 x ULN
    - Nivolumab may be resumed if the total bilirubin improves to Grade 2 or better (≤3 x ULN)

Doses of nivolumab should be discontinued permanently for the following LFT abnormalities:

- AST or ALT >8 x ULN or drug-induced liver injury (DILI)
- Total bilirubin >5 x ULN or DILI
- Concurrent AST or ALT >3 x ULN and total bilirubin >2 x ULN

5.3.5 Storage and Handling

Nivolumab should be stored at 2–8°C and protected from light, freezing, and shaking. Care should be taken when handling and preparing nivolumab. Partially used vials should be disposed at the site per the procedures for the disposal of anticancer drugs.

Drug accountability instructions are provided in the Pharmacy Binder.

5.3.6 Packaging and Labeling

Drug product vials may be labeled as nivolumab, the USAN and the INN, or as BMS-936558, the compound code; the 2 names can be used interchangeably.

5.3.7 Preparation

The drug product solution should be visually inspected for particulate matter and discoloration prior to administration. The vial should be discarded if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. The vial should not be shaken.

Detailed drug preparation instructions are provided in the Pharmacy Binder.

5.4 Required Premedication and Postmedication

Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of study drug(s).

5.4.1 Patients in Parts 1 and 2

Prophylactic premedication for prevention of infusion-related reactions is to be administered prior to combination treatment on Day 1 of each 21-day cycle beginning with Cycle 2. Hydrocortisone 100 mg IV or equivalent, and an antihistamine (e.g., diphenhydramine 25–50 mg IV or equivalent) should be given at least 30 minutes prior to infusion of brentuximab vedotin. Patients who experience an infusion-related reaction with this premedication regimen should receive premedication with methylprednisolone 40 mg IV (or equivalent) with an antihistamine for all subsequent cycles. Additional premedications for symptom management (e.g., acetaminophen and/or ondansetron) may also be given at the discretion of the investigator.

If treatment with nivolumab or brentuximab vedotin is discontinued, premedications may be reduced or stopped at the discretion of the investigator during single-agent treatment for subsequent cycles.

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

5.4.2 Patients in Part 3

Prophylactic premedication with antihistamines for prevention of infusion-related reactions is to be administered prior to combination treatment on Day 1 of each 21-day cycle beginning with Cycle 1. Antihistamines (e.g., diphenhydramine 50 mg IV or equivalent and famotidine 40 mg IV or equivalent) should be given at least 30 minutes prior to infusion of brentuximab vedotin. Patients who experience an infusion-related reaction with this premedication regimen should receive additional premedication with dexamethasone 0.2 mg/kg (maximum 10 mg IV or equivalent) for all subsequent cycles.

Additional premedications for symptom management (e.g., acetaminophen and/or ondansetron) may also be given at the discretion of the investigator.

If treatment with nivolumab or brentuximab vedotin is discontinued, premedications may be reduced or stopped at the discretion of the investigator during single-agent treatment for subsequent cycles.

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

5.5 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period for brentuximab vedotin or 100 days after the patient's last dose of nivolumab, whichever occurs later. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.5.1 Required Concomitant Therapy

Patients should be up-to-date on any recommended vaccinations prior to study entry. Additional vaccination(s) during each cycle of study treatment must be approved by the medical monitor.

Required premedications to prevent infusion-related reactions are described in Section 5.4.1 and Section 5.4.2.

5.5.2 Allowed Concomitant Therapy

The use of platelet and/or RBC supportive growth factors or transfusions when applicable is allowed. The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy.

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

Routine prophylaxis with vaccines is permitted prior to study entry; it is recommended that vaccines used do not contain live micro-organisms.

Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Stable adrenal replacement steroid doses >10 mg daily prednisone, or prednisone equivalent, are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Treatment with 0.5 to 2 mg/kg/day methylprednisolone IV (or oral equivalent), followed by a taper, is recommended for certain immune-mediated AEs; see Section 5.3.4.3 for dose modifications and relevant management algorithms in Appendix 3 of the nivolumab Investigator's Brochure. Treatment with 0.5 to 1 mg/kg corticosteroids, followed by taper, is recommended for Grade 2 or 3 creatinine elevation or nephritis.

Peripheral blood stem cells may be mobilized following Cycle 4 at the discretion of the investigator. However, stem cell collection may occur in prior cycles after discussion with the medical monitor. Collection of peripheral blood stem cells for ASCT, if applicable, should occur per institutional standard of care. If stem cell collection after Cycle 4 is inadequate, additional collection of peripheral blood stem cells for ASCT may be performed per institutional standards, if applicable.

At the discretion of the treating physician, consolidative radiotherapy or consolidative treatment with single-agent brentuximab vedotin may be given post-ASCT.

Allowed medications to manage infusion-related reactions are described in Section 5.6.1.1 and Section 5.6.1.2.

5.5.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the study. Exceptions are noted in Section 5.5.2.

5.6 Management of Adverse Reactions

5.6.1 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of study treatment(s). 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.

Infusion or hypersensitivity reactions may occur to either brentuximab vedotin or nivolumab. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

5.6.1.1 Patients in Parts 1 and 2

Premedication for the prevention of infusion reactions should be administered beginning with Cycle 2, at least 30 minutes prior to dosing study drug(s), and should include an antihistamine and low-dose corticosteroid, as described in Section 5.4.1. If the onset of a reaction occurs during an infusion, the infusion may be interrupted for treatment of the infusion-related reaction, including treatment with antihistamines, corticosteroids, bronchodilator therapy, and/or antipyretics, as appropriate. Patients who experience a Grade 3 infusion-related reaction to brentuximab vedotin or nivolumab may potentially receive additional treatment with the study drug(s) at the discretion of the investigator after discussion with the sponsor.

If anaphylaxis or a Grade 4 infusion-related reaction occurs, administration of the implicated agent(s) (brentuximab vedotin and/or nivolumab) should be immediately and permanently discontinued.

In case of late-occurring hypersensitivity symptoms to nivolumab (e.g., appearance of a localized or generalized pruritus within 1 week after nivolumab treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

5.6.1.2 Patients in Part 3

For patients in Part 3, prophylactic premedication with antihistamines for prevention of infusion-related reactions is to be administered prior to combination treatment on Day 1 of each 21-day cycle as described in Section 5.4.2. Patients who experience an infusion-related reaction with this premedication regimen should receive additional premedication with dexamethasone 0.2 mg/kg (maximum 10 mg IV or equivalent) as well as the antihistamines

as described in Section 5.4.2 for all subsequent cycles. Additional premedication for symptom management (e.g., acetaminophen and/or ondansetron) may also be given at the discretion of the investigator. If the onset of a reaction occurs during an infusion, the infusion may be interrupted for treatment of the infusion-related reaction, including treatment with antihistamines, corticosteroids, and/or bronchodilator therapy, as appropriate. Patients who experience a Grade 3 infusion-related reaction to brentuximab vedotin or nivolumab may potentially receive additional treatment with the study drug(s) at the discretion of the investigator after discussion with the sponsor.

If anaphylaxis or a Grade 4 infusion-related reaction occurs, administration of the implicated agent(s) (brentuximab vedotin and/or nivolumab) should be immediately and permanently discontinued.

In case of late-occurring hypersensitivity symptoms to nivolumab (e.g., appearance of a localized or generalized pruritus within 1 week after nivolumab treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

5.6.2 Management of Suspected Progressive Multifocal Leukoencepalopathy

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

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

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

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

5.6.3 Management of Immune-Adverse Events

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immune-oncology agents may mitigate severe toxicity. The following groups of AEs should be managed per the algorithms found in Appendix 3 of the nivolumab Investigator's Brochure:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic, with the following exceptions:

- Patients with a baseline LFT level in the Grade 1 range (AST or ALT >ULN to 3.0 x ULN and/or total bilirubin >ULN to 1.5 x ULN) should be managed by AE Grade-specified algorithms as applied to the absolute increase in AE Grade level above base line. For example, management of a Grade 3 AST elevation for a patient who had a baseline AST level in the Grade 1 range would be per the Grade 2 algorithm.

- Endocrinopathy
- Skin
- Neurological

See Section 5.5.2 for allowed high-dose corticosteroid treatment.

5.7 Treatment Compliance

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

6 STUDY ACTIVITIES

6.1 Schedule of Events

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.

AEs and concomitant medications will be recorded from Day 1 (predose) through 30 days after the last dose of brentuximab vedotin (see Section 7.6.1.3) or 100 days after the last dose of nivolumab, whichever occurs later. Any study protocol-related AE should be recorded from the time of informed consent as well as any concomitant medications given for treatment of the AE.

All procedures on dosing days must be performed predose unless otherwise specified. Clinical laboratory assessments (serum chemistry panel, complete blood count [CBC] with differential [see Section 7.6.2]), physical examination, and weight may be performed within 1 day prior to study drug administration. With the exception of gamma-glutamyl transpeptidase levels and thyroid function tests, the results from all other clinical laboratory assessments must be reviewed prior to study drug dosing.

6.2 Screening Visit (Days −28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history; medical history at screening includes an inflammatory condition review (see Section 7.1)
- Electrocardiogram (ECG)
- Serology for hepatitis B and EBV

- Hepatitis C serology with reflex to hepatitis C virus (HCV) RNA by PCR (see Section 7.6.2)
- Dedicated CT of chest, neck, abdomen, and pelvis
- Positron emission tomography (PET)
- Tumor biopsy specimen taken after relapse or progression from frontline therapy is required (Note: excisional biopsy if feasible); archival sample taken at diagnosis to be available
- Pulmonary function test

6.2.1 Baseline Visit (Days −7 to Day 1)

- Height and weight
- Pregnancy test for females of childbearing potential
- Physical examination
- Vital signs
- Performance status
- Serum chemistry panel (see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Estimated creatinine clearance
- Antinuclear antibodies (ANA)

6.3 Treatment Period (Day 1 to Day 21)

6.3.1 Cycle 1 Day 1 (±1 day)

- B symptom assessment
- Serum chemistry panel (includes thyroid stimulating hormone [TSH], free T3, and free T4; see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Blood samples for PK and ATA assessments
- Blood samples for biomarker assessments and flow cytometry
- Physical examination
- Weight
- Brentuximab vedotin administration
- Patients in Part 3 only: measurement of oxygen saturation by pulse oximetry
- Patients in Part 3 only: nivolumab administration (approximately 30 minutes after completion of brentuximab vedotin administration)

6.3.2 Cycle 1 Day 2 (+2 days)

- Blood samples for PK assessments (patients in Part 1 only)
- Blood samples for biomarker assessments (patients in Part 1 only)

6.3.3 Cycle 1 Day 8 (±1 day)

- Serum chemistry panel (see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Measurement of oxygen saturation by pulse oximetry prior to nivolumab administration (patients in Parts 1 and 2 only)
- Nivolumab administration (patients in Parts 1 and 2 only)
- Blood samples for PK assessments
- Blood samples for biomarker assessments and flow cytometry

6.3.4 Cycle 1 Day 15 (±1 day)

- Blood samples for PK assessments (patients in Parts 1 and 3)
- Blood samples for biomarker assessments and flow cytometry

6.3.5 Cycle 2 Day 1 (±1 day)

- Serum chemistry panel (see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Blood samples for PK and ATA assessments
- Blood samples for biomarker assessments and flow cytometry
- Measurement of oxygen saturation by pulse oximetry
- Weight
- Brentuximab vedotin administration
- Nivolumab administration (approximately 30 minutes after completion of brentuximab vedotin administration)

6.3.6 Cycle 2 Day 8 (±1 day)

- Blood samples for biomarker assessments (serum biomarkers and cytokines; plasma cytokines only) and flow cytometry (patients in Parts 2 and 3)

6.3.7 Cycle 2 Day 15 (+6 days)

- Perform dedicated CT of diagnostic quality including all involved sites of disease determined at baseline. Patients with SD or better may continue on treatment. Patients in Part 3 with an IR according to LYRIC (Appendix D) also may continue on treatment. Patients with confirmed/unequivocal PD must discontinue treatment and proceed to the EOT visit.

6.3.8 Cycle 3 Day 1 (±1 day)

- Serum chemistry panel (includes TSH, free T3, and free T4; see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Blood samples for PK and ATA assessments
- Blood samples for biomarker assessments and flow cytometry
- Measurement of oxygen saturation by pulse oximetry

- Physical examination
- Weight
- Brentuximab vedotin administration
- Nivolumab administration (approximately 30 minutes after completion of brentuximab vedotin administration)

6.3.9 Cycle 4 Day 1 (±1 day)

- Serum chemistry panel (see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Blood samples for PK and ATA assessments
- Blood samples for biomarker assessments and flow cytometry (patients in Part 1 only)
- Measurement of oxygen saturation by pulse oximetry
- Weight
- Brentuximab vedotin administration
- Nivolumab administration (approximately 30 minutes after completion of brentuximab vedotin administration)

6.3.10 Cycle 4 Day 2 (+2 days)

- Blood samples for PK assessments (patients in Part 1 only)
- Blood samples for biomarker assessments (patients in Part 1 only)

6.3.11 Cycle 4 Day 8 (±1 day)

- Blood samples for PK assessments (patients in Part 1 only)
- Blood samples for biomarker assessments and flow cytometry (patients in Part 1 only)

6.3.12 Peripheral Blood Stem Cell Collection

Collection of peripheral blood stem cells for ASCT, if applicable, should occur per institutional standard of care.

6.4 End of Treatment Visit (30 to 37 days after last dose of study drug except where noted)

EOT visits should occur 30 to 37 days after the last dose of study drug(s) unless delayed due to an AE. However, EOT evaluations must be performed before initiation of a new therapy, other than mobilization of stem cells for ASCT. If EOT evaluations are completed before 30 days after the last study treatment, the patient will be contacted 30 to 37 days following the last treatment to assess for adverse events. The following activities will be conducted at EOT:

- B symptom assessment
- Performance status

- Physical examination
- Inflammatory condition review (only for those patients with certain inflammatory conditions of interest at Screening/Baseline)
- Serum chemistry panel (includes TSH, free T3, and free T4; see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- ANA
- Blood samples for PK and ATA assessments
- Blood samples for biomarker assessments and flow cytometry
- Tumor biopsy; optional at progression of disease or if evidence of residual disease is suspected (Note: Strongly recommended to confirm that radiological evidence of progression is correlated with active HL; when possible, excisional biopsies should be performed)
- For patients in Parts 1 and 2: PET and dedicated CT of chest, neck, abdomen, and pelvis; PET and CT scans to be performed 23 to 37 days after last dose of study drug (as described in Section 7.2.1)
- For patients in Part 3: PET and dedicated CT of chest, neck, abdomen, and pelvis; PET and CT scans to be performed 15 to 30 days after last dose of study drug (as described in Section 7.2.2)
- Bone marrow biopsy (for patients planning to proceed to ASCT)

6.5 Autologous Stem Cell Transplant

Patients who will have an ASCT must have the following performed prior to transplant:

- Dedicated CT of chest, neck, abdomen, and pelvis; not needed if performed within the prior 6 weeks
- PET; not needed if performed within the prior 6 weeks
- Bone marrow biopsy; not needed if performed at the EOT visit

6.6 Safety Visit (100 days [+2 weeks] after last dose of nivolumab)

The final safety visit should occur 100 days after the last dose of nivolumab or 30–37 days post last dose of brentuximab vedotin (EOT visit), whichever is later. The following assessments will be performed:

- Physical examination, including assessment for potential immune-mediated adverse events
- Serum chemistry panel (see Section 7.6.2)
- CBC with differential (see Section 7.6.2)
- Blood samples for ATA assessments

6.7 Long-term Follow-up (±2 weeks)

Patients who discontinue from both study drugs (brentuximab vedotin and nivolumab) will remain on the study for follow-up until withdrawal of consent, death, or study closure,

whichever occurs first. Long-term follow-up assessments will be performed at the following time points post-ASCT (or post-EOT for patients who do not undergo ASCT): 100 days and then 6, 9, 12, 18, 24, 30, and 36 months and then per institutional standard thereafter. Patients who have discontinued treatment due to PD or who have initiated subsequent systemic chemotherapy will not have response assessed but will be followed for survival. Patients will be followed at this schedule until withdrawal of consent, death, or study closure, whichever occurs first. The following assessments will be performed until disease progression; patients will be followed for survival thereafter.

- Dedicated CT of chest, neck, abdomen, and pelvis; performed at 100 days and then 6, 12, 24, and 36 months post-ASCT or post-EOT long-term follow-up visits or if progression is suspected based on clinical signs and symptoms
- PET; performed with CT scans until the patient achieves a complete metabolic response (CmR) by PET
- Interval medical history to assess changes in health status since prior visit
- Physical examination
- Disease progression status and post-study treatment received

6.8 End of Study/End of Follow-up

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

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.

Tissue samples will be sent to the central pathology lab for disease confirmation and further evaluation of CD30 and PD-L1 expression.

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. Included with medical history is a review of any inflammatory conditions; patients with certain inflammatory conditions of interest at Screening/Baseline will have an additional review at the EOT visit.

Pulmonary function tests are required for all patients at screening. DLCO over 60% (adjusted for hemoglobin) must be confirmed by a pulmonary function test prior to study enrollment.

7.2 Response/Efficacy Assessments

7.2.1 Parts 1 and 2

For patients in Parts 1 and 2, the determination of antitumor activity will be based on response assessments made according to the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) and treatment decisions by the investigator will be based on these assessments.

Staging will be performed by PET and CT of diagnostic quality, with disease involvement determined by focal fluorodeoxyglucose (FDG) uptake in nodal and extranodal sites (including spleen, liver, bone marrow, and thyroid) that is consistent with lymphoma, according to the pattern of uptake and/or CT characteristics. Up to six of the largest nodes, nodal masses, or other involved lesions that are measurable in two diameters should be identified as target lesions; if possible they should be from disparate regions of the body, and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

At Cycle 2 (Day 15 + 6 days), a CT scan of diagnostic quality will be performed to assess for PD; a limited scan that includes sites of disease identified at baseline is acceptable. For subsequent response assessments, both PET and CT scans will be required until the patient achieves a CmR by PET assessment. After the patient achieves a CmR by PET, response will be followed by CT scans of diagnostic quality only. For PET-based assessments, a clinical response of progressive metabolic disease (PmD), no metabolic response (NmR), partial metabolic response (PmR), or CmR will be determined. If only CT-based assessment is performed, response will be categorized as PD, SD, PR, or CR. PmD/PD includes radiological evidence of progression per Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014). If clinical progression is determined by the investigator, radiographic staging should also be performed to determine response assessment per Lugano Classification Revised Staging System for malignant lymphoma. The PET scan metabolic uptake will be graded using the Deauville 5-point scale (Biggi 2013) (Barrington 2010) with a score of ≤ 3 considered to represent a CmR.

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

7.2.2 Part 3

For patients in Part 3, the determination of antitumor activity will be assessed using the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of LYRIC (Appendix D) (Cheson 2016). Treatment decisions by the investigator will be based on these assessments. Staging will be performed by PET/CT of diagnostic quality, with disease involvement determined by focal FDG uptake in nodal and extranodal sites (including spleen, liver, bone marrow, and thyroid) that is consistent with lymphoma according to the pattern of uptake and/or CT characteristics. Up to six of the largest nodes, nodal masses, or other involved lesions that are measurable in two diameters

should be identified as target lesions at baseline. If possible, target lesions should be from different regions of the body, and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

At Cycle 2 (Day 15 + 6 days), a CT scan of diagnostic quality will be performed to assess for PD; a limited scan that includes sites of disease identified at baseline is acceptable. For all other response assessments, a clinical response of PD, SD, PR, or CR will be determined unless tumor flare or pseudo-progression is suspected. If tumor flare or pseudoprogression is not suspected, PD is defined by radiological evidence of progression according to the Lugano criteria (Cheson 2014). If clinical progression is determined by the investigator, radiographic staging should also be performed to determine response assessment per Lugano classification criteria. The PET scan metabolic uptake will be graded using the Deauville 5-point scale (Barrington 2010; Biggi 2013), with a score of ≤3 considered to represent a complete metabolic response. Except for the Cycle 2 response assessment, both PET and CT scanning will be required until disease is PET negative; responses will then be followed by CT scan of diagnostic quality only.

If tumor flare or pseudo-progression is suspected by the investigator during treatment, then a clinical response of indeterminate response (IR) will be determined until subsequent evaluation of radiographic imaging or biopsy confirms or refutes PD. IR is defined according to the following:

1. An increase in overall tumor burden (as assessed by the sum of the products of the largest diameter [SPD]) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration;

2. Appearance of new lesions, or growth of one or more existing lesion(s) ≥50% at any time during treatment, occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during treatment; and

3. An increase in FDG uptake using the 5-Point Scale per the Deauville Criteria of one or more lesion(s) without a concomitant increase in lesion size or number.

See Appendix D for further details and criteria for follow-up of a determination of IR.

For patients with an IR, investigators should use clinical judgement to determine the appropriate course of action for further evaluation. Repeat imaging should be performed according to the Schedule of Events (or sooner if clinically indicated), and PD must be confirmed or refuted based on LYRIC follow-up criteria for IR (Cheson 2016). In addition, biopsy of sites of disease involvement should be strongly considered.

If a patient has a second determination of IR, then subsequent repeat imaging should be performed between 4 and 8 weeks (or earlier if clinically indicated). Follow-up radiographic assessment for patients with IR is not required if a follow-up biopsy has been performed that confirms the patient's response.

Patients' clinical data must be available for CRF source verification. All imaging studies must be copied to CDs and provided to the sponsor. At the end of the study, the images may either be sent to a central radiology facility for confirmation of disease response or destroyed.

7.3 Pharmacokinetic and Immunogenicity Assessments

Serum concentrations of brentuximab vedotin and nivolumab, and plasma concentrations of MMAE (unconjugated) will be measured. ATA against brentuximab vedotin and ATA against nivolumab will also be assessed.

PK and ATA sample collection timepoints are presented for patients in Parts 1 and 2 in Table 2 and for patients in Part 3 in Table 3. Refer to the Research Specimen Manual for information on collection, processing, storage, and shipment of samples.

Table 2: Pharmacokinetic and ATA sampling timepoints, Parts 1 and 2

Cycle	Study Day	Time	Window	Relative Time	Brentuximab Vedotin PK	Nivolumab PK	Brentuximab Vedotin + Nivolumab ATA
Baseline							
1	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X		X
		End of infusion	Within 15 min post end of brentuximab vedotin infusion	End of brentuximab vedotin infusion	X		
	Day 2[a]	24 hr postdose	±4 hr	Start of brentuximab vedotin infusion	X		
	Day 8	Predose	Within 24 hr prior to start of nivolumab infusion	Start of nivolumab infusion	X[a]	X	
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion		X	
	Day 15[a]	336 hr postdose	±24 hr	Start of brentuximab vedotin infusion	X	X	
2 and 3	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion	X	X	
4	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion	X	X	
	Day 2[a]	24 hr postdose	±4 hr	Start of brentuximab vedotin infusion	X	X	
	Day 8[a]	168 hr postdose	±24 hr	Start of brentuximab vedotin infusion	X	X	
EOT			30 + 7 days post last dose of study drug(s)		X	X	X
Safety follow-up			100 days post last dose of nivolumab				X

a Patients in Part 1 only

Table 3: Pharmacokinetic and ATA sampling timepoints, Part 3

Cycle	Study Day	Time	Window	Relative Time	Brentuximab Vedotin PK	Nivolumab PK	Brentuximab Vedotin + Nivolumab ATA
Baseline							
1	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion	X	X	
	Day 8	168 hr postdose	±24 hr	Start of brentuximab vedotin infusion	X	X	
	Day 15	336 hr postdose	±24 hr	Start of brentuximab vedotin infusion	X	X	
2	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion	X	X	
3	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion	X	X	
4	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion	X	X	
EOT			30 + 7 days post last dose of study drug(s)		X	X	X
Safety follow-up			100 days post last dose of nivolumab				X

7.4 Biomarker Studies

Blood and tumor samples will be collected for measurement of potential pharmacodynamic and patient stratification biomarkers. Assessments may include, but are not limited to:

- Flow cytometry of peripheral blood leukocytes to assess the expression of CD30, CD153, PD-1, PD-L1, and PD-L2 in specific T cell (Th1, Th2, Th17, native, activated, effector and central memory), B cell (naive, activated, memory, plasmablast and plasma cell), and myeloid cell (monocyte, dendritic cell) populations via panels which may include, but not be limited to:
    - CD3, CD4, CD8, CD30, Ki67, HLA-DR+, PD-1, PD-L1, PD-L2, CD153
    - CD3, CD4, CD8, CD30, CD127, CXCR3, CCR4, CCR6, CD25, CD153
    - CD3, CD4, CD8, CD30, CD45RA, CD153, CD197
    - CD19, CD10, CD38, CD27, IgD, CD30, CD153, CD20
    - CD14, CD16, CD11c, CD3/CD19, CD56, CD30, CD153, CD123, HLA-DR, CD7
- Soluble biomarkers, including but not limited to, CD30 (sCD30), CD153 (sCD153), PD-1 (sPD-1), and PD-L1 (sPD-L1)
- Inflammatory cytokines/chemokines including, but not limited to, IFN-γ, IL-6, IL-18, CXCL11 (I-TAC), CXCL9, CXCL10, MIP1 beta, and TNF-α
- Peripheral blood T cell receptor (TCR) repertoire and anti-CMV/EBV/FLU T cell responses from PBMC to assess the impact of brentuximab vedotin alone and in combination with nivolumab on immune status
- RNA expression profiling

Sampling timepoints are listed in Table 4 and Table 5.

Table 4: Biomarker sampling timepoints, Parts 1 and 2

Cycle	Study Day	Time	Window	Relative Time	Flow Cytometry	Plasma and Serum Cytokines	Serum Biomarkers	RNA	PBMC	TCR
1	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 2[a]	24 hr postdose	±4 hr	Start of brentuximab vedotin infusion		X	X	X		
	Day 8	Predose	Within 24 hr prior to start of nivolumab infusion	Start of nivolumab infusion	X	X	X	X	X	X
	Day 15	336 hr postdose	±24 hr	Start of brentuximab vedotin infusion	X	X	X	X	X	X
2	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 8[b]	168 hr postdose	±24 hr	Start of brentuximab infusion	X	X	X			
3	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
4	Day 1[a]	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 2[a]	24 hr postdose	±4 hr	Start of brentuximab vedotin infusion		X	X	X		
	Day 8[a]	168 hr postdose	±24 hr	Start of brentuximab vedotin infusion	X	X	X	X	X	X
EOT	30 + 7 days post last dose of study drug(s)				X	X	X	X	X	X

a For patients in Part 1 only
b For patients in Part 2 only

Table 5: Biomarker sampling timepoints, Part 3

Cycle	Study Day	Time	Window	Relative Time	Flow Cytometry	Plasma and Serum Cytokines	Serum Biomarkers	RNA	PBMC	TCR
1	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 8	168 hr postdose	±24 hr	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 15	336 hr postdose	±24 hr	Start of brentuximab vedotin infusion	X	X	X	X	X	X
2	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 8	168 hr postdose	±24 hr	Start of brentuximab infusion	X	X	X			X
3	Day 1	Predose	Within 24 hr prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
EOT	30 + 7 days post last dose of study drug(s)				X	X	X	X	X	X

7.4.1 Tumor Biopsies

Formalin fixed paraffin-embedded tumor tissue blocks taken after relapse of prior therapy will be collected at screening to assess biomarkers implicated in sensitivity or resistance to brentuximab vedotin and/or nivolumab (e.g., CD30 expression, PD-L1/L2 amplification, and expression). If tumor tissue block is not available, a minimum of approximately 20 unstained charged slides of the tumor tissue will be required. If multiple blocks are available, the one with the highest tumor content is preferred. If archival tumor tissues (i.e., tumor tissue obtained at the time of the patient's original diagnosis and/or at the time of subsequent procedures conducted as part of the patient's standard care) are available, they will be collected under the same criteria to understand the impact of prior treatment on CD30 and PD-L1/L2 expression. If any tissue remains, the tumor pathology block may be returned to the original site by the Sponsor or designee at the end of the study upon request. See the Laboratory Manual for details.

Efforts should be made to take additional biopsies in patients who demonstrate disease progression, indeterminate response on study, or residual disease at the EOT visit. These optional samples are to be tested for the expression of CD30 and PD-L1/L2 expression and other potential markers to understand potential delayed response and/or resistance mechanism.

Assessments may include histopathology and immunohistochemistry of tumor biopsies for:

- Expression of PD-L1/L2, CD30, immune cell markers and expression of other immune checkpoint molecules in malignant Reed-Sternberg cells and tumor infiltrating lymphocytes by IHC, as well as amplification of 9p24.1
- Tumor infiltrating lymphocytes (CD3, CD4, CD8, Foxp3+ and ratios thereof)
- Expression of CD30 and PD-1 among T, B, macrophage and myeloid cell populations including, but not limited to CD4, CD8, Foxp3, CD68, and CD163
- Amplification and expression of PD-L1 and PD-L2 by malignant Reed-Sternberg cells and tumor infiltrating lymphocytes
- Expression (by RNA or protein) of other immune checkpoint molecules, including, but not limited to Galectin-1, if an assay becomes available
- Epstein-Barr Virus infection status if not previously known
- Expression analysis of 23-gene predictor for outcome post-ASCT in classical HL

7.5 Biospecimen Repository

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

7.6 Safety Assessments

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

Safety will be monitored over the course of the study by an SMC as described in Section 9.3.9.

7.6.1 Adverse Events

7.6.1.1 Definitions

Adverse Event

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

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

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

Serious Adverse Events

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

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/incapacitating:	Resulted in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, version 4.03. These criteria are provided in the study manual.

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

Relationship of the Adverse Event to Study Treatment

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

Related:	There is evidence to suggest a causal relationship between the drug and the AE, 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 AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

The Investigator's Brochures for brentuximab vedotin and nivolumab individually describe adverse events commonly observed relative to either agent (i.e., neutropenia or peripheral neuropathy with brentuximab vedotin; immune-mediated adverse events with nivolumab), as well as less common serious findings. The respective Investigator's Brochure should be referenced when attributing causality; however, the final decision regarding causality is at the discretion of the investigator.

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 versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by

standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Adverse reactions associated with the infusion of study drugs must be recorded as both the NCI CTCAE term for infusion-related reaction (e.g., cytokine release syndrome, acute infusion reaction, or allergic or hypersensitivity reaction) and with each sign or symptom recorded as an individual adverse event. Level of severity for both the overall infusion-related reaction term and the individual signs and symptoms should also be recorded.

Recording Serious Adverse Events

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

The following should be considered when recording SAEs:

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

Progression of the Underlying Cancer

Do not use the term 'disease progression' alone when reporting AEs, including SAEs, because it is too nonspecific. Symptoms of disease progression that meet the criteria for an SAE must be reported. When possible, report the specific disease (clinical) manifestation of the progression (e.g., "malignant pleural effusion", "spinal bone metastases", "lymphadenopathy", "brain metastases"). Otherwise, it is acceptable to report the specific disease (e.g., non-Hodgkin lymphoma) as an SAE.

Pregnancy

Notification to Drug Safety: complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of brentuximab vedotin or 8 months after the last dose of nivolumab, whichever is later, including any pregnancies that occur in the partner of a male study patient. Only report pregnancies that occur in a male patient's partner if the estimated date of conception is after the male patient's first study drug(s) dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF: all pregnancies (as described above) that occur within 6 months after the last dose of brentuximab vedotin or 8 months of the last dose of nivolumab, whichever is later, 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 brentuximab vedotin dose or 100 days after the last nivolumab dose, whichever is later. However, all study protocol-related AEs are to be recorded 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, regardless of the relationship of the event to the study treatment regimen.

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

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

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

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

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity as well as other SAEs that are not study endpoints, but are known consequences of the underlying disease or condition that are anticipated to occur in the study population should not be reported to the Food and Drug Administration (FDA) as individual

IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Reporting Requirements for INDs and Bioavailability (BA) and Bioequivalence (BE) Studies (December 2012).

In this study, the SAEs that do not require individual IND safety reports to the FDA are progression of the underlying cancer and SAEs related to the mobilization of stem cells for ASCT. These anticipated SAEs will be reviewed periodically by an SMC and Seattle Genetics Drug Safety Department. If, upon review, an SAE is occurring at a higher rate than that which would be expected for HL patients being treated with either study treatment (brentuximab vedotin or nivolumab), then an IND safety report for the SAE will be submitted to the FDA.

7.6.2 Clinical Laboratory Tests

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

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, amylase, lipase, and gamma-glutamyl transpeptidase, serum glucose, and uric acid. Additionally, TSH, free T3, and free T4 must also be tested at Cycle 1, Cycle 3, and EOT.
- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, RBC count, bands and blasts, hemoglobin, and hematocrit.

The following additional laboratory assessment(s) will be performed by local laboratories at the designated timepoints (see Appendix A):

- Hepatitis B and C serologies; if hepatitis C serology is positive, HCV RNA test by PCR is required to confirm
- Epstein-Barr virus serology
- A serum or urine β-hCG pregnancy test for females of childbearing potential

7.6.3 Physical Examination

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

7.6.4 Other Safety Assessment

7.6.4.1 Pulmonary-related signs or symptoms

Oxygen saturation by pulse oximetry should be obtained prior to each dose of nivolumab and at any time a patient has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual patient throughout the study. However, if the patient's status changes, the investigator can alter the extent of exertion based upon their medical judgment. If a patient shows changes on pulse oximetry or other pulmonary-related signs (e.g., hypoxia, fever) or symptoms (e.g., dyspnea, cough) consistent with possible pulmonary adverse events, the patient should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 3 of the nivolumab Investigator's Brochure. See Section 5.3.4 for nivolumab dose modifications and Section 5.5.2 for allowed concomitant therapy for pulmonary-related signs or symptoms.

7.7 Appropriateness of Measurements

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

ATA is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to brentuximab vedotin and nivolumab. 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, or representatives of regulatory authorities.

8.2 Data Management Procedures

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

8.3 Access to Source Data

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

records must also be available for inspection by representatives of regulatory authorities and IRB/IEC.

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 Research and Development 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 Research and Development Quality Assurance group of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

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

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

8.6.2 Investigator Record Retention

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

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size

It is anticipated that a total of approximately 55 patients will be enrolled in Parts 1 and 2 of the study. This number was chosen in order to enable an adequately powered analysis of the primary endpoint of CR rate and to characterize the safety profile of the combination treatment. This number will be greater if multiple dose regimens are investigated in Part 1 of the study as only those patients from Part 1 who are treated with the dose regimen chosen for Part 2 will be included in the analysis of the primary endpoint.

The sample size needed to provide adequate power to test the primary endpoint is at least 53. With this sample size a one-sided exact binomial test at level α=0.05 will reject the null hypothesis of a CR rate less than or equal to 30% approximately 90% of the time when the true CR rate is 50%. For the given parameters the null will be rejected when 22 or more CRs are observed (i.e., CR rate ≥41.5% is observed).

For the safety assessment of the combination treatment, a sample size of 55 patients will provide a 94% chance of observing at least one occurrence of an adverse event with a true event rate of 5%.

For Part 3, no formal hypothesis test is specified. The sample size of 30 patients was chosen to allow adequate precision of estimates for response rates and safety data. For example, if 63% (19/30) of patients have a CR, then the 95% exact CI is (44%, 80%). The sample size of 30 patients is sufficient to perform exploratory biomarker analyses.

East 5.4 was used to perform sample size calculations.

9.2 Study Endpoint Definitions

9.2.1 Primary Efficacy Endpoint

9.2.1.1 Complete Response (CR) Rate

CR rate is defined as the proportion of patients with best response of CR prior to ASCT or initiation of subsequent antitumor treatment not specified in the protocol. In Parts 1 and 2, response will be determined by investigator assessment according to the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014); see Section 7.2 for details of the modified criteria. For Part 3, response will be determined by investigator assessment according to the Lugano Classified Revised Staging System (Cheson 2014) with the incorporation of LYRIC (Appendix D) (Cheson 2016). Patients whose response to treatment cannot be adequately assessed according to the specified criteria will be classified as non-responders for the purpose of calculating CR rate.

9.2.2 Secondary Efficacy Endpoints

9.2.2.1 Objective Response Rate (ORR)

ORR is defined as the proportion of patients with best response of CR or PR prior to ASCT or initiation of subsequent antitumor treatment not specified in the protocol. Response is by investigator assessment according to the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014); see Section 7.2 for details of the modified criteria. Patients whose response to treatment cannot be adequately assessed according to the specified criteria will be classified as non-responders for the purpose of calculating ORR.

9.2.2.2 Progression-Free Survival (PFS) after ASCT

PFS after ASCT is defined as the time from ASCT to the first documentation of PD or to death due to any cause, whichever comes first. Patients who do not undergo ASCT will not be included in the analysis of this endpoint. Documentation of PD must be consistent with the criteria described in Section 7.2. Specifically, PFS will be calculated as:

PFS = Date of first documented PD or death – Date of ASCT + 1.

PFS data will be censored as described below:

- Patients who do not have PD and are still on study at the time of an analysis will be censored at the date of the most recent disease assessment prior to the analysis which was adequate to document PD
- Patients who have started an antitumor treatment (excluding high-dose conditioning regimens pre-ASCT, consolidative radiotherapy pre- or post-ASCT, or consolidative treatment with single-agent brentuximab vedotin post-ASCT) other than the study treatment prior to documented PD will be censored at the date of the most recent disease assessment which was adequate to document PD prior to start of new therapy
- Patients who are removed from study prior to documentation of PD will be censored at the date of the most recent disease assessment prior to study discontinuation which was adequate to document PD.

If a patient does not have any adequate disease assessments after ASCT their PFS will be censored at one day.

9.2.2.3 Duration of Response

Duration of response is defined as the time from start of the first documentation of OR (CR or PR) to the first documentation of PD or to death due to any cause, whichever comes first. Duration of response will only be calculated for the group of patients achieving an objective response while on study. Documentation of PD must be consistent with the criteria described in Section 7.2. Duration of response data will be censored as described below:

- Patients who do not have PD and are still on study at the time of an analysis will be censored at the date of the most recent disease assessment prior to the analysis which was adequate to document PD
- Patients who have started an antitumor treatment (excluding stem cell transplant or post-ASCT consolidative therapy) other than the study treatment prior to documented PD will be censored at the date of the most recent disease assessment prior to start of new therapy which was adequate to document PD
- Patients who are removed from study prior to documentation of PD will be censored at the date of the most recent disease assessment prior to study discontinuation which was adequate to document PD.

If a patient does not have any disease assessments adequate to detect PD after the first documentation of objective response, their duration of response will be censored at one day.

An additional exploratory analysis of PFS may be conducted in which clinical assessment will be considered adequate to detect disease progression. Other exploratory analyses of PFS may also be performed. These analyses may involve different definitions of events and/or different censoring rules; details will be provided in the statistical analysis plan (SAP).

9.2.3 Additional Efficacy Endpoints

9.2.3.1 Overall Survival (OS)

Overall survival is defined as the time from date of enrollment to date of death due to any cause. In the absence of confirmation of death, overall survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond the date of enrollment will have their overall survival time censored to 1 day.

9.2.3.2 PFS

PFS is defined as the time from enrollment to the first documentation of PD or to death due to any cause, whichever comes first. Documentation of PD must be consistent with the criteria described in Section 7.2. Specifically, PFS will be calculated as:

PFS = Date of first documented PD or death – Date of enrollment + 1.

PFS data will be censored as described below:

- Patients who do not have PD and are still on study at the time of an analysis will be censored at the date of the most recent disease assessment prior to the analysis that was adequate to document PD
- Patients who have started an antitumor treatment (excluding high-dose conditioning regimens pre-ASCT, consolidative radiotherapy pre- or post-ASCT, or consolidative treatment with single-agent brentuximab vedotin post-ASCT) other than the study treatment prior to documented PD will be censored at the date of the most recent disease assessment that was adequate to document PD prior to start of new therapy

- Patients who are removed from study prior to documentation of PD will be censored at the date of the most recent disease assessment prior to study discontinuation that was adequate to document PD.

If a patient does not have any adequate disease assessments after enrollment their PFS will be censored at one day.

An additional exploratory analysis of PFS may be conducted in which clinical assessment will be considered adequate to detect disease progression. Other exploratory analyses of PFS may also be performed. These analyses may involve different definitions of events and/or different censoring rules; details will be provided in the SAP.

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

This is a phase 1/2 open-label study with a formal statistical hypothesis for the primary efficacy endpoint of CR rate. There are no formal pre-specified hypotheses associated with the primary safety objective.

In general, descriptive statistics (mean, median, standard deviation, minimum, maximum) will be used to summarize continuous variables collected. Frequencies and percentages will be used when presenting categorical variables. Summaries will be presented overall and by dose regimen unless otherwise specified.

9.3.1.1 Randomization and Blinding

No randomization will be carried out and no blinding will be enforced as this is an open-label trial.

9.3.1.2 Adjustments for Covariates

Adjustment for covariates will not take place for analysis of the primary efficacy endpoint of CR rate. Subgroup analyses and stratified analyses may be carried out for particular covariates of interest. Exploratory analysis of biomarker and pharmacodynamic endpoints may also incorporate covariate adjustment.

9.3.1.3 Handling of Dropouts and Missing Data

Missing data will not be imputed, with the exception of AE dates while calculating duration of events. Patients with missing values of a variable other than response endpoints (CR and ORR) and time-to-event endpoints (PFS and OS) will be excluded from the analysis of that endpoint. Patients whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate and ORR. Censoring rules will be applied to the

estimation of the distribution of the time-to-event endpoints; details will be provided in the SAP.

9.3.1.4 Multicenter Studies

Due to the size of the trial and the number of study sites, it is not anticipated that any one site will accrue enough patients to warrant an analysis by site.

9.3.1.5 Multiple Comparisons and Multiplicity

No adjustment for multiplicity is planned as there is only a single planned hypothesis test of the primary efficacy endpoint.

9.3.1.6 Data Transformations and Derivations

Age in years will be calculated with the SAS INTCK function using informed consent date and birth date.

Study Day will be calculated as Date – First Dose Date + 1 for dates on or after the first dose date. For dates prior to the first dose date, Study Day will be calculated as Date – First Dose Date. For all calculations of Study Day, the First Dose Date will be the earliest date of treatment administration for brentuximab vedotin.

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

The following unit conversion will be implemented unless otherwise specified:

Months = Days / 30.4375

Years = Days / 365.25

Baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug.

The EOT date will be the date the EOT visit is performed, or 30 days after the last dose of study drug if an EOT visit is not performed.

For efficacy assessments, the date of response will be the latest of all radiologic scan dates for the given disease assessment. The date of progression will be the earliest of all radiologic scan dates for the given restage assessment.

9.3.1.7 Analysis Sets

All Enrolled Patients Analysis Set

The All Enrolled Patients analysis set includes all patients enrolled in the study. The All Enrolled Patients set will be used for the primary efficacy analysis. Secondary and additional efficacy endpoints will also be analyzed using this analysis set.

All Treated Patients Analysis Set

The All Treated Patients analysis set includes all patients who receive any amount of brentuximab vedotin or nivolumab. The All Treated Patients set will be used for presentation of safety data and may be used for exploratory analyses of efficacy endpoints.

Efficacy Evaluable Analysis Set

The Efficacy Evaluable analysis set includes all patients who had an adequate baseline disease assessment, received any amount of either drug, and subsequently had an adequate response assessment. The Efficacy Evaluable set will be used for exploratory analysis of efficacy endpoints.

9.3.1.8 Examination of Subgroups

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

9.3.1.9 Timing of Analyses

Analysis of the primary endpoint will be carried out after all patients have had their EOT assessments. Interim summaries of various endpoints may be presented at scientific congresses prior to the final analysis of the primary endpoint. Interim summaries will also be presented to the SMC. Database cutoff will be determined after all patients have completed treatment.

9.3.2 Patient Disposition

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

9.3.3 Patient Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

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

CR rate at the EOT visit will be calculated using the All Enrolled Patients analysis set and will include all patients in this analysis set who were enrolled on the dose regimen chosen for Part 2. A two-sided 90% exact binomial CI will be calculated (Clopper 1934) and the test will be carried out for the following null and alternative hypotheses:

- H_0: CR rate ≤30%
- H_1: CR rate >30%

The test will be carried out using a one-sided exact binomial test at level α=0.05, thus the null will be rejected in favor of the alternative if P <0.05 is observed.

9.3.5.2 Secondary Efficacy Analyses

ORR at EOT will be calculated using the All Enrolled Patients set and its two-sided 95% exact binomial CI will be presented (Clopper 1934). Additional summaries of ORR may be presented based on patient demographics of interest. Summaries may also be presented using the All Treated Patients and the Efficacy Evaluable analysis sets. PFS and duration of response estimates will be based on Kaplan-Meier methodology and Kaplan-Meier plots will be presented. The median PFS and duration of response times will be determined and their two-sided 95% CI calculated using the log-log transformation method (Collett 1994).

9.3.5.3 Additional Efficacy Analyses

OS and PFS estimates will be based on Kaplan-Meier methodology and Kaplan-Meier plots will be presented. The median OS time will be determined and its two-sided 95% CI calculated using the log-log transformation method (Collett 1994).

9.3.6 Pharmacokinetic and ATA Analyses

Pharmacokinetic parameters to be estimated for brentuximab vedotin and MMAE include the area under the concentration-time curve (AUC), maximum concentration (C_{max}) or concentration at the end of infusion (C_{eoi}), the time C_{max} occurred (T_{max}), and trough concentration (C_{trough}) for brentuximab vedotin. For nivolumab, C_{eoi} and C_{trough} will be summarized. The incidence of ATA to brentuximab vedotin and to nivolumab will also be assessed.

9.3.7 Biomarker Analyses

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

9.3.8 Safety Analyses

9.3.8.1 Extent of Exposure

Exposure for each treatment agent, including duration of treatment, number of cycles, total dose, dose modifications, and dose intensity will be summarized using the All Treated Patients analysis set.

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 either brentuximab vedotin or nivolumab. The incidence of all AEs, treatment-emergent AEs, and treatment-related AEs will be tabulated. 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 MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one patient, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to premature discontinuation of study drug 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. 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 may be tabulated as appropriate for laboratory results and scheduled visit. Laboratory values will be listed with grade per NCI CTCAE and out of normal reference range flags.

9.3.9 Interim Analyses

In Part 1 of the study, an SMC will monitor the trial for safety and provide guidance regarding possible enrollment of additional patients in Part 1 and possible expansion of enrollment in Part 2. Initially 6 patients will be enrolled in Part 1. If a patient discontinues treatment for reasons other than a DLT prior to 6 patients completing the DLT evaluation period then they will be replaced (as long as the arm remains open). These patients will be monitored for DLT throughout the DLT evaluation period (see Section 3.1.4 for details regarding the definition of DLT and DLT-evaluable). The SMC will review safety data and provide recommendations when either of the following occurs:

1. 2 or more of the patients in the current arm are determined to have had a DLT based on the protocol definition.
2. 6 patients complete the DLT evaluation period (by either remaining on treatment or having a DLT).

On review of all available data, the SMC may determine that the classification of DLT was not appropriate for one or more of the patients, in which case enrollment may resume if the target of 6 patients has not yet been reached. However, if 2 or more patients were determined to have experienced DLT, then expansion will not occur as the next step. Based on SMC recommendations, additional patients may be enrolled at modified treatment and/or dosing levels (details in Section 3.1). These additional patients will then be assessed for DLT in the same manner described above to determine if it is appropriate to expand

enrollment. If it is determined by the SMC that due to safety concerns no additional dose levels or schedules should be enrolled, then the study will be closed to enrollment.

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

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R1); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

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 to this study, 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 (if applicable), 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 GCP, and all applicable local and/or regional laws, rules, and regulations.

10.3.1 Investigator Information

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

10.3.2 Protocol Amendments and Study Termination

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

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

10.4 Study Documentation, Privacy and Records Retention

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

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

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

10.5 Clinical Trial Agreement

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

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APPENDIX A: SCHEDULE OF EVENTS

	Patients in Part 1	Screening	Baseline	Enrollment	Cycle 1				Cycle 2		Cycle 3	Cycle 4[I]			EOT[J]	Prior to ASCT	Safety Follow-up	Long-term Follow-up[L]
	Visit Window	D –28 to 1	D –7 to 1	D –7 to 1	D1 (±1 day)	Day 2 (+2 days)	D8 (±1 day)	D15 (±1 day)	D1 (±1 day)	D15 (+ 6 days	D1 (±1 day)	D1 (±1 day)	Day 2 (+2 days)	D8 (±1 day)	30–37 Days Post Last Dose	After EOT visit performed	100 Days Post Last Dose of Nivolumab	±2 weeks
Screening/ baseline assessments	Informed Consent	X		Eligibility documentation submitted to Sponsor prior to study start														
	Inclusion/exclusion criteria	X																
	Medical history	X																
	Inflammatory condition review	X													X[M]			
	Serology (hepatitis B, C, EBV)[Q]	X																
	Height		X															
	Weight[R]		X		X				X		X	X						
	Electrocardiogram	X																
	Pregnancy test		X															
	Pulmonary function test	X																
Treatment	Brentuximab vedotin				X				X		X	X						
	Nivolumab						X		X[E]		X[E]	X[E]						
PK samples	ADC/MMAE				X[F]	X	X	X	X[F]		X[F]	X[F]	X	X	X			
	Nivolumab						X[G]	X	X[G]		X[G]	X[G]	X	X	X			
ATA	ATA sample				X[B]				X		X	X			X		X	
Biomarker samples[A]	Flow cytometry (whole blood)				X		X	X	X		X	X		X	X			
	Serum and plasma cytokines				X	X	X	X	X		X	X	X	X	X			
	Serum biomarkers				X	X	X	X	X		X	X	X	X	X			
	RNA expression profiling				X	X	X	X	X		X	X	X	X	X			
	PBMC				X		X	X	X		X	X		X	X			
	TCRB sequencing				X		X	X	X		X	X		X	X			
	Tumor biopsy	X[C,D]													X[K]			
Response assessments	Dedicated CT of chest, neck, abdomen, pelvis	X								X[H]					X[V]	X[N]		X[S]
	PET	X													X[V]	X[N]		X[T]
	B symptom assessment				X										X			
	Bone marrow biopsy														X[O]	X[O]		
	Survival and disease status																	X
	Interval medical history																	X
Safety assessments	Physical examination[R]		X		X						X				X		X	X
	Vital signs		X															
	Pulse oximetry						X		X		X	X						
	Performance status		X												X			
	Serum chemistry[R]		X		X		X		X		X	X			X		X	
	Thyroid panel				X[P]						X[P]				X[P]			
	CBC with differential[R]		X		X		X		X		X	X			X		X	
	Estimated creatinine clearance		X															
	Antinuclear antibodies		X												X			
	Con meds and AEs	Collect any related to study procedures			Collect from Day 1 (predose) through safety reporting period of study drug(s)													

	Patients in Part 2	Screening	Baseline	Enrollment	Cycle 1			Cycle 2			Cycle 3	Cycle 4[I]	EOT[J]	Prior to ASCT	Safety Follow-up	Long-term Follow-up[L]
	Visit Window	D –28 to 1	D –7 to 1	D –7 to 1	D1 (±1 day)	D8 (±1 day)	D15 (±1 day)	D1 (±1 day)	D8 (±1 day)	D15 (+ 6 days	D1 (±1 day)	D1 (±1 day)	30–37 Days Post Last Dose or as noted for scans[V]	After EOT visit performed	100 Days Post Last Dose of Nivolumab	±2 weeks
Screening/ baseline assessments	Informed Consent	X		Eligibility documentation submitted to Sponsor prior to study start												
	Inclusion/exclusion criteria	X														
	Medical history	X														
	Inflammatory condition review	X											X[M]			
	Serology (hepatitis B, C, EBV)[Q]	X														
	Height		X													
	Weight[R]		X		X			X			X	X				
	Electrocardiogram	X														
	Pregnancy test		X													
	Pulmonary function test	X														
Treatment	Brentuximab vedotin				X			X			X	X				
	Nivolumab					X		X[E]			X[E]	X[E]				
PK samples	ADC/MMAE				X[F]			X[F]			X[F]	X[F]	X			
	Nivolumab					X[G]		X[G]			X[G]	X[G]	X			
ATA	ATA sample				X[B]			X			X	X	X		X	
Biomarker samples[A]	Flow cytometry (whole blood)				X	X	X	X	X		X		X			
	Serum and plasma cytokines				X	X	X	X	X		X		X			
	Serum biomarkers				X	X	X	X	X		X		X			
	RNA expression profiling				X	X	X	X			X		X			
	PBMC				X	X	X	X			X		X			
	TCRB sequencing				X	X	X	X			X		X			
	Tumor biopsy	X[C,D]											X[K]			
Response assessments	Dedicated CT of chest, neck, abdomen, pelvis	X								X[H]			X[V]	X[N]		X[S]
	PET	X											X[V]	X[N]		X[T]
	B symptom assessment				X								X			
	Bone marrow biopsy												X[O]	X[O]		
	Survival and disease status															X
	Interval medical history															X
Safety assessments	Physical examination[R]		X		X						X		X		X	X
	Vital signs		X													
	Pulse oximetry					X		X			X	X				
	Performance status		X										X			
	Serum chemistry[R]		X		X	X		X			X	X	X		X	
	Thyroid panel				X[P]						X[P]		X[P]			
	CBC with differential[R]		X		X	X		X			X	X	X		X	
	Estimated creatinine clearance		X													
	Antinuclear antibodies		X										X			
	Con meds and AEs	Collect any related to study procedures			Collect from Day 1 (predose) through safety reporting period of study drug(s)											

	Patients in Part 3	Screening	Baseline	Enrollment	Cycle 1			Cycle 2			Cycle 3	Cycle 4[I]	EOT[J]	Prior to ASCT	Safety Follow-up	Long-term Follow-up[L]
	Visit Window	D –28 to 1	D –7 to 1	D –7 to 1	D1 (±1 day)	D8 (±1 day)	D15 (±1 day)	D1 (±1 day)	D8 (±1 day)	D15 (+ 6 days	D1 (±1 day)	D1 (±1 day)	30–37 days post last dose or as noted for scans[U]	After EOT visit performed	100 Days post last dose of nivolumab	±2 weeks
Screening/ baseline assessments	Informed Consent	X		Eligibility documentation submitted to Sponsor prior to study start												
	Inclusion/exclusion criteria	X														
	Medical history	X														
	Inflammatory condition review	X											X[M]			
	Serology (hepatitis B, C, EBV)[Q]	X														
	Height		X													
	Weight[R]		X		X			X			X	X				
	Electrocardiogram	X														
	Pregnancy test		X													
	Pulmonary function test	X														
Treatment	Brentuximab vedotin				X			X			X	X				
	Nivolumab				X[E]			X[E]			X[E]	X[E]				
PK samples	ADC/MMAE				See Table 3 for PK and ATA sampling timepoints											
	Nivolumab															
ATA	ATA sample															
Biomarker samples[A]	Flow cytometry (whole blood)				See Table 5 for biomarker sampling timepoints											
	Serum and plasma cytokines															
	Serum biomarkers															
	RNA expression profiling															
	PBMC															
	TCRB sequencing															
	Tumor biopsy	X[C,D]											X[K]			
Response Assessments	Dedicated CT of chest, neck, abdomen, pelvis	X								X[H]			X[U]			X[S]
	PET	X											X[U]			X[T]
	B symptom assessment				X								X			
	Bone marrow biopsy												X[O]	X[O]		
	Survival and disease status															X
	Interval medical history															X
Safety assessments	Physical examination[R]		X		X						X		X		X	X
	Vital signs		X													
	Pulse oximetry				X			X			X	X				
	Performance status		X										X			
	Serum chemistry[R]		X		X	X		X			X	X	X		X	
	Thyroid panel				X[P]						X[P]		X[P]			
	CBC with differential[R]		X		X	X		X			X	X	X		X	
	Estimated creatinine clearance		X													
	Antinuclear antibodies		X										X			
	Con meds and AEs	Collect any related to study procedures			Collect from Day 1 (predose) through safety reporting period of study drug(s)											

A. All biomarker samples are predose on the day of blood draw, if applicable.
B. ATA includes the pre-dose brentuximab vedotin and nivolumab samples at Cycle 1 Day 1.
C. Sample taken after relapse of prior therapy required; archival sample at diagnosis to be available.
D. Prior to first dose brentuximab vedotin.
E. Nivolumab administration should be at least 30 minutes after completion of brentuximab vedotin administration.
F. See Table 2 for timing of samples for brentuximab vedotin PK and ATA.
G. See Table 2 for timing of samples for nivolumab PK and ATA.
H. Cycle 2 CT scan only to check for progression of disease; a limited scan that includes sites of disease identified at baseline is acceptable. Patients with stable disease or better may continue on treatment, while patients with progression of disease are to discontinue treatment and have an EOT visit. Patients in Part 3 with an indeterminate response as defined by LYRIC may also continue on treatment.
I. For patients who receive consolidative high-dose therapy and ASCT, peripheral blood stem cells may be mobilized following Cycle 4, as applicable. If mobilized prior to Cycle 4 after discussion with the medical monitor, subsequent cycles should not begin until adequate recovery of peripheral blood counts and stem cell collection has occurred per institutional standards. A delay of >7 days is discouraged.
J. EOT evaluations should be obtained before initiation of non-protocol therapy. If EOT evaluations are completed before 30 days after the last treatment, the site will conduct a phone screen 30–37 days following the patient's last treatment to ensure that no changes in the AE profile have occurred.
K. Optional at progression of disease or if evidence of residual disease is suspected.
L. Follow-up to be performed at the following timepoints post-ASCT (or post-EOT for patients not receiving an ASCT): 100 days and then 6, 9, 12, 18, 24, 30, and 36 months, and then per institutional standard thereafter CT scans will only be done if progression is suspected based on clinical signs and symptoms.
M. Only for patients with findings at Screening/Baseline.
N. Not required if performed within the prior 6 weeks.
O. For patients planning to proceed to ASCT, a bone marrow biopsy is required; may be performed at the EOT visit.
P. Thyroid panel includes TSH, free T3, and free T4.
Q. If hepatitis C serology is positive, HCV RNA test by PCR is required to confirm.
R. May be performed within 1 day prior to dosing; results from clinical laboratory tests must be reviewed prior to dosing.
S. Not to be performed at 9, 18, and 30 months unless progression is suspected based on interval medical history and/or physical examination.
T. Not required if patient achieves CmR.
U. For patients in Part 3 only, CT and PET scans to be performed 15-30 days post last dose of study drug.
V. For patients in Parts 1 and 2 only, CT and PET scans to be performed 23-37 days post last dose of study drug.

APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		Lansky		ECOG	
Percent	Description	Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.		
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, play activity.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet active play and activities.		
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.		
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.		
0	Dead.	0	Dead.	5	Dead.

APPENDIX C: NEW YORK HEART ASSOCIATION CLASSIFICATION

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Patients

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Online source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX D: OVERVIEW OF LYRIC CRITERIA (PART 3 ONLY)

If tumor flare or pseudo-progression is suspected, then a clinical response of indeterminate response (IR) should be reported based on the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016).

Definition of Indeterminate Response

- **IR1:** An increase in overall tumor burden (as assessed by the sum of the products of the largest diameter [SPD]) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration

  In general, patients should be experiencing clinical stability or improvement and must be able to tolerate continued treatment and not at risk of serious complications should tumor growth occur. Symptoms related to tumor growth, such as pain at the tumor site or compression of adjacent structures, may not be considered as clinical deterioration in this context.

- **IR2:** Appearance of new lesions, or growth of one or more existing lesion(s) ≥50% at any time during treatment, occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during treatment; and

  This may occur early or late in the treatment course. A biopsy is strongly encouraged when a patient experiences this phenomenon. If the biopsy does not confirm the presence of viable tumor in the new or enlarging lesion(s), then the lesion(s) are not considered active disease and should not be used in subsequent SPD assessments.

- **IR3:** An increase in fluorodeoxyglucose (FDG) uptake (using the 5-Point Scale per the Deauville Criteria of one or more lesion[s]) without a concomitant increase in lesion size or number.

  Increased immune activity at the site of tumor may manifest as an increase in FDG uptake. Therefore, by itself changes in uptake should not trigger an assignment of progressive disease (PD). The magnitude of increase in uptake in an immune-mediated flare compared to that in true tumor progression is not yet known. It is important to investigate this finding, especially in conjunction with a biopsy (if possible) of the lesion in question, an increase in FDG avidity of one or more lesions suggestive of lymphoma, without a concomitant increase in size of those lesions meeting PD criteria does not constitute PD.

It is possible that, at a single time point a patient could fulfill criteria for both IR 1 or 2 AND IR3. For example, there could be a new FDG-avid lesion in the absence of overall progression (IR2), and at the same time, increase in FDG uptake of a separate lesion (IR3). In such cases, the designation of IR1 or 2 should take priority (e.g., IR2 in the above example).

Follow-Up of Indeterminate Response

At 12 weeks (or earlier if clinically indicated) after a response of IR is determined by the Investigator, repeat imaging is mandatory and PD must be confirmed or refuted based on LYRIC follow-up criteria for IR. PD should be reported if the SPD of the target lesion has increased further, with the considerations below:

- In the case of IR1, the comparison should be between the first IR1 and the current SPD, with an increase of ≥10% constituting PD. In addition, there should be an increase of ≥5 mm (in either dimension) of at least one lesion for lesions ≤2 cm, and 10 mm for lesions >2 cm, to be consistent with the Lugano classification (Cheson 2016). If the target SPD increase is <10%, the response would still be categorized as IR1, and the patient could continue treatment until a subsequent scan shows either PD (≥10% increase from first IR1 time point and an increase of >5 mm in either dimension of at least one lesion) or response (≥50% decrease from baseline). In this situation, it is reasonable to repeat imaging in 4–8 weeks to ensure absence of significant further increase.
- In the case of IR2, the new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. If the SPD of the newly defined set of target lesions has increased ≥50% from their nadir value (which may precede the IR time point), the patient should be considered to have PD.
- In the case of IR3, since inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions, as noted above.

APPENDIX E: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "A phase 1/2 study evaluating brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma after failure of frontline therapy."

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 F: DOCUMENT HISTORY

Version	Date
Original	27-May-2015
Amendment 1	21-Oct-2015
Amendment 2	17-Mar-2016
Amendment 3	29-Jul-2016
Amendment 4	23-Jan-2017

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Synopsis, Figure 1, 6.7, 7.2	Added long-term follow up assessments to the scanning schedule: CT scans (chest, neck, abdomen, and pelvis) and PET scans will be performed at baseline, at the End of Treatment (EOT), pre-ASCT, and during long-term follow-up; PET is performed with CT scans until the patient is in compete metabolic response (CmR) by PET.	Clarify that PET scans are needed until the patient has CmR.
3.1, 3.2.1	Removed dose levels of brentuximab vedotin and nivolumab	Revisions provide a more high-level summary of dosing; exact dose levels to be determined by the SMC are noted in dosing and administration sections.
5.2.2	Added dose levels to the administration section and clarified the timing for completing the brentuximab vedotin administration when combined with nivolumab at Cycles 2–4.	To align with the synopsis; clarify potential for dose de-escalation based on SMC recommendation after the first 6 patients complete treatment; clarify that brentuximab vedotin treatment should be completed 30 minutes prior to nivolumab infusion at cycles 2–4 (not cycle 1).
5.3.2	Correction.	To clarify that BMS will provide nivolumab.
5.3.3	Added 1 mg/kg dose level to the administration.	To clarify potential for dose de-escalation based on SMC recommendation after the first 6 patients complete treatment.
5.3.4	Added the following sentences: Based on available information, autoimmune complications are the most likely AEs attributable to nivolumab. Dose modifications for AEs are described in this section as well as in Appendix 2 of the nivolumab IB. Removed the following sentence: ~~There are no recommended dose modifications for hypothyroidism or hyperthyroidism.~~	Revisions to clarify what the most likely nivolumab-related AEs are based on current data and the location of dose modifications for nivolumab-related toxicities. Removed sentence because it is not consistent with recommended dose modifications for hypothyroidism and hyperthyroidism in following sections.
5.3.4.3	Revised dose modifications for total bilirubin elevations as follows: • If a patient has a baseline total bilirubin that is within normal limits, delay dosing for nivolumab-related Grade 2 elevations (>1.5 to 3 x ULN) ◦ Nivolumab may be resumed if the bilirubin improves to Grade 1 ~~(≤3 x ULN)~~ or better (≤1.5 x ULN) • If a patient has a baseline Grade 1 elevation of total bilirubin ~~that is in the Grade 1 range~~ (ULN to ≤1.5 x ULN), delay dosing for nivolumab-related Grade 3 elevations in the range of (>3 to 5 x ULN) ◦ Nivolumab may be resumed if the total bilirubin improves to Grade	Revisions to clarify that the ranges in this protocol for LFT abnormalities are not an exact match of the CTCAE definitions of grade.

Section(s)	Change	Rationale
	2 ~~(1 to 3 x ULN)~~ or better (≤3 x ULN) Removed grade levels from discontinuation paragraph.	
5.5.2	Added the following sentence: At the discretion of the treating physician, consolidative radiotherapy or consolidative treatment with single-agent brentuximab vedotin may be give post-ASCT.	To align with censoring rules for PFS.
5.5.2, 6.3.12	Revised stem cell collection as follows: Collection of peripheral blood stem cells for ASCT, if applicable, should occur per institutional standard of care~~, generally between 10-21 days after last dose of study drug(s)~~.	Protocol calls for scans at EOT (30–37 days post last dose), which are performed before collection of stem cells. Change was made to reconcile the timing of the scans and the stem cell collection period and clarify that the scans should occur prior to the collection of stem cells for ASCT.
6.1	Added the following: With the exception of gamma-glutamyl transpeptidase levels and thyroid function tests, the results from all other clinical laboratory assessments must be reviewed prior to study drug dosing.	Clarify which labs must be reviewed prior to dosing.
6.2.1, Appendix A	Moved assessment of weight from screening visit to baseline visit; removed requirement for fasting glucose at baseline.	Moved weight to be consistent with study drug dosing calculations; clarified that fasting glucose is not required.
6.4	Added the following note to the CT and PET assessments: (may be performed 23 to 37 days after last dose of study drug to allow for collection of peripheral blood stem cells for ASCT, if applicable)	Clarify the timing of scans should occur prior to collection of PBSC for ASCT.
7.2	Added definitions and summary of assessments for complete metabolic response, partial metabolic response, no metabolic response, and progressive metabolic disease.	To align with Lugano Classification Revised Staging System for malignant lymphoma language.
7.4	Added biomarker tests for serum and/or plasma sPD-1 and sPD-L2, as well as anti-CMV/EBV/FLU T cell responses from PBMC.	List new tests to be assessed.
Table 2, Table 3	Revised tables to split brentuximab vedotin PK, ATA, and biomarker sampling versus nivolumab PK, ATA, and biomarker sampling.	Clarify when each sample should be taken with regard to study drug(s) dosing.

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Title	Change medical monitor per admin letter 02	New medical monitor
5.3.2	Nivolumab will be provided by ~~supplied to study sites by~~ Bristol-Myers Squibb and supplied to the study sites by Seattle Genetics.	Clarify procurement of nivolumab
6.4	PET (both PET and CT) may be performed within 23-37 days after EOT	Clarify that a combined CT and PET may be performed at this time
7.1	Tissue samples will be sent to the central pathology lab for disease confirmation and further evaluation of CD30 and PD-L1 expression. ~~A subset of slides will be archived to support the sponsor's efforts toward the development of a companion diagnostic test for CD30 and PD-L1 expression.~~	We are not developing this companion diagnostic test
7.3, Table 2, Table 4	Provided window and relative time clarifications for PK and biomarker sampling	Clarify timing for PK and biomarker sample collection
Table 4, 6.3.4, 6.3.6, 6.3.9, Appendix A	Biomarker sampling for patients in Part 2 changed as follows: Added Cycle 1 Study Day 15 and Cycle 2 Study Day 8 biomarker sampling; removed Cycle 4 Day 1 sampling	Optimize biomarker sampling timepoints
7.4	Biomarker sampling clarifications	Provide sampling flexibility for biomarker studies
Appendix A	Added PET assessment for patients not in CmR during long-term follow-up	Correction to schedule of events from prior amendment adding PET to long-term follow-up visits
	Footnotes changed as follows: B ATA includes the pre-dose brentuximab vedotin sample at Cycle 1 Day 1 and pre-dose nivolumab samples at Cycle 1 Day 8 F See Table 2 for timing of samples for brentuximab vedotin PK and ATA G See Table 2 for timing of samples for nivolumab PK and ATA	Clarify PK sampling timepoints

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
5.4, 5.6.1	Premedication required at Day 1 of each 21-day cycle beginning at Cycle 2	To provide prophylactic premedications for potential infusion-related reactions with the combination of brentuximab vedotin and nivolumab, and to allow investigators to provide patients with appropriate premedications to minimize patient discomfort following treatment with brentuximab vedotin and nivolumab.
6.6	Updated timing of 100-day (+2 weeks) safety visit	To clarify timing of the final safety visit for patients who discontinue prematurely from nivolumab
7.6.1.2	Edited safety reporting of adverse reactions associated with infusion of study drugs	To align with the safety reporting for the combination of brentuximab vedotin and nivolumab

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Title	Change medical monitor per admin letter 03	New medical monitor
List of Abbreviations	Added abbreviations that were missing from the list; deleted abbreviations that were used only once in the document	Correction
Synopsis, 2.3, 3.1, 3.1.1, 3.2, 3.2.1, 5.3.3	Added a new part to the study enrolling 30 additional patients to be treated with brentuximab vedotin and nivolumab on Day 1 of all treatment cycles. Details added in text to specify Parts 1 and 2 versus Part 3 and differences in dosing schedules in Cycle 1. Added Figure 2, which represents study design for Part 3.	To compare the efficacy and safety of staggered versus same-day dosing
Figure 1	Added text to footnote b to indicate the window for EOT scans is 23–37 days post last dose of study drug	Clarification
Synopsis, 3.1, 9.2.1.1, Appendix D	Added LYRIC response criteria (in addition to Lugano) for patients in Part 3	To include formal definitions for indeterminate response and enable continuation of treatment in patients with indeterminate response at Cycle 2
1.3.1	Added: Possible additional mechanisms of anticancer activity include bystander effects on nearby cells in the tumor microenvironment, immunogenic cell death, and antibody-dependent cellular phagocytosis (Oflazoglu 2007; Li 2014; Muller 2014; Gardai 2015; Kim 2015).	To update the description of the mechanism of action of brentuximab vedotin
1.3.1	Added description of patients with HL who were retreated with brentuximab vedotin.(Bartlett 2014)	To provide rationale for enrolling patients previously treated with brentuximab vedotin
Synopsis, 2.3	Added 2 objectives: To compare biomarker data obtained with staggered versus same-day dosing To assess efficacy in patients who previously	Objectives are specific for patients enrolled in Part 3

Section(s)	Change	Rationale
	received brentuximab vedotin	
3.2.2	Added statement regarding prior study SGN35-006, which evaluated the benefits of retreatment with brentuximab vedotin; Added brief description of the Diefenbach (E4412) study (Diefenbach 2016)	To provide rationale for retreating with brentuximab vedotin and for reduced dose of brentuximab vedotin (if necessary) for patients enrolled for retreatment; To provide rationale for treating patients with HL with the combination of brentuximab vedotin and nivolumab
4.1 Inclusion criterion 9	9. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 7 days prior to the first dose of brentuximab vedotin. Females with false positive results and documented verification that the patient is not pregnant are eligible for participation. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy	General update
Synopsis, 4.2 Exclusion criterion 4	~~4. Previous treatment with brentuximab vedotin~~ 4. For patients in Parts 1 and 2, previous treatment with brentuximab vedotin; for Part 3, patients with HL that is refractory to a brentuximab vedotin-containing regimen in first line, or patients who discontinue brentuximab vedotin due to unacceptable toxicity are ineligible. Refractory disease is defined as never achieving a CR to frontline therapy or having a CR but then progressing within 3 months of completing frontline therapy.	As Part 3 will enroll patients for retreatment with brentuximab vedotin, wording of this criterion was updated to indicate specific details for Parts 1 and 2 versus details for Part 3.
Synopsis, 5.2.2	Added details on reduced dose for patients being retreated with brentuximab vedotin	To provide guidance on dosing in patients to be enrolled for retreatment with brentuximab vedotin in Part 3
Table 1 in 5.2.3	Footnote a, which is not new, was added for	Clarification

Section(s)	Change	Rationale
	clarification to text in dose modification table to Grade 2 peripheral neuropathy and Grade 3/4 hematologic AEs	
5.4.2	Added new instructions on required premedication for patients in Part 3. These instructions differ from those for patients in Parts 1 and 2	To eliminate from Part 3 mandatory corticosteroids as prophylactic premedication for infusion-related reactions. Premedication in Part 3 follows protocol E4412 (Diefenbach 2016)
5.5.1, 5.5.2	Removed text describing premedications and treatment of infusion-related reactions and replaced it with links to the pertinent sections describing these	To eliminate redundant information that would have required editing to make it align with instructions for different parts of the study
5.6.1.2	Added instructions for management of infusion-related reactions for patients in Part 3	To provide information specific to Part 3
6.3.1	Added nivolumab dosing Cycle 1 Day 1 for Part 3 only	To add same-day dosing for Cycle 1 Day 1 for Part 3
6.3.3, 6.3.4, 6.3.6, 6.4	Added text to identify portions that are specific for Part 1, 2, or 3	To add safety, biomarker, and PK sampling schedule for Part 3 and identify what applies to Part 1 and/or 2
6.3.7	Added language regarding patients with indeterminate response	Clarification relevant to Part 3
7.2.2	Added text describing response/efficacy assessments for patients in Part 3	To include details related to LYRIC
7.3	Added Table 3 with PK and ATA sampling timepoints specific for Part 3 only	To provide schedule of PK and ATA sampling for patients in Part 3 only
7.6.1	Changed the definition of ICH from International Conference on Harmonisation to International Council for Harmonisation	Update of name change
7.4	Added Table 5 with biomarker sampling timepoints specific for Part 3 only	To provide schedule of biomarker sampling for patients in Part 3 only
8.3	Added “and IRB/IEC” to the sentence “All source data and study records must also be available for	To supplement the details on who is authorized to inspect the source data.

Section(s)	Change	Rationale
	inspection by representatives of regulatory authorities.	
9.1	Add text related to sample size selection for Part 3	Specify details related to Part 3
9.3.1	Added: Summaries will be presented overall and by dose regimen unless otherwise specified.	To clarify with additional information
Throughout	Minor edits and corrections, including many related to harmonizing style throughout the document	Corrections